

Chemical Information Review Document

for

Valerian (*Valeriana officinalis* L.)

[CAS No. 8057-49-6]

and Oils

[CAS No. 8008-88-6]

**Supporting Nomination for Toxicological Evaluation by the
National Toxicology Program**

November 2009



NTP

National Toxicology Program

U.S. Department of Health and Human Services

National Toxicology Program
National Institute of Environmental Health Sciences
National Institutes of Health
U.S. Department of Health and Human Services
Research Triangle Park, NC
<http://ntp.niehs.nih.gov/>

Abstract

Valerian has been used to treat a variety of ailments including insomnia, mood disorders, anxiety, menstrual cramps, and psychological stress conditions. Valerian is classified as a "dietary supplement" under the Dietary Supplement Health and Education Act of 1994. Overall, the data on the efficacy of valerian as a sleep aid are conflicting with some studies showing valerian to be an effective sleep aid while others indicating the effects to be comparable to placebo. Noted side effects included headache, mental dullness, depression, and dizziness. A few cases of hepatotoxicity have been reported with the use of valerian products; however, valerian could not be defined as the cause of the observed liver damage in a majority of the reports. Acute toxicity studies indicate that the LD₅₀s of valerian oil and extract were 15,000 mg/kg and 3300 mg/kg by the oral and intraperitoneal (i.p.) routes, respectively. The LD₅₀ values for valerian constituents were reported to be ~62 mg/kg (valtrate) for i.p. administration and >3160 mg/kg (valeranone) and ≥4600 mg/kg (valtrate) for oral administration. Subchronic exposure studies have produced conflicting results. In mice, oral administration of aqueous suspensions of a marketed valerian product (2000 mg/kg) daily for 7 days produced piloerection, hyperthermia, increased motor activity, defecations, reflex impairment, staggering, and sedation. In rats, administration (route not specified) of an alcoholic extract of valerian root (300 or 600 mg/kg/day) for 30 days produced no significant decreases on growth, weight of selected organs, arterial pressure, or evaluated hematological or biochemical parameters when compared to control animals. Valerian has been reported to have synergistic and antagonistic effects. For example, no effect doses of powdered valerian root suspension and *Leonurus cardiaca* administered concurrently produced maximum prolongation of barbiturate-induced sleep in mice, suggesting a potentiation of effect. Additionally, aqueous extracts of *Valeriana officinalis* antagonized rotenone-induced apoptosis in human SH-SY5Y cells, while an ethanol extract of the valerian root and rhizome inhibited phorbol ester activation of the Epstein-Barr virus early antigen in Raji cells. Overall, valerian constituents and mixtures containing valerian constituents possess cytotoxic properties; comparatively, valerian extracts produced conflicting results. Fetal ossification was affected after valerian administration to pregnant animals. Reproductive endpoints (e.g., weight of the caudae epididymis and frequency of aneuploids) in male mice also were altered by valerian administration. High concentrations of dichloromethane extracts of valerian (≥40 µg/mL) induced DNA damage in human epithelial ECV304 cells. Conflicting genotoxic results were observed with valepotriates. In one study, valepotriates were mutagenic in *Salmonella typhimurium* TA100 and *Escherichia coli* WP2 and WP2 uvrA- in the presence of S9, while in another study, valtrate, didrovaltrate, and acevaltrate were not mutagenic in *S. typhimurium* strains TA98 and TA100. Valtrate, didrovaltrate, and deoxy-didrovaltrate also inhibited DNA and protein synthesis in rat hepatoma cells. *In vivo*, aqueous suspensions of commercially available valerian produced a statistically significant increase in the frequency of micronucleated polychromatic erythrocytes (PCE) and a decrease in the PCE/normochromatic erythrocytes in Swiss albino mice. Additional activities associated with valerian extracts and its constituents include neurological effects (e.g., anxiolytic, sedative, and antidepressant effects), modulation of enzyme activity (e.g., inhibition of glucuronidase activity), immunomodulatory effects (e.g., inhibition of NF-κB activity in HeLa cells by the ethyl acetate extract of *V. officinalis*), and endocrine effects (e.g., induction of an estrogen responsive element luciferase reporter construct in estrogen receptor α positive cell line).

Executive Summary

Basis for Nomination

Valerian (*Valeriana officinalis* [*V. officinalis*]) was nominated by the National Institute of Environmental Health Sciences for comprehensive toxicological characterization based on of its widespread use in dietary supplements, the lack of adequate toxicological data, and concerns regarding potential adverse developmental and reproductive effects, particularly for women of child-bearing age. Commercially available valerian products have numerous applications including treatment of insomnia and anxiety.

Nontoxicological Data

Valerian is a hardy herbaceous perennial plant with a strong odor that is a member of the Valerianaceae family. It is native to Europe and parts of Asia. Constituents of valerian, typically identified using a variety of analytical methods such as high performance liquid chromatography, gas chromatography/mass spectrometry, and absorption spectrometry, include monoterpenes, sesquiterpenes, alkaloids, caffeic acid derivatives, valepotriates, flavinoids, lignans, and amino acids. Valerian products, which are sold as valerian alone or in combination with other herbs and supplements, are commercially available from numerous retail outlets. *V. officinalis* appears to be the most commonly used species for commercial products. *V. procera* Kunth (Mexican valerian), *V. jetamansi* Jones, *V. edulis* Nutt, and *V. sitchensis* Bong also have been prepared for commercial use. Valerian has been used to treat a variety of ailments including insomnia, mood disorders, anxiety, menstrual cramps, and psychological stress conditions. It is typically processed by chopping and drying the underground parts of the plant. The dried materials may then be used to prepare an extract with water and/or an alcohol. Because valerian is an herb, it is classified as a "dietary supplement" under the Dietary Supplement Health and Education Act of 1994.

Human Data

The majority of efficacy studies have focused on valerian, alone and in combination, as a sleep aid. Fewer studies have been conducted on valerian's use for the treatment of anxiety/panic disorder. The most commonly studied preparations are an ethanolic valerian extract and valerian in combination with other herbs and supplements. Overall, the data on the efficacy of valerian as a sleep aid are conflicting with some studies showing valerian to be an effective sleep aid while others indicate that the effects are comparable to placebo. Preliminary findings of treatment using *V. edulis* in children with an intellectual deficit suggested valerian as a potential long-term treatment of their intransigent sleep difficulties and improvement in sleep quality was seen in probands given Hamonicum Much[®] (valepotriates from *V. edulis*). Adverse effects reported with the use of ethanolic extracts include headache, gastrointestinal upset, mental dullness, and depression, while adverse effects reported with the use of aqueous extracts include dizziness and nausea. A few cases of hepatotoxicity have been reported with the use of valerian-containing products; however, valerian could not be defined as the cause of the observed liver damage in a majority of the reports. There is no consistent pattern of adverse reproductive, developmental or immunological effects from well-conducted studies. Valerian may synergistically increase the sedative effects of barbiturates, anesthetics, and other central nervous system depressants; however, no potentiation of the negative effects of alcohol on driving performance was observed with the simultaneous intake of valerian and alcohol. *In vivo* studies also showed that valerian has minimal effect on cytochrome P450 isoform activity. Studies in healthy subjects showed that the maximum serum concentrations of valerenic acid (after a single dose of valerian) occurred 1-2 hours after administration. The elimination half-life for valerenic acid was ~1 hour.

Toxicological Data

No chronic exposure, carcinogenicity, initiation/promotion, cogenotoxicity, or immunotoxicity studies were available for valerian or its constituents.

Chemical Disposition, Metabolism, and Toxicokinetics

V. officinalis extract was incubated with rat hepatocytes to evaluate metabolite formation. Levels of acetoxyvalerenic acid, didrovaltrate, isovaltrate, and valtrate decreased, while hydroxyvalerenic acid levels increased.

In vitro studies of valerenic acid metabolism by isolated perfused rat livers from two different strains identified seven valerenic acid glucuronides (M1-M7). The metabolites included two glucuronides of valerenic acid, four glucuronides of hydroxylated valerenic acid, and one glucuronide of hydroxylated dehydro-valerenic acid. Hepatic extraction ratio and valerenic acid clearance were similar between species.

Different metabolites are produced from the valerian constituents valtrate and isovaltrate and their degradation products baldrinol and homobaldrinol. Approximately 70% of a baldrinol and homobaldrinol mixture orally administered to female mice was excreted as 1-*O*-(4-hydroxymethylcyclopenta[*c*]-pyrane-8-carbonyl) β -D-glucuronide. Comparatively, the same metabolite was only observed after administration of a high dose of a valtrate/isovaltrate mixture.

Acute Exposure

The LD₅₀ values for valerian oil and extracts were reported to be 15,000 mg/kg (oil, oral, rats) and 3300 mg/kg (ethanolic extract, intraperitoneal [i.p.], mice). The LD₅₀ values for valerian constituents were reported to be ~62 mg/kg (0.15 mmol/kg, valtrate) for i.p. administration and >3160 mg/kg (14.21 mmol/kg, valeranone) and \geq 4600 mg/kg (10.89 mmol/kg, valtrate) for oral administration. Intraperitoneal administration of 50-400 mg/kg valerenic acid to mice produced a variety of effects including reduced spontaneous motility, ataxia, and muscle spasms. At a dose of 400 mg/kg, heavy convulsions were observed, which led to death in six of seven mice within 24 hours.

Short-Term and Subchronic Exposure

Subchronic exposure studies have produced conflicting results. In mice orally administered 500-2000 mg/kg aqueous suspensions of a marketed valerian product daily for 7 days, piloerection, hyperthermia, increased motor activity, defecations, reflex impairment, staggering, and sedation were noted at 2000 mg/kg. In a separate study, a daily dose of >200 mg valerian root essential oil for 8 weeks produced adverse symptoms which were not specified. Additionally, a dose of 250 mg valerian root essential oil led to the death of two of five tested rats within 3 weeks of dosing initiation. Comparatively, administration (route not specified) of an alcoholic extract of valerian root (300 or 600 mg/kg/day) for 30 days to rats produced no significant decreases on growth, weight of selected organs, arterial pressure, or evaluated hematological or biochemical parameters when compared to control animals. The maximum nontoxic dose of a commercially available valerian extract in rats was calculated to be 2.79 g/kg/day after an 8-day dosing period.

Significant decrease in body weight was noted on days 7, 21, and 28 in CBA/HZg mice fed a standard diet containing a plant extract mixture that included *Valeriana radix* (7.8%; m/m) for up to 6 months. However, body weights were similar to control animals at later time points. No weight changes or histologic or macroscopic alterations were noted in the spleen, kidneys, testicles, and liver of test mice. An increase in the catalytic concentration of aspartate aminotransferase was noted on day seven.

Synergistic/Antagonistic Effects

Synergism/Antagonism of Valerian Effects

Compounds with free thiol groups antagonized the cytotoxic effects of valtrate and didrovaltrate in cultured hepatoma cells.

Synergistic/Antagonistic Effects Produced by Valerian

No effect doses of powdered valerian root suspensions and *Leonurus cardiaca* administered concurrently produced maximum prolongation of barbiturate-induced sleep in mice; suggesting a potentiation effect. Intraperitoneal administration of extracts of *V. officinalis* rhizomes and *V. officinalis* aerial parts decreased withdrawal symptoms in morphine-dependent mice.

Aqueous extracts of *V. officinalis* antagonized rotenone-induced apoptosis in human SH-SY5Y cells. Ethanolic valerian extracts antagonized formation of thiobarbituric acid reactive substances produced by quinolinic acid, 3-nitropropionic acid, sodium nitroprusside, iron sulfate, and iron/ethylenediaminetetraacetic acid in rat brain homogenates. Valerian also antagonized the *in vitro* contractions of human uterine muscles produced by acetylcholine, phenylephrine, and histamine.

Anticarcinogenicity

Ethanolic valerian extract inhibited phorbol ester activation of the Epstein-Barr virus early antigen at $\geq 10 \mu\text{g/mL}$ in Raji cells, with cellular viability $\geq 70\%$. The results suggested that the extract interferes with at least one phorbol-ester mediated mechanism involved in tumor promotion. *In vivo* studies are conflicting on the anti-tumor activity of valepotriates.

Cytotoxicity

Overall, studies showed that valerian constituents (e.g., valtrate, isovaltrate, acevaltrate, and didrovaltrate) and mixtures containing valerian constituents (e.g., valmane) possess cytotoxic properties in human and murine cell lines (e.g., MKN-45, GLC4, COLO 320, and L1210 cells). For example, valmane induced apoptosis, down regulated survivin mRNA and protein expression, and upregulated p53 protein expression in MKN-45 cells, a gastric cancer cell line, after exposure for 24 to 72 hours. In two human cancer cell lines, GLC4 and COLO 320, a variety of valerian constituents displayed a range of cytotoxic activity. Diene-type valepotriates (e.g., valtrate) exhibited the highest activity, while valerenic acids (e.g., valerenic acid) exhibited lower activity. Monoene-type valepotriates (e.g., didrovaltrate) were less toxic than the diene-type valepotriates. Baldrinal and homobaldrinal were both less toxic than the parent compounds. Valtrate, isovaltrate, and didrovaltrate also inhibited cellular proliferation of murine granulocyte/macrophage, T-lymphocyte, and erythrocyte colonies.

Compared to the isolated constituents, valerian extracts produced differing effects. Methylene chloride, but not methanol, extracts of valerian were cytotoxic against mouse leukemia L1210 cells. Valerian also was cytotoxic to cultured human hepatoma cells. A high concentration (20 mg/mL) of valerian significantly increased cell death in human liver hepatoma HG2P128 cells; no effects were observed at a low concentration (2 mg/mL). Comparatively, other studies showed that valerian extracts (with sodium hydroxide) were not cytotoxic to RAW264.7 and N11 microglia.

Thirteen acylated iridoids and nine known valpotriates, which were isolated from *V. jatamansi*, were tested for cytotoxic potential in A549, PC-3M (metastatic prostate), HCT-8 (colon cancer), and Bel7402 (hepatoma) cells. All but two of the newly identified acylated iridoids were cytotoxic to the PC-3 cells and five of the nine valpotriates were cytotoxic in all cell lines.

Reproductive and Teratological Effects

Studies in pregnant rats showed that valerian extract and valerian compositions had little effect on the mother or the fetuses when administered up to gestation day (GD) 19. When 2.79 g/kg/day valerian extract was administered on GD 1-8 or 8-15, no significant differences in a variety of reproductive endpoints were noted (e.g., mean number of implantations per dam). The number of ossified metacarpals in fetuses of the GD 1-8 group was significantly lower compared to controls. Comparatively, the number of ossified metacarpals in fetuses of the GD 8-15 valerian group was significantly higher compared to controls. Similar results were observed when a composition containing three valerian constituents was

administered on GD 1-19 at doses of 6-24 mg/kg. A significant increase in the number of fetuses with retarded ossification was noted at ≥ 12 mg/kg.

In male mice, valerian produced effects on reproductive endpoints. Mice administered 125-500 mg/kg suspensions of valerian capsules daily for 90 days showed significant increases in the weight of the caudae epididymis and seminal vesicles and increased frequency of aneuploids, sex-univalents, and polyploids at 500 mg/kg. All doses increased the total percent of aberrations in testis chromosomes, and doses ≥ 250 mg/kg significantly increased sperm count. In male mice administered 500-2000 mg/kg suspensions of valerian capsules for 7 days, a statistically significant increase in the frequency of micronucleated polychromatic erythrocytes (PCE) and a decrease in the PCE/normochromatic erythrocytes was noted at 2000 mg/kg. The frequency of sex-univalents, morphological alterations of the spermatozoa, and polyploids were significantly increased at ≥ 1000 mg/kg.

Genotoxicity

Dichloromethane extracts of valerian induced DNA damage in ECV304 cells, a human endothelial cell line, at concentrations ≥ 40 $\mu\text{g/mL}$. Conflicting results were observed with valepotriates. In one study, valepotriates were mutagenic in *Salmonella typhimurium* TA100 and *Escherichia coli* WP2 and WP2 uvrA- in the presence of S9, while in another study, valtrate, didrovaltrate, and acevaltrate were not mutagenic in *S. typhimurium* strains TA98 and TA100. Valtrate, didrovaltrate, and deoxy-didrovaltrate also inhibited DNA and protein synthesis in rat hepatoma cells. Valepotriates also showed alkylating activity. *In vivo*, aqueous suspensions of commercially available valerian capsules (administered by gastric intubation) produced a statistically significant increase in the frequency of micronucleated polychromatic erythrocytes (PCE) and a decrease in the PCE/normochromatic erythrocytes in Swiss albino mice at a dose of 2000 mg/kg for 7 days.

Other Data

Neurological Effects

Overall, *in vivo* studies showed that valerian and its constituents produced sedative, anxiolytic, and antidepressant effects. *In vitro* studies suggest that the effects of valerian and its components may occur through modulation of a variety of neurotransmitter systems including γ -aminobutyric acid, adenosine, and serotonin systems. Valerian components and extracts may specifically bind to receptors and modulate neurotransmission.

Anti-inflammatory Effects

The ethyl acetate extract of *V. officinalis* inhibited NF- κ B activity in HeLa cells, and transforming growth factor beta 1 expression was downregulated by *V. officinalis* var. *latifolia* in dietary-induced hypercholesterolemia in male rats. Polysaccharides isolated from *V. officinalis* exhibited mitogenic and co-mitogenic activity in rat thymocytes. Comparatively, a short-term *in vivo* study showed that research grade valerian had no effect on natural killer cell activity in rats.

Effect on Enzymes

Components of valerian and valerian extracts modulate a variety of enzyme activities (e.g., inhibited glucuronidase activity and stimulated glutamic acid decarboxylate). There are conflicting studies on the effects of valerian on cytochrome P450 activities.

Endocrine Activity

A petroleum ether extract of *V. officinalis* (root) exhibited binding affinity for estrogen receptors α and β in MCF-7 cells. Both petroleum ether and dichloromethane extracts induced luciferase activity in an estrogen receptor α positive cell line.

Structure-Activity Relationships

No data were directly applicable. Appendix C provides brief information on the biological activity of selected constituents not discussed in the main report.

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1.0 Basis for Nomination

Valerian (*Valeriana officinalis* [*V. officinalis*]) was nominated by the National Institute of Environmental Health Sciences for comprehensive toxicological characterization based on of its widespread use in dietary supplements, the lack of adequate toxicological data, and concerns regarding potential adverse developmental and reproductive effects, particularly for women of child-bearing age. Commercially available valerian products have numerous applications including treatment of insomnia and anxiety.

2.0 Introduction

Valerian is a member of the Valerianaceae family that is native to Europe and parts of Asia. It also has been naturalized in North America for commercial use (Wichtl, 1994; cited by [Office of Dietary Supplements, 2008](#)). It is a hardy herbaceous perennial plant with feather-like leaves and clusters of small pink to white flowers (see image below) that bloom from June to September. Valerian can grow up to 6.5 feet tall (typically ~4 to 5 feet tall) and has a strong odor. It is self-seeding and can be cultured by replanting, dividing the roots, or planting seeds in indoor flats or outdoor seed beds ([North Carolina Arboretum, undated](#)).



Source: [NCCAM \(2008\)](#)

Valerian constituents include monoterpenes, sesquiterpenes, alkaloids, caffeic acid derivatives, valepotriates, flavinoids, lignans, and amino acids (Fernández et al., 2004 [PMID:14751470]; Houghton, 1999 [PMID:10411208]; PDR, 2000). Details about some select compounds found in root and rhizome extracts and oils are presented in Appendix C.

2.1 Chemical Identification and Analysis

Valerian most commonly refers to extracts of the underground rhizomes and roots, including tinctures, essential oils, terpenes, terpene-free fractions, and residues from the species *V. officinalis* L. [CAS No. 8057-49-6] and its subspecies, which sometimes exclude *officinalis* from the name. Valerian oil [CAS No. 8008-88-6], as used in the U.S. and European official pharmacopoeias, also refers to *V. officinalis*. Other common names and trade names for preparations of valerian include:

Valerian oil; Valerian rhizome and root oil; Oil of valerian; Valerian root extract; Valerian root oil; Valerian root oil (*Valeriana officinalis* L.); *Valeriana officinalis* root oil; Baldrian oel (*öl*); *Baldrianwurzel*; *Valerianae radix*; balderbrackenwurzel; baldrion; laege-baldrian; Nervex[®]; Neurol[®]; Orasedon[®]; *racine de valeriane*; radix valerian; Sanox-N[®]; Sedonium[®]; theriacaria; Ticalma[®]; Valeriana radiz; Valerianaheel[®]; Valmane[®]; and ZE 911.

V. officinalis also may be called:

All-Heal; Amantilla; Belgium Valerian; blessed herb; capon's tail; Common Valerian; English valerian; Fragrant valerian; Garden Heliotrope (wrongly); Garden valerian; German valerian; Great wild valerian; Herba Benedicta; Japanese valerian; *Katzenwurz*; Phu; Phu germanicum; Phu parvum; pinnis dentatis; Setewale capon's tail; Setwall; Setwell; *Valériane officinale*; Vandal root; Vermont valerian; and Wild valerian. The most commonly used subspecies (also called varieties) include: *alternifolia*, *angustifolia*, *latifolia*, *collina*, *sambucifolia*, and *officinalis*.

Other *Valeriana* species have been used to produce valerian sedative preparations. These include:

Indian Valerian; Mexican Valerian; Pacific Valerian; Tagar; Tagar-Ganthoda; Tagara; *Valeriana edulis*; *Valeriana edulis* Nutt; *Valeriana faurieri*; *Valeriana foliis pinnatis*; *Valeriana jatamansi* (*jatamansii*); *Valeriana jatamansi* Jones; *Valeriana sitchensis*; *Valeriana sitchensis* Bong; *Valeriana procera* Kunth (Mexican valeriana); *Valeriana pseudofficinalis*; and *Valeriana wallichii* (or *wallichii*).

Source: Natural Standard (2008)

Key Constituents

The three sesquiterpenes, valerenic acid and its hydroxy and acetoxy derivatives, are the primary characteristic markers of *V. officinalis*.

Valerenic acid (C₁₅H₂₂O₂; mol. wt = 234.33; CAS No. 3569-10-6), also called:

2-Propenoic acid, 3-[(4S,7R,7aR)-2,4,5,6,7,7a-hexahydro-3,7-dimethyl-1H-inden-4-yl]-2-methyl-, (2E)-
 2-Propenoic acid, 3-(2,4,5,6,7,7a-hexahydro-3,7-dimethyl-1H-inden-4-yl)-2-methyl-, [4S-[4α(E),7β,7aα]]-
 Indene-4-acrylic acid, 2,4,5,6,7,7a-hexahydro-α,3,7-trimethyl- (7CI, 8CI)

PubChem CID: [6440940](#)

InChI: 1/C15H22O2/c1-9-4-6-12(8-11(3)15(16)17)14-10(2)5-7-13(9)14/h8-9,12-13H,4-7H2,1-3H3,(H,16,17)/b11-8+/t9-,12+,13-/m1/s1/f/h16H

Smiles: CC1CCC(C2=C(CCC12)C)C=C(C)C(=O)O

Valtrate (C₂₂H₃₀O₈; mol. wt. = 422.47; CAS No. 18296-44-1), also called:

Baldrisedon
 Butanoic acid, 3-methyl-, 1,1'-[(1S,2'R,6S,7aS)-4-[(acetyloxy)methyl]-6,7a-dihydrospiro[cyclopenta[c]pyran-7(1H),2'-oxirane]-1,6-diyl] ester
 Butanoic acid, 3-methyl-, (1S,2'R,6S,7aS)-4-[(acetyloxy)methyl]-6,7a-dihydrospiro[cyclopenta[c]pyran-7(1H),2'-oxirane]-1,6-diyl ester (9CI)
 Butanoic acid, 3-methyl-, 4-[(acetyloxy)methyl]-6,7a-dihydrospiro[cyclopenta[c]pyran-7(1H),2'-oxirane]-1,6-diyl ester, [1S-(1α,6α,7β,7aα)]-
 Halazuchrome B
 Spiro[cyclopenta[c]pyran-7(1H),2'-oxirane], butanoic acid deriv.
 Valepotriate
 Valtratum

PubChem CID: [493850](#)

InChI: 1/C22H30O8/c1-12(2)6-18(24)29-17-8-16-15(9-26-14(5)23)10-27-21(20(16)22(17)11-28-22)30-19(25)7-13(3)4/h8,10,12-13,17,20-21H,6-7,9,11H2,1-5H3/t17-,20+,21-,22?/m0/s1

Smiles: CC1=COC(C2C1=CC(C23CO3)OC(=O)CC(C)C)OC(=O)CC(C)C

Didrovaltrate (C₂₂H₃₂O₈; mol. wt. = 424.48; CAS No. 18296-45-2), also called:

Butanoic acid, 3-methyl-, (1S,2'R,4aS,6S,7aS)-6-(acetyloxy)-4a,5,6,7a-tetrahydro-4-[(3-methyl-1-oxobutoxy)methyl]spiro[cyclopenta[c]pyran-7(1H),2'-oxiran]-1-yl ester

Butanoic acid, 3-methyl-, 6-(acetyloxy)-4a,5,6,7a-tetrahydro-4-[(3-methyl-1-oxobutoxy)methyl]spiro[cyclopenta[c]pyran-7(1H),2'-oxiran]-1-yl ester, [1S-(1 α ,4 α ,6 α ,7 β ,7 α)]-

Didrovaltratum

Dihydroisovalpotrate

Dihydroisovaltrate

Dihydroisovaltratum

Spiro[cyclopenta[c]pyran-7(1H),2'-oxirane], butanoic acid deriv.

PubChem CID: [65689](#)

InChI: 1/C22H32O8/c1-12(2)6-18(24)26-9-15-10-27-21(30-19(25)7-13(3)4)20-16(15)8-17(29-14(5)23)22(20)11-28-22/h10,12-13,16-17,20-21H,6-9,11H2,1-5H3/t16-,17+,20-,21+,22-/m1/s1

Smiles: CC(C)CC(=O)OCC1=COC(C2C1CC(C23CO3)OC(=O)C)OC(=O)CC(C)C

Isovaltrate (C₂₂H₃₀O₈; mol. wt. = 422.47; CAS No. 31078-10-1), also called:

Butanoic acid, 3-methyl-, (1S,2'R,6S,7aS)-6-(acetyloxy)-6,7a-dihydro-4-[(3-methyl-1-oxobutoxy)methyl]spiro[cyclopenta[c]pyran-7(1H),2'-oxiran]-1-yl ester

Butanoic acid, 3-methyl-, 6-(acetyloxy)-6,7a-dihydro-4-[(3-methyl-1-oxobutoxy)methyl]spiro[cyclopenta[c]pyran-7(1H),2'-oxiran]-1-yl ester, [1S-(1 α ,6 α ,7 β ,7 α)]-

Isovaltratum

Spiro[cyclopenta[c]pyran-7(1H),2'-oxirane], butanoic acid deriv.

PubChem CID: [92275](#)

InChI: 1/C22H30O8/c1-12(2)6-18(24)26-9-15-10-27-21(30-19(25)7-13(3)4)20-16(15)8-17(29-14(5)23)22(20)11-28-22/h8,10,12-13,17,20-21H,6-7,9,11H2,1-5H3/t17-,20+,21-,22+/m0/s1

Smiles: CC(C)CC(=O)OCC1=COC(C2C1=CC(C23CO3)OC(=O)C)OC(=O)CC(C)C

Acevaltrate (C₂₄H₃₂O₁₀; CAS No. 25161-41-5), also called:

(Acetyloxy)valepotriate

Acetovaltrate

Acetoxyvaltrate

Acevaltratum

Butanoic acid, 3-(acetyloxy)-3-methyl-, (1S,2'R,6S,7aS)-4-[(acetyloxy)methyl]-6,7a-dihydro-1-(3-methyl-1-oxobutoxy)spiro[cyclopenta[c]pyran-7(1H),2'-oxiran]-6-yl ester

Butanoic acid, 3-(acetyloxy)-3-methyl-, 4-[(acetyloxy)methyl]-6,7a-dihydro-1-(3-methyl-1-oxobutoxy)spiro[cyclopenta[c]pyran-7(1H),2'-oxiran]-6-yl ester, [1S-(1 α ,6 α ,7 β ,7 α)]-

Spiro[cyclopenta[c]pyran-7(1H),2'-oxirane], butanoic acid deriv.

PubChem CID: [65717](#)

InChI: 1/C24H32O10/c1-13(2)7-19(27)33-22-21-17(16(11-30-22)10-29-14(3)25)8-18(24(21)12-31-24)32-20(28)9-23(5,6)34-15(4)26/h8,11,13,18,21-22H,7,9-10,12H2,1-6H3/t18-,21+,22-,24+/m0/s1

Smiles: CC(C)CC(=O)OC1C2C(=CC(C2CO3)OC(=O)CC(C)(C)OC(=O)C)C(=CO1)COC(=O)C

Baldrinal (C₁₂H₁₀O₄; mol. wt. = 218.21; CAS No. 18234-46-3), also called:

Cyclopenta[c]pyran-7-carboxaldehyde, 4-[(acetyloxy)methyl]-
Cyclopenta[c]pyran-7-carboxaldehyde, 4-(hydroxymethyl)-, acetate (8CI)

PubChem CID: [159846](#)

InChI: 1/C12H10O4/c1-8(14)16-6-10-5-15-7-12-9(4-13)2-3-11(10)12/h2-5,7H,6H2,1H3

Smiles: CC(=O)OCC1=COC=C2C1=CC=C2C=O

Homobaldrinal (C₁₅H₁₆O₄; mol. wt. = 260.29; CAS No. 67910-07-0), also called:

Butanoic acid, 3-methyl-, (7-formylcyclopenta[c]pyran-4-yl)methyl ester

PubChem CID: [49999](#)

InChI: 1/C15H16O4/c1-10(2)5-15(17)19-8-12-7-18-9-14-11(6-16)3-4-13(12)14/h3-4,6-7,9-10H,5,8H2,1-2H3

Smiles: CC(C)CC(=O)OCC1=COC=C2C1=CC=C2C=O

Sources: ChemIDplus (undated); [Natural Medicines Comprehensive Database \(2008\)](#); Natural Standard (2008); PubChem (undated); Registry (2008a-g)

Analytical Methods

Valerian constituents can be measured using a variety of analytical methods including high performance liquid chromatography (HPLC), thin layer chromatography (TLC), gas chromatography/mass spectrometry (GC/MS), and absorption spectrometry. Some examples of these methods are described below for quantifying constituent concentrations in various valerian preparations.

Concentrations of valerenic acid and its derivatives reported in Australian valerian products (n=31), including teas, tablets, capsules and liquids, that were analyzed by HPLC, ranged from <0.01 to 6.32 mg/g product. Valerenic acid concentrations were higher in powder capsules (2.46 mg/g) than in liquids (0.47 mg/mL) (Shohet et al., 2001 [PMID:[11817170](#)]).

Methanol extracts of air-dried and powdered rhizomes of *V. officinalis* (n=1) and *V. jatamansi* (n=11) were analyzed for valerenic acid using high performance TLC. Valerenic acid was identified in the *V. officinalis* sample (0.42%) and in two of the *V. jatamansi* samples (0.12%) (Singh et al., 2006).

Elemental composition of valerian roots, their teas, and one tincture commercially available in Argentina were measured by flame atomic emission/absorption spectrometry, electrothermal

atomic absorption spectrometry, or ultrasonic nebulization coupled to inductively coupled plasma-optical emission spectrometry. Iron, aluminum, calcium, and vanadium concentrations in the root samples were within the 100–1000 mg/kg range and the manganese, zinc, and lead concentrations were within the 10–100 mg/kg range; up to 0.0125 mg/kg cadmium also was reported (Arce et al., 2005 [PMID:15759744]).

Results from GC/MC analysis of hydrodistillation of aerial parts of wild Valeriana species from Serbia and Montenegro (*V. officinalis* L., *V. panicii* Halacsy et Bald., *V. bertiscea* Panic, *V. montana* L., and *V. braunii-blanquetii* Lakusic) reported α -kessyl acetate (14.4%) and bornyl acetate (14.2%) in *V. officinalis* oil; patchouli alcohol (36.8%) in *V. panicii* oil; and isovaleric acid (13.2-39.0%) and 3-methylvaleric acid (10.0-30.8%) in *V. bertiscea*, *V. montana*, and *V. braunii-blanquetii* oils (Pavlovic et al., 2007).

A capillary electrophoresis method that was developed for measuring the three main sesquiterpenes that characterize *V. officinalis*, valerenic acid, hydroxyvalerenic acid, and acetoxvalerenic acid (detection limit: 5.8 $\mu\text{g/mL}$), was used to analyze six marketed valerian products. Only one product contained detectable amounts of the sesquiterpenes (0.54% hydroxyvalerenic acid and 0.13% valerenic acid). Results from HPLC analysis were comparable (Mikell et al., 2001 [PMID:11802657]).

Valerenic acid content was evaluated in a variety of valerian pharmaceutical products (e.g., tablet, caplet, drops). Products were extracted by maceration with methanol and analyzed by TLC and reversed phase HPLC. Valerenic acid content ranged from 0.03 to 2.8% (Ghafari et al., 2009).

A GC/MS method, which included using supercritical fluid extraction and headspace solid phase micro-extraction, was used to evaluate the major volatile components of *V. officinalis* var. *latifolia* and *V. officinalis* roots. This technique was compared to hydrodistillation extraction and the results showed that the compounds extracted from *V. officinalis* var. *latifolia* differed from those of *V. officinalis*. The differences varied depending on the extraction method and conditions used (Huang et al., 2009).

2.2 Physical-Chemical Properties

Property	Information	Reference(s)
Valerenic acid		
Boiling Point (°C)	374.5 \pm 21 @ 760 mm Hg	Registry (2008a)
Melting Point (°C) *	140-142	Registry (2008a)
Flash Point (°C)	274.1 \pm 13	Registry (2008a)
Vapor Pressure (mm Hg)	1.22 $\times 10^{-6}$ @ 25 °C	Registry (2008a)
Density (g/cm ³)	1.06 \pm 0.1 @ 20 °C/760 torr	Registry (2008a)
Log P	5.127 \pm 0.305 @ 25 °C	Registry (2008a)
Bioconcentration Factor	4632.05 – 1.0 (pH 1-10 @ 25 °C)	Registry (2008a)
Valtrate		
Boiling Point (°C)	525.9 \pm 50.00 @ 760 mm Hg	Registry (2008b)
Melting Point (°C)	Not available	
Flash Point (°C)	226.5 \pm 30.2	Registry (2008b)
Vapor Pressure (mm Hg)	3.75 $\times 10^{-11}$ @ 25 °C	Registry (2008b)
Density (g/cm ³)	1.22 \pm 0.1 @ 20 °C/760 torr	Registry (2008b)

Property	Information	Reference(s)
Log P	2.360 ± 0.746 @ 25 °C	Registry (2008b)
Bioconcentration Factor	36.62 (pH 1-10 @ 25 °C)	Registry (2008b)
<i>Didrovaltrate</i>		
Boiling Point (°C)	507.5 ± 50 @ 760 mm Hg	Registry (2008c)
Melting Point (°C)	Not available	
Flash Point (°C)	217.8 ± 30.2	Registry (2008c)
Vapor Pressure (mm Hg)	2.01 x 10 ⁻¹⁰ @ 25 °C	Registry (2008c)
Density (g/cm ³)	1.20 ± 0.1 @ 20 °C/760 torr	Registry (2008c)
Log P	2.069 ± 0.722 @ 25 °C	Registry (2008c)
Bioconcentration Factor	21.98 (pH 1-10 @ 25 °C)	Registry (2008c)
<i>Isovaltrate</i>		
Boiling Point (°C)	525.9 ± 50.0 @ 760 mm Hg	Registry (2008d)
Melting Point (°C)	Not available	
Flash Point (°C)	226.5 ± 30.2	Registry (2008d)
Vapor Pressure (mm Hg)	3.75 x 10 ⁻¹¹ @ 25 °C	Registry (2008d)
Density (g/cm ³)	1.22 ± 0.1 @ 20 °C/760 torr	Registry (2008d)
Log P	2.360 ± 0.746 @ 25 °C	Registry (2008d)
Bioconcentration Factor	36.62 (pH 1-10 @ 25 °C)	Registry (2008d)
<i>Acevaltrate</i>		
Boiling Point (°C)	538.7 ± 50.0 @ 760 mm Hg	Registry (2008e)
Melting Point (°C)	Not available	
Flash Point (°C)	229.1 ± 30.2	Registry (2008e)
Vapor Pressure (mm Hg)	1.13 x 10 ⁻¹¹ @ 25 °C	Registry (2008e)
Density (g/cm ³)	1.26 ± 0.1 @ 20 °C/760 torr	Registry (2008e)
Log P	1.915 ± 0.777 @ 25 °C	Registry (2008e)
Bioconcentration Factor	16.82 (pH 1-10 @ 25 °C)	Registry (2008e)
<i>Baldrial</i>		
Boiling Point (°C)	451.4 ± 30.0 @ 760 mm Hg	Registry (2008f)
Melting Point (°C)	Not available	
Flash Point (°C)	206.3 ± 24.6	Registry (2008f)
Vapor Pressure (mm Hg)	2.44 x 10 ⁻⁸ @ 25 °C	Registry (2008f)
Density (g/cm ³)	1.29 ± 0.1 @ 20 °C/760 torr	Registry (2008f)
Log P	-0.937 ± 0.419 @ 25 °C	Registry (2008f)
Bioconcentration Factor	1.0 (pH 1-10 @ 25 °C)	Registry (2008f)
<i>Homobaldrial</i>		
Boiling Point (°C)	462.1 ± 30.0 @ 760 mm Hg	Registry (2008g)
Melting Point (°C)	Not available	
Flash Point (°C)	207.5 ± 24.6	Registry (2008g)
Vapor Pressure (mm Hg)	1.02 x 10 ⁻⁸ @ @ 25 °C	Registry (2008g)
Density (g/cm ³)	1.19 ± 0.1 @ 20 °C/760 torr	Registry (2008g)
Log P	0.474 ± 0.423 @ 25 °C	Registry (2008g)
Bioconcentration Factor	1.35 (pH 1-10 @ 25 °C)	Registry (2008g)

*Except for this property, all data are calculated properties using Advanced Chemistry Development (ACD/Labs) Software Solaris V8.14 (©1994-2008 ACD/Labs).

Note: Physical state, odor, water solubility, and octanol-water partition coefficient (logK_{ow}) were not provided in the Registry records, and these properties were not specifically sought in literature searches. They were also not found in any other sources cited in this document.

2.3 Commercial Availability

Valerian is sold in the United States as a dietary supplement ([Office of Dietary Supplements, 2008](#)). *V. officinalis* appears to be the most commonly used species for preparation of commercial products. *V. procera* Kunth (Mexican valerian) is occasionally a substitute for *V.*

officinalis L. Valerian species such as *V. jetamansi* Jones, *V. edulis* Nutt, and *V. sitchensis* Bong also have been prepared for commercial use (Natural Standard, 2008).

Valerian products (essential oils, teas, powdered root, root extracts, and tinctures) are commercially available from numerous sources via the Internet (e.g., [abundantlifeessentials.com](#), undated; [eZoetic.com](#), undated; [folio-gothichippy.com](#), undated; [Google](#), 2008a,b; [TradeTalk](#), 2008; [VitaCart.com](#), 2008). Key valerian constituents (e.g., valerenic acid, valtrate, didrovaltrate, and acevaltrate) are available from chemical suppliers (e.g., see ChemExper, 2008). Valerian also has been marketed with other herbs and supplements such as hops (*Flores humuli*), lemon balm (*Melissa officinalis*), and 5-hydroxytryptophan (Natural Standard, 2008; Rodenbeck et al., 1998). [Note: A Google products search indicated that no commercial products were available that contained extracts or portions of the leaves or other aerial parts.]

Internet searches for information about the eight best-selling herbal supplements showed that valerian was identified on 18% (79/443) of the websites (Morris and Avorn, 2003 [PMID:13129992]). Several products (e.g., 4Life Stress Formula; Enzymatic Therapy Alluna Sleep; GNC B-Formula with C; GNC Herbal Plus Concentrated Valerian Root; and Natrol Stress Complex) contain valerian as the active ingredient ([Dietary Supplements Labels Database](#), 2007). [Note: The addresses of all manufacturers are in the United States.]

A 1998 survey of herbal products reported that valerian was one of the top 10 herbs largely sold in 20 retail stores in the United States. The paper evaluated the variation between the product's benchmark (including ingredients and the recommended daily dose) and its label information. The authors evaluated three areas of "consistency": (a) ingredients and dosage consistent with benchmark (benchmark for valerian was 400-900 mg/day of standardized extract), (b) ingredients consistent but dosage not consistent with benchmark, or (c) ingredients not consistent with benchmark or information insufficient. Of the 49 valerian products evaluated, 16% (8/49) were consistent in dosage and ingredient, 18% (9/49) were consistent in ingredients but not dosage, and 65% (32/49) were not consistent in either ingredient or dosage ([Garrard et al.](#), 2003). [Note: Table 2 in the article notes that 37% (32/49) of the tested valerian products were not consistent in ingredient or dosage.]

Commercial products that have been evaluated in clinical trials include: Natures Way Valerian (United States), Baldisedron (Germany), Baldrian-Dispert (Germany), Dixa S.A. (Switzerland), Sedonium[®] (Germany), Valdispert (Germany), Caldispert forte (Germany), Valverde Sleeping Syrup (Germany), and Valverde (Natural Standard, 2008). Extracts of *V. edulis* and *V. wallichii* that are commercially available and have been used in clinical trials include Harmonicum Much[®] and Valmane[®]. Combinations of valerian with other ingredients that have been tested include Alluna[®], Hova[®], Seda-Kneipp[®], Songha Night[®], Euvegal[®], and *V. natt*[®] ([Taibi et al.](#), 2007).

Baldrinal and homobaldrinal are the most commonly studied degradation products of the valtrates. Other degradation products identified include the 2,9-dioxatricyclodecanes, reported as degradation products of didrovaltrate and homodidrovaltrate (Rücker et al., 1983).

3.0 Production Processes

Valerian roots and rhizomes are used in the preparation of supplements including capsules, tables, and liquid extracts and teas (NCCAM, 2008). Processing valerian typically consists of chopping and drying the underground parts of the plant (e.g., rhizomes, roots). The dried materials are then extracted with water and/or an alcohol (Isetts, 2007; PDR, 2000). The use of supercritical carbon dioxide (CO₂) to produce valerian extracts also has been described (Zizovic, et al., 2007).

A patented method for preparing a pharmaceutically active extract of *V. officinalis* L. was published. Valerian root was extracted with an ethanol solution and heated (70-80 °C) for about two hours. The mixture was cooled, filtered, and rinsed with an alcoholic extraction solvent (Andrews and Basu, 2002 pat.). A more recent patent described three variations of a method for preparing valeriana extract using combinations of static and dynamic extraction of pulverized Valeriana in the presence of varying concentrations of CO₂ entrain then isolating the final Valeriana extract by vacuum distillation (Duan et al., 2009 pat.).

Studies indicate that the drying and distillation process may alter the constituent composition of essential oils obtained from fresh and dried roots of *V. officinalis*. Dried roots contained higher levels of free isovaleric acid, borneol, and sesquiterpene hydrocarbons compared to fresh roots. Evaluation of oil fractions obtained from dried roots that were steam distilled showed that the levels of selected constituents varied within the collected fractions (Lopes et al., 2005).

Studies showed that long-term storage of dried valerian (*V. officinalis*) root powder altered valerenic acid and acetoxyvalerenic acid concentrations. Wills and Shohet (2009) described a study where the powder was stored for 6 months at different temperatures (5, 14, and 30 °C) and humidities. The concentrations of valerenic acid and acetoxyvalerenic acid decreased over time. The largest decrease in valerenic acid occurred at 30 °C in low humidity. Comparatively, the largest decrease in acetoxyvalerenic acid occurred at 30 °C and high humidity. Willis and Shohet (2009) studied the effect of storing the powder for 6 months at different temperatures (5, 14, and 30 °C) and humidities. The results showed that the concentrations of valerenic acid and acetoxyvalerenic acid decreased with time and that valerenic acid content decreased faster in low humidity where as acetoxyvalerenic acid decreased faster at high humidity. Hydroxyvalerenic acid was not detected in fresh samples of root powder, however, it was found in stored samples and the concentration correlated with the decrease in acetoxyvalerenic acid concentration.

Several articles on planting and cultivation procedures for maximizing plant yield (e.g., see Kleitz et al., 2003) also were available. A recent article also described the complete synthesis of valerenic acid (Ramharter and Mulzer, 2009 [PMID:19178294]).

4.0 Production and Import Volumes

Valerian is one of the top selling herbal supplements in the U.S. market. However, total figures reported for sales of valerian products appear to vary between sources. The sales figures included \$6.1 million in 1997, \$8 million in 1997-1998, and \$30-58 million from 1997-2000 (Blumenthal, 1998; Grant 1999; IARC, 2002). More recent data report that valerian ranked 13th among the top-selling herbal dietary supplements from food, drug, and mass market retail outlets for 2008; the sales figure was \$3.3 million (11.29% increase from 2007). From health and

natural food outlets, valerian ranked 11th among the top-selling herbal dietary supplements; the sales figure was \$6.5 million (Cavaliere et al., 2009).

5.0 Uses

Valerian is typically taken orally to treat insomnia, dyssomnia, restlessness, anxiety, and mood disorders such as depression. Other applications include treatment of infantile convulsions, mild tremors, chronic fatigue syndrome, muscle and joint pain, and in psychological stress conditions such as nervous asthma, hysterical states, excitability, hypochondria, headache, migraine, and stomach upset. Treatment of menstrual cramps, menopausal symptoms, shingles, sciatica, neuralgia, multiple sclerosis, and epilepsy with valerian also has been reported (Morris and Avorn, 2003 [PMID:13129992]; [Natural Medicines Comprehensive Database, 2008](#)). As a bath additive it may be used topically for treating sleep disorders ([Natural Medicines Comprehensive Database, 2008](#)). Mixtures of lemon balm (*Melissa officinalis*) and valerian (*V. officinalis*) also have been used as a mild sedative, anxiolytic, and hypnotic (Natural Standard, 2008). Valerian extracts and essential oil also have been used as flavoring for foods and drinks (Burdock and Fenaroli, 2001; [Natural Medicines Comprehensive Database, 2008](#)).

The most frequently prescribed herbal medication for sleep disorders contain extracts of valerian root (*V. officinalis*) (Dimpfel, 2007). Extracts are generally standardized to 0.3% valerenic acid, while some products are standardized to contain 0.8% valerenic or valeric acid (Natural Standard, 2008). For treatment of insomnia, doses from 300-600 mg (equivalent to 2-3 g of dried valerian root) were recommended; in tinctures, the dose range was 2.5-5 mL ([Hadley and Petry, 2003](#); Natural Standard, 2008; [Thorne Research, Inc., 2004](#)).

Other recommended doses for use of valerian products included 2-3 g of dried root and rhizome per cup of fluid 1-5 times per day up to a total of 10 g; 0.5-1 teaspoon of tinctures (1:5, 70% ethanol) once to several times per day; and 2-3 g of drug in extract once to several times per day. The proposed dose for topical use as a bath additive was 100 g in a full bath tub (Blumenthal, 1998; [WHO, 1999](#)). The essential oil also may be used for aromatherapy (e.g., 5 drops in a full tub) to promote relaxation and sleep. Valerian standardized tinctures contain ~2% essential oil (Caron and Riedlinger, 1999). Powdered and liquid extracts available on the U.S. market were standardized to total valerenic and acetoxyvalerenic acids contained 0.3-0.9% valerenic acids or less, providing up to 4.0 mg in the daily oral intake ([ConsumerLab.com, 2006a,b,c](#)).

A composition containing Baldrianal was proposed for the treatment of benign prostatic hyperplasia (Xiao and Bian, 2008 pat.). Valerian also was reported to be among the herbal remedies "commonly used" in treating attention deficit hyperactivity disorder (ADHD). Doses for children younger than 15 years are 220 mg three times a day for restlessness and sleep disorders (Chan, 2002 [PMID:11875289]).

6.0 Environmental Occurrence and Persistence

V. officinalis subspecies grow wild in temperate and subpolar regions of Europe and Asia, commonly growing in damp environments. It is cultivated for medicinal purposes in Belgium, England, Eastern Europe, France, Germany, the Netherlands, Russia, and the United States ([WHO, 1999](#)).

7.0 Human Exposure

General Population Exposure

Exposure to valerian is largely due to its use in dietary supplements taken to treat insomnia and/or relieve anxiety and muscle spasms (intestinal, colic, and stomach). Numerous studies and surveys have reviewed valerian use by the general population. Results from some of the more recent reports/studies of general population exposure are summarized below. Additional information is available in **Section 9.1.1**, where results from studies of the efficacy as well as adverse effects of valerian in humans are presented.

In a study of the California Poison Control System (phone calls between April and September 2002), valerian was one of the main nonphedra products for which exposures and adverse events were frequently reported by consumers. It was also one of the most common single-ingredient products that caused severe adverse events; effects included anaphylactic reaction, sedation, and a suicide attempt. Alluna (containing valerian root extract and hops extract) was one of the most common multiple-ingredient products included in reports of severe adverse events (Dennehy et al., 2005 [PMID:15998927]).

Among the 31,044 respondents to the 2002 U.S. National Health Interview Survey (NHIS) on the use of complementary and alternative medicine (CAM), 5.9% had used a valerian preparation at least once in the 12 months prior to the survey (Barnes et al. 2004; Bliwise and Ansari, 2007). The ratio of women to men among valerian users was 2.6:1. Of the total number of valerian users, 23.4% used it for anxiety/depression and 29.9% used it for insomnia. The calculated population-weighted use for insomnia was 40.4% of those aged 18-40 years; 45.7%, 41-60 years; and 13.9%, ≥61 years. A medical professional had recommended valerian to only 32% of those using it for insomnia (Bliwise and Ansari, 2007).

Of 201 students surveyed at a private southeastern university in 2008 (88% <24 years old; 75% women; and ~67% upper classmen), 19 (9.5%) had used valerian during the previous week; a considerably higher percentage than that reported for the 2002 NHIS respondents. The valerian median dose frequency was 4 times/week (Stasio et al., 2008 [PMID:18400666]).

A survey of 2,526 adults in Victoria, Australia, reported that 4.3% of participants said they had used valerian in the year prior to the survey (February-April, 2007). Of these users, 63.8% used valerian as a single herb and 31.8% used it as part of an herbal mixture; the remaining participants used valerian as a single herb and in herba mixtures or did not know the form they had used (Zhang et al., 2008 [PMID:18816875]).

Occupational Exposure

Farmers who cultivate the valerian plants can receive occupational exposure to valerian dust. In a group of 74 Polish farmers who were examined for exposure to valerian, 30.7% reported work-related symptoms. The major symptoms were conjunctivitis (20%) and blocking of the nose (9.3%). Other reported effects were dry or non-productive cough, hoarseness, fatigue, itchiness of the body, and rash. Chest auscultation indicated crepitation in one worker and wheezing in another. However, there were no significant differences between the spirometric values in the valerian-exposed farmers and the controls (i.e., urban dwellers not exposed to any organic dust) (Skorska et al., 2005). [See **Section 9.1.1** (Immunotoxicity) for additional observations.]

Potentially Vulnerable Subpopulations

Among 734 pregnant women who delivered at a Boston, MA, hospital and who had responded to a questionnaire sometime after reaching 20 weeks gestational age and prior to delivery, three had used valerian. This represented 5.8% of the expectant mothers who took herbal remedies (Hepner et al., 2002). Among 334 pregnant women (≥ 20 weeks) in the United Kingdom that had used herbal remedies during their pregnancy, four indicated that they had used valerian (Holst et al., 2009 [PMID:19538045]).

In a study of all births listed in the Swedish Medical Birth Register from 1995-2004, valerian was one of the most used herbal drugs reported by women during early pregnancy (98 of 811 users) for treatment of insomnia and/or restlessness. The valerian users compared to the general population of herbal drug users had significantly more smokers than nonsmokers, more non-Nordic women than Swedish/other Nordic women, and more women simultaneously using psycholeptics with valerian (Holst et al., 2008 [PMID:17992658]).

Results from a limited number of studies of valerian use in children suggested that use of valerian in this subpopulation is limited. In a Washington, DC, survey of pediatric patients, none of the parents that had treated their children with CAM in the past year used valerian (Ottolini et al., 2001 [PMID:11888385]). Primary caregivers of children receiving psychiatric assessment at five Texas community mental health centers were queried about herbal use by the children. Of 23 patients (15%) with depression or ADHD who used herbal products, only two (9%) had been treated with valerian root (Cala et al., 2003 [PMID:12587812]).

Surveys of several patient populations (e.g., cardiovascular disease, cancer) indicated that a small number reported using valerian (Chagan et al., 2005; Norred, 2002 [PMID:11969062]). For example, among 227 cancer patients first treated at a Midwestern cancer clinic between November 2001 and October 2003, 3.5% had used valerian during the 30 days prior to the survey. The percentage dropped to 1.3% of the 80 patients who had had chemotherapy within the last 30 days prior to the survey (Gupta et al., 2005; [PMID:15856334]). A more recent study of cancer patients undergoing chemotherapy in Norway between March 2006 and March 2007 reported that of the 101 different combinations of herb/chemotherapeutic agent that were tested in 42 concurrent users, valerian was taken in combination with two chemotherapeutic agent classes (Engdal et al., 2009 [PMID:19174505]).

Heavy Metal, Pesticide, Mold, and Yeast Contamination

Some studies have shown that commercial valerian products may contain traces of a variety of heavy metals and pesticides (ConsumerLab.com, 2006a,b,c; Grippo et al., 2006 [PMID:16554287]; Huggett et al., 2001). Huggett and colleagues (2001) reported finding arsenic, cadmium chromium, lead, and nickel in solid valerian formulations (10 samples) purchased on the U.S. market in addition to 14 organochlorine pesticides. The pesticides were calculated as presenting a carcinogenic risk of at least one per million in 45% of the valerian samples for persons ingesting the products at the 1000-mg level daily for 350 days per year. No risk was predicted due to the presence of the heavy metals. A study by Tournas (2009) concluded that commercial valerian products obtained from local supermarkets were not contaminated with mold or yeast.

Sewage sludge is used to fertilize agricultural soils, and may be contaminated with heavy metals. Heavy metal concentrations in washed *V. officinalis* roots grown in sewage sludge showed increases of 82-2800% over values for roots grown in unamended soils in the United Kingdom (Weightman, 2006).

8.0 Regulatory Status

Because valerian is an herb, it is regulated as a "dietary supplement" under the Dietary Supplement Health and Education Act of 1994 (DSHEA). Under the DSHEA, the manufacturer is responsible for ensuring that its dietary supplement products are safe before they are marketed. Unlike drug products that must be proven safe and effective for their intended use before marketing, there are no provisions in the law for the U.S. Food and Drug Administration (FDA) to "approve" dietary supplements for safety or effectiveness before they reach the consumer. Once the product is marketed, FDA has the responsibility for showing that a dietary supplement is "unsafe," before it can take action to restrict the product's use or removal from the marketplace (U.S. FDA, 2009a). Valerian is also permitted for direct addition to food for human consumption by the FDA. Specifically, valerian rhizome and roots (*V. officinalis* L.) are listed as natural flavoring substances that can be used in the minimum quantity required to produce their intended physical or technical effect and in accordance with all the principles of good manufacturing practice [21CFR172.510] (U.S. FDA, 2009b). Valeric acid, 3-methylvaleric acid, isovaleric acid, and salts of isovaleric acid (e.g., ammonium, sodium, and zinc) are listed as synthetic flavoring substances permitted for direct addition to food [21CFR172.515] (U.S. FDA, 2009c). In place of the lack of regulation, the monographs published by the German Commission E, which required manufacturers to provide evidence of pharmaceutical quality for traditional herbal ingredients and traditional medicine, present "standards for efficacy, safety, and acceptable extracts" and "the acceptable labeling for botanicals in wide commercial use in Germany prior to 1978" (Grant, 1999). Commission E approved valerian as a sleep-promoting and sedative agent for the treatment of restlessness and sleeping disorders caused by anxiety (Blumenthal, 1998). Other countries (e.g., the United Kingdom and Switzerland) have included valerian in their pharmacopeia and most specify that the crude herb/whole root is to contain not <0.5% essential oil and for the cut material not <0.3% (Thorne Research, Inc., 1999).

9.0 Toxicological Data

9.1 General Toxicology

Several reviews of studies of the efficacy of valerian, particularly as a sleep aid and sedative, in adults and children have been published (e.g., see Givens and Cupp, 2000; Hadley and Petry, 2003; Thorne Research, Inc. 2004; Volz, 1997). Key information provided in the Natural Standard Monograph for *V. officinalis* L. (Natural Standard, 2008), which provides a comprehensive overview of this herb, has been summarized and included in this current review. No attempt was made to incorporate all of the information from the monograph into this review; rather, the reader is referred to the monograph. A number of efficacy studies summarized in Section 9.1.1 were obtained from the monograph.

9.1.1 Human Data

Efficacy

The majority of efficacy studies have focused on valerian as a sleep aid, whether taken alone or in combination with other substances. Significantly fewer studies of its use for treatment of anxiety/panic disorder have been published.

The most commonly studied commercial valerian preparation is an ethanolic extract called LI 156 (Sedonium[®]) (Taibi et al., 2007). Valerian combinations (e.g., valerian with hops and/or lemon balm and/or motherwort) have also been examined (e.g., Cerny and Schmid, 1999; Dimpfel and Suter, 2008 [PMID:18559301]; Taibi et al., 2007; Widy-Tyszkiewicz and Schminde, 1997). Numerous controlled studies and clinical trials have been conducted on the efficacy of valerian, alone or in a mixture, as a sleep aid and the results were inconclusive. Some studies suggested valerian was an effective sleep aid (e.g., Cerny and Schmid, 1999; Dimpfel, 2007; Dimpfel and Suter, 2008 [PMID:18559301]; Hintelmann, 2002; Lindahl and Lindwall, 1989 [PMID:2678162]; Morin et al., 2005 [PMID:16335333]; Oxman et al., 2007), while others showed its effect to be comparable to placebo (e.g., Coxeter et al., 2003 [PMID:15022653]; Diaper and Hindmarch, 2004 [PMID:15551388]; Jacobs et al., 2005 [PMID:16010204]).

Reviews of most of the efficacy studies have also been published (e.g., Hadley and Petry, 2003; Thorne Research, Inc., 2004). One systematic review and meta-analysis (16 eligible studies, 1093 patients) concluded that the evidence suggested valerian might improve sleep quality without adverse effects (Bent et al., 2006 [PMID:17145239]), while a more recent review (37 eligible studies, >1900 patients) concluded that the evidence did not support the efficacy of valerian or combinations for reducing sleep disturbance or insomnia symptoms (Taibi et al., 2007). The latter review also considered the types of products evaluated. The overall conclusion from many of the studies was that valerian (up to 1800 mg) administered as a single or repeated dose does not appear to produce significant psychomotor/cognitive impairment, sedation, or mood-altering effects (e.g., Ang-Lee et al., 2002 abstr.; Arushanian et al., 2004 [PMID:15707009]; Glass et al., 2003 [PMID:12826988]; Gutierrez et al., 2004 [PMID:15159134]; Hallam et al., 2003 [PMID:14696021]; Kuhlmann et al., 1999 [PMID:10599933]).

A study of the effectiveness of a valerian extract-St. John's wort combination for treating depression with comorbid anxiety reported that the combination of valerian extract and St. John's wort was more effective than treatment with St. John's wort alone in treating the depression and anxiety. Results from one study of the use of an herbal combination containing valerian extract for the treatment of menopausal symptoms reported that the preparation was effective in reducing the symptoms of menopause (e.g., hot flashes). For both conditions, the effects of valerian alone were unknown (Natural Standard, 2008).

Other forms of valerian also have been studied in human subjects. For example, preliminary findings from treatment of children with an intellectual deficit with *V. edulis* suggested valerian was a potential long-term treatment for their intransigent sleep difficulties (Francis and Dempster, 2002 [PMID:12120807]). Significant improvement in sleep quality was also seen in probands given Hamonicum Much[®] (valepotriates from *V. edulis*) for 9 days (Gessner et al., 1983).

Absorption, Distribution, Metabolism, and Excretion

When healthy subjects were given a single dose of valerian (600 mg), maximum serum concentrations of valerenic acid (0.9-2.3 ng/mL) were seen 1-2 hours after administration in five of six subjects. Maximum serum concentrations occurred at one and five hours in the remaining subject. The elimination half-life for valerenic acid was 1.1 ± 0.6 hours and the area under the concentration time curve (measure of valerenic acid exposure) was variable (4.80 ± 2.96 $\mu\text{g/mL} \times \text{hour}$) (Anderson et al., 2005; cited by Natural Standard, 2008).

Acute Toxicity

In the recent review of the clinical efficacy of valerian as a sleep aid for insomnia, results reported in the examined studies indicated that valerian was a safe herb, having only mild neurological and gastrointestinal (GI) symptoms (Taibi et al., 2007). The adverse effects that were reported for ethanolic extracts of valerian included headache, morning hangover, GI complaints such as diarrhea, drowsiness, mental dullness, depression, irritability, dizziness, and nausea. Effects reported with the aqueous extracts included dizziness, significantly increased morning sleepiness with a higher dose (900 mg versus 450 mg), and nausea, while those reported with valepotriate preparations were all GI complaints (indigestion, diarrhea, stomach discomfort, and bitter taste in the mouth) (Taibi et al., 2007). These side effects have been reported in <10% of subjects in randomized trials (Thorne Research, Inc., 2004). Although usually taken orally, intravenous (i.v.) injection of a crude valerian root extract (dose not provided) resulted in severe hypotension, hypocalcemia, and hypokalemia in a patient (Wells, 1995 abstr.; cited by Natural Standard, 2008).

Withdrawal symptoms have also been observed with valerian use. A 41-year-old woman with no significant past medical history reported experiencing agitation, visual hallucinations, and tinnitus four days after discontinuing her regular intake of valerian along with acetaminophen/hydrocodone. Blood pressure, pulse, and respiration were also increased. She had significant tremors and nystagmus. The patient was treated with various drugs, including lorazepam and risperidone, and returned to normal within 24 hours. Her withdrawal symptoms were similar to that from other γ -aminobutyric acid (GABA)ergic agents (Wiener et al., 2003 abstr.). In a patient who had a history of coronary artery disease, cardiac complications and delirium were observed after withdrawal of long-term valerian use (i.e., years). Valerian withdrawal was suspected and treated successfully with benzodiazepines (Garges et al., 1998; cited by Givens and Cupp, 2000, and Natural Standard, 2008).

Hepatotoxicity

A few cases of hepatotoxicity have been reported with valerian-containing products. Four cases of temporary liver damage were first reported in 1989 and one other case in 2008 (described below). It was noted that in several recent reviews and meta-analyses of the efficacy of valerian (>1000 patients) and in numerous cases of valerian overdose, no occurrence of hepatotoxicity was reported (Cohen and Del Toro, 2008 lett.; Natural Standard, 2008).

Four women in Wales who had no significant medical history of liver disease began exhibiting evidence of jaundice, usually with dark urine and pale stools. It was discovered that all were taking herbal medicines (specifically Neurelax or Kalms which contained valerian and skullcap,

among other ingredients) for relieving stress. Liver biopsy revealed moderate to severe acute hepatitis in two of three women taking Kalms and chronic aggressive hepatitis with advanced fibrosis in the woman taking Neurelax. Upon discontinuation of the herbal drugs, results from liver function test for the four patients returned to normal within 2-19 months. It was believed that skullcap and valerian were the hepatotoxic components (MacGregor et al., 1989). [Note: Researchers now believe that germander, a plant from the mint family and also believed to be present in the herbal medicines, was the cause of the liver damage (Keville and Korn, 1996).]

In a more recent study, the first in almost 20 years, a woman from Nicaragua with no significant medical history began experiencing epigastric pain, fatigue, heartburn, and occasional nausea and was found to have mild epigastric tenderness and hepatomegaly. Aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, and total bilirubin levels were increased. A liver ultrasound confirmed the mild hepatomegaly. The patient reported taking only valerian (300-mg capsules of Valerian Root, Mason Vitamins, Miami, FL) two times per day for the previous three months. One month after its discontinuation, bilirubin and enzyme levels returned to normal and no signs of disease were observed. Valerian was believed to be the cause of the hepatotoxicity (Cohen and Del Toro, 2008 lett.).

The authors of the two studies above acknowledged that herbal medicines contain multiple ingredients and that no specific diagnostic test exists to confirm valerian as the cause of the liver damage. Additionally, all ingredients may not be listed on a product label and those listed may not all be in a pure form. Formulations may also change over time, as was the case for the Kalms tablet, which contained skullcap only before October 1984 (Cohen and Del Toro, 2008 lett.; MacGregor et al., 1989).

A 1994 case study of fulminant hepatitis in a 13-year-old girl who had no history of liver damage reported that she presented with jaundice and acute hepatitis (confirmed with liver function tests). Liver biopsy showed extensive liver cell necrosis (>90% of hepatocytes destroyed) and a liver transplantation was performed. The patient had used Euphytose[®], an herbal medicine containing valerian, ballote, hawthorn, passiflora, and kola, to relieve mild anxiety for about two months. Valerian and ballote were noted as two potential hepatotoxicants in this herbal medicine (Bagheri et al., 1998).

Reproductive and Developmental Effects

No clinical studies were identified and no case studies reported any problems in pregnant or lactating women or in children exposed to valerian (Thorne Research, Inc., 2004). In an epidemiology study of pregnant women in Budapest who were hospitalized during the period 1960-1979 for intoxication with drugs and other agents, one woman was reported to have ingested valerian dry extract (2.5 g) and phenobarbital (0.5 g) during the 10th gestation week in a suicide attempt. No congenital anomalies were observed in her female offspring. Another pregnant woman had taken a mixture of drugs that included valerian dry extract (3.0 g) during the 20th week of gestation in an attempt to commit suicide. Although her son was born mentally retarded, the effect of valerian on this condition was not clear since the same woman gave birth to a second mentally retarded son two years later after another suicide attempt that did not include valerian (Czeizel et al., 1988 [PMID:3190450]). A second population-based prospective epidemiological study of pregnant women hospitalized during the period 1985-1993 for

attempted suicide by drug overdose, reported no congenital abnormalities in two fetuses of mothers who consumed valeriana (2 or 5 g) and phenobarbital (Czeizel and Mosonyi, 1997 [PMID:9329649]). In a study of all births listed in the Swedish Medical Birth Register from 1995-2004, valerian was one of the most used herbal drugs reported by women during early pregnancy (98 of 811 users) for treatment of insomnia and/or restlessness. No effects were observed on infant characteristics—i.e., prematurity, low birth weight, small for gestational age, large for gestational age, low Apgar scores at 5 minutes, and congenital malformation (Holst et al., 2008 [PMID:17992658]).

In a phase I clinical study, healthy males were administered five tablets of a valerian extract standardized to 0.43% valerenic acid daily for 10 days (i.e., three times the recommended daily dose). Subjects exhibited a decrease in the percentage of disknetic forms of spermatozoids and a temporary increase in the percentage of normokinetic spermatozoids, but no negative effects on fertility were observed. The fertility parameters measured were the Farris Fertility index, volume of ejaculate, number of spermatozoids in 1 mL of ejaculate, total number of spermatozoids in whole in whole ejaculate, and percentage of normokinetic spermatozoids. In addition, no significant changes in the testicles (i.e., swelling, local hyperemia, dilation of veins, or increase in appendage) were reported (Mkrchtayan et al., 2005 [PMID:16008115]; Oppel, 2006).

Immunotoxicity

In farmers cultivating valerian, a low frequency (1.3-4.0%) of positive skin reactions to antigens of several microorganisms associated with organic dusts and antigens of herbs (chamomile and peppermint extracts) was observed; none was significantly greater than that of controls (i.e., urban dwellers not exposed to any organic dust). In precipitin tests, a significantly high frequency (45.5%) of positive reactions to the antigen of Gram-negative bacterium *Pantoea agglomerans* was seen in farmers having a threefold concentrated sera. A weak positive or no response was seen with the other microbial and herbal antigens tested. In the test for specific inhibition of leukocyte migration, significantly high frequencies (15%) of positive reactions occurred with *P. agglomerans* and *Saccharopolyspora rectivirgula*. [Noted: *P. agglomerans* was reported to be a potent allergen and endotoxin] (Skorska et al., 2005).

When administered as a single dose (not provided in abstract) to 15 healthy volunteers, valerian failed to significantly suppress the wheal and flare responses to histamine skin prick testing (More et al., 2003). In atopic eczema/dermatitis syndrome patients, however, inhalation of valerian oil (dose not provided in abstract) reduced skin wheal responses induced by latex allergen. Additionally, *in vitro* latex-specific immunoglobulins E and G4 production was reduced and cytokine pattern was skewed towards a T-helper type 1 (Kimata, 2004).

Synergistic/Antagonistic Effects

Valerian may synergistically increase the sedative effects of barbiturates, anesthetics, and other central nervous system depressants. No potentiation of the negative effects of alcohol on driving performance, however, was observed with the simultaneous intake of valerian and alcohol (Hadley and Petry, 2003; Thorne Research, Inc., 2004). A summary of the interactions of valerian with other drugs, herbs/supplements, and lab tests can be found in the Natural Standard Monograph (Natural Standard, 2008).

Enzyme Effects

Administration of valerian root extract (125 mg) three times daily for 28 days to healthy volunteers (followed by a 30-day washout period) produced no significant changes in human cytochrome P450 (CYP) 1A2, 2D6, 2E1, and 3A4/5 activity, indicating it is unlikely to induce CYP-mediated herb-drug interactions. It was noted that only trace amounts of valerianic acid were found in the test product, thus, the results may not be representative of all valerian products (Gurley et al., 2005). In subjects orally given dextromethorphan and alprazolam to measure the effect of valerian on CYP2D6 and CYP3A4 activity, respectively, nightly administration of two tablets of a valerian supplement containing 500 mg of dry valerian root extract (5.51 mg valerianic acid/tablet) for 14 days had no effect on CYP2D6 activity and minimal effect on CYP3A4 activity (Donovan et al., 2004). Mixed results were observed in *in vitro* studies (e.g., Budzinski et al., 2000; Lefebvre et al., 2004; Strandell et al., 2004 [all cited by Gurley et al., 2005]).

9.1.2 Chemical Disposition, Metabolism, and Toxicokinetics

Valerian extract (from *V. officinalis*) was incubated with freshly prepared rat hepatocytes to evaluate metabolite formation. Levels of acetoxyvalerianic acid, didrovaltrate, isovaltrate, and valtrate decreased 9-, 2-, 18-, and 16-fold, respectively. Comparatively, hydroxyvalerianic acid levels increased 9-fold (Simmen et al., 2005 [PMID:16041642]).

Valerianic acid (20 μ M) was incubated with isolated perfused liver from Wistar and Mrp2-deficient TR(-) rats; seven valerianic acid glucuronides (M1-M7) were formed. The glucuronide metabolites included two glucuronides of valerianic acid, four glucuronides of hydroxylated valerianic acid, and one glucuronide of hydroxylated dehydro-valerianic acid. Hepatic extraction ratio and valerianic acid clearance were almost identical in Wistar and Mrp2-deficient TR(-) rat livers (excretion ratio: 0.983 ± 0.006 vs. 0.981 ± 0.004 ; clearance: 35.4 ± 0.21 mL/min vs. 35.3 ± 0.14 mL/min). A decrease in cumulative biliary excretion (1-9%) of valerianic acid and efflux of conjugates was noted in Mrp2-deficient TR(-) rat livers. This decrease was accompanied by a 1.5- to 10-fold increase in efflux into the perfusate (Maier-Salamon et al., 2009 [PMID:19156843]).

A valepotriate mixture of valtrate and isovaltrate (50 and 150 mg/kg) or baldrinal and homobaldrinal (30 mg/kg) were orally administered to female NMRI mice and plasma, urine, and bile were collected to measure the metabolites. Approximately 70% of the baldrinal and homobaldrinal mixture was excreted as 1-*O*-(4-hydroxymethylcyclopenta[*c*]-pyrane-8-carbonyl) β -D-glucuronide. The same metabolite was observed only after administration of the higher dose of the valepotriate mixture (Dieckmann et al., 1989 abstr.).

Using *in silico* and *in vitro* methods, molecular descriptors and effective permeability in Caco-2 cells were estimated for selected herbal extracts and their active components. For valerian, the effective permeability of hydroxy valerianic acid and valerianic acid were evaluated. Using *in silico* methods, the predicted octanol-water partition coefficient, polar surface area, and minimal cross-sectional area were determined. The SimBioDAS system was used to assess effective permeability (Pade and Stavchansky, 2008 [PMID:18481869]). The results are presented below in **Table 1**.

Table 1. Estimated Molecular Descriptors and Effective Permeability of Valerian Constituents in Caco-2 Cells

Active Component	CLogP	PSA (Å ²)	MCSA (Å ²)	P _{eff} ± SD (cm/s)
Hydroxy valerenic acid	2.650	172.723	116.400	5.800 ± 1.006
Valerenic acid	4.737	117.788	124.200	39.664 ± 10.328

Abbreviations: CLogP = predicted octanol-water partition coefficient, MCSA = minimal cross-sectional area; P_{eff} = effective permeability; PSA = polar surface area; SD = standard deviation

9.1.3 Acute Exposure

Acute toxicity values for valerian extracts and constituents are presented in **Table 2**.

Table 2. Acute Toxicity Values for Valerian Extracts and Constituents

Route	Species (sex and strain)	LD ₅₀	Reference(s)
oral (valeranone)	Rats and mice (sex and strain n.p.)	>3160 mg/kg (14.21 mmol/kg)	Rücker et al. (1978) [PMID:580202]
oral (valtrate)	Mice (sex and strain n.p.)	≥ 4600 mg/kg (10.89 mmol/kg)	von Eickstedt and Rahman (1969; cited by Tortarolo et al., 1982)
oral (valerian oil)	Rats (sex and strain n.p.)	15,000 mg/kg	Skramlik (1959)
i.p. (valtrate)	Mice (sex and strain n.p.)	~ 62 mg/kg (0.15 mmol/kg)	von Eickstedt and Rahman (1969; cited by Tortarolo et al., 1982)
i.p. (ethanolic extract of valerian root)	Mice (sex and strain n.p.)	3300 mg/kg	Rosencrans et al. (1961; cited by ESCOP (2003)

Abbreviations: i.p. = intraperitoneal; LD₅₀ = lethal dose for 50% of test animals; n.p. = not provided

Intraperitoneal administration of 50-400 mg/kg valerenic acid to mice (17-25 g body weight) produced a variety of effects including reduced spontaneous motility (50 mg/kg), ataxia (100 mg/kg), and muscle spasms (150-200 mg/kg). At a dose of 400 mg/kg, heavy convulsions were observed which led to death in six of seven mice within 24 hours (Hendriks et al., 1985; cited by ESCOP, 2003).

9.1.4 Short-Term and Subchronic Exposure

Male Swiss albino mice (6-8 weeks, 25-28 g) were orally administered 500, 1000, or 2000 mg/kg aqueous suspensions of a marketed valerian product (containing 800 mg valerian root and 220 mg valerian dried extract, standardized to 0.8% valerenic acid) daily for 7 days via gastric intubation. Piloerection, hyperthermia, increased motor activity, defecations, reflex impairment, staggering, and sedation were noted at the highest dose tested (Al-Majed et al., 2006 [PMID:16879905]).

Administration (route not specified) of 100 to 200 mg valerian root essential oil (source not provided) for a period of 8 weeks to rats produced no effects on weight or grooming. At doses >200 mg, growth declined and adverse symptoms were noted (not specified). At a daily dose of

250 mg, two of five tested rats died within 3 weeks of dosing initiation (Skramlik, 1959; cited by ESCOP, 2003).

Two non-pregnant Sprague-Dawley rats were administered varying doses of valerian extract (donated by a commercial source; containing 500 mg/mL valerian) for 8 days to evaluate the maximum non-toxic dose (as evaluated by general activity, posture, presence of piloerection, and response to handling). The maximum non-toxic dose of extract was 2.79 g/kg/day (Yao et al., 2007 [PMID:17611059]). Administration (route not specified) of an alcoholic extract of valerian root (source not provided; 300 or 600 mg/kg) daily for 30 days to rats produced no significant decreases on growth, weight of selected organs, arterial pressure, or evaluated hematological or biochemical parameters when compared to control animals (Fehri et al., 1991; cited by ESCOP, 2003).

The toxicological effects of a plant extract mixture (P-9801091) containing *Valerianae radix* (7.8%; m/m) was evaluated in CBA/HZg mice. Animals were fed standard diets containing lyophilized P-9801091 at a dose of 20 mg/kg/day for up to 6 months. Significant decrease in body weight was noted on days 7, 21, and 28 of the study; however, body weights were similar to control animals later in the study. Additionally, no weight changes or histologic or macroscopic alterations were noted in the spleen, kidneys, testicles, and liver of test mice. Biochemical analyses showed an increase only in the catalytic concentration of aspartate aminotransferase on day 7 of the study (Petlevski et al., 2008).

9.1.5 Chronic Exposure

No chronic exposure duration studies were identified.

9.1.6 Synergistic/Antagonistic Effects

No studies were available for antigenotoxic effects.

Synergism/Antagonism of Valerian Effects

Compounds with free thiol groups (e.g., cysteine) antagonized the cytotoxic effects of valtrate and didrovaltrate in cultured hepatoma cells (Keochanthala-Bounthanh et al., 1990 [PMID:2353067]).

Synergistic/Antagonistic Effects Produced by Valerian

In mice, no effect doses of powdered valerian root suspensions and *Leonurus cardiaca* administered concurrently produced maximum prolongation of barbiturate-induced sleep, suggesting a potentiation of effect (Gedevanishvili et al., 2006 [PMID:16783086]).

Intraperitoneal administration of aqueous, methanolic, and chloroform extracts of *V. officinalis* rhizomes and aqueous and methanolic extracts of *V. officinalis* aerial parts caused a decrease in withdrawal symptoms (i.e., jumping) in morphine-dependent mice (Sharifzadeh et al., 2006 [PMID:16800827]).

Aqueous extracts of *V. officinalis* antagonized rotenone-induced apoptosis in human SH-SY5Y cells. Cells incubated with 300 nM rotenone for 48 hours exhibited significant changes in

cellular morphology. Inclusion of *V. officinalis* extract (0.049, 0.098 and 0.195 mg/mL) increased cell viability >7% (de Oliveria et al., 2009 [PMID:18512151]).

Ethanollic valerian extracts (0-60 µg/mL) antagonized formation of thiobarbituric acid-reactive substances produced by quinolinic acid, 3-nitropropionic acid, sodium nitroprusside, iron sulfate, and iron/ethylenediaminetetracetic acid in rat brain homogenates in a concentration dependent manner. Additionally, quinolinic acid-induced formation of reactive oxygen species in cortical slices was antagonized (Sudati et al., 2009 [PMID:19191025]).

Valerian antagonized the contractions of human uterine muscles *in vitro* produced by acetylcholine, phenylephrine, and histamine, in a concentration dependent manner (Occhiuto et al., 2009 [PMID:19178774]).

Anticarcinogenicity Effects

Ethanol extract of the valerian root and rhizome (herb purchased from commercial source) inhibited phorbol ester activation of the Epstein-Barr virus early antigen at 10 and 100 µg/mL in Raji cells (cellular viability $\geq 70\%$). The results suggested that the extract interferes with at least one phorbol-ester mediated mechanism involved in tumor promotion (Kapadia et al., 2002 [PMID:11884218]). Bounthanh and colleagues (1981; cited by Tortarolo et al., 1982) also showed that valepotriates were anti-tumor agents *in vivo*.

The growth of three transplanted and two chemically induced rat tumors (description not provided in abstract) was not significantly influenced by i.v. or peroral administration of a standardized mixture of valepotriates (Berger et al., 1986 [PMID:3814222]).

9.1.7 Cytotoxicity

Apoptosis, mRNA expression of survivin, and protein expression of p53 and survivin were assessed in the human gastric carcinoma cell line MKN-45 following 24-72 hour exposure to caspase-3, -8, or -9 inhibitors; valmane; or caspase-3, -8, and -9 inhibitors and valmane. [Note: Article identifies the chemical tested as valepotriate but the registry number provided in the abstract was for valmane, an acevaltrate mixture with didrovaltrate and valtrate.] With the exception of cells treated with caspase-8 inhibitor and valmane, the highest rate of apoptosis was observed in cells treated with valmane alone (24 hours: 8.14%, 48 hours: 12.31%, 72 hours: 26.41%). Valmane downregulated survivin mRNA expression in a dose- and time-dependent manner. Survivin protein expression also was down regulated, but p53 protein expression was up-regulated (Ye et al., 2007).

Pan-iridoids, the iridoid glycosides and esters extracted from valerian, exhibited cytotoxic effects on K562, HL60, U937, HepG2, and Hale cell lines. The overall order of observed activity was iridoids with conjugate-bonds > iridoids with mono-alkene > iridoid glycosides (Xue et al., 2005).

Constituents of three *Valeriana* species (*V. officinalis*, *V. wallichii*, and *V. edulis*) were evaluated for cytotoxic effects on two human cancer cell lines, GLC4, a small-cell lung cancer cell line, and COLO 320, a colorectal cancer cell line. Diene-type valepotriates (e.g., valtrate, isovaltrate, and acevaltrate) exhibited the highest activity with IC₅₀ values of 1-6 µM, while valerenic acids

(e.g., valerenic acid, acetoxyvalerenic acid) exhibited low activity with IC_{50} values between 100 and 200 μ M. Monoene-type valepotriates (e.g., didrovaltrate) were 2- to 3-fold less toxic than the diene-type valepotriates. Baldrinal and homobaldrinal were both less toxic than the parent compounds. Studies with stored tinctures showed that valepotriates decomposed with time, which coincided with a reduction in cytotoxic activity (Bos et al., 1998).

Isolated from highly enriched *V. Mexicana* and *v. wallichii*, valtrate/isovaltrate and didrovaltrate inhibited cellular proliferation of murine granulocyte/macrophages, T-lymphocytes, and erythrocytes *in vitro* in a dose-dependent manner. [Note: Article identifies the chemical tested as dihydrovaltrate.] Valtrate/isovaltrate was more potent than didrovaltrate (ID_{50} ~23 nM - 3.7 μ M versus 42 nM - 17 μ M). The observed effect in granulocyte/macrophage colony growth was not reversed after cells were washed prior to seeding for growth assessment, suggesting the compounds were cytotoxic (Tortarolo et al., 1982).

Methylene chloride extracts of valerian (plant material used not specified) demonstrated anti-thrombin activity and were cytotoxic (10 μ g extract) against mouse leukemia L1210 cells. Methanol extracts had no effect on L1210 cells (Goun et al., 2002 [PMID:12127234]). Valerian (purchased from Indena; suspended in Dulbecco's modified Eagle's medium) also was cytotoxic to cultured human hepatoma HG2P128 cells at 20 mg/mL. No effects were observed at 2 mg/mL (Vo et al., 2003 [PMID:14516421]). Comparatively, valerian extracts (with sodium hydroxide; containing 1% valerenic acid) were not cytotoxic to RAW264.7 and N11 microglia at 100 μ M (Shanmugam et al., 2008 [PMID:18186104]).

Thirteen acylated iridoids and nine known valpotriates, which were isolated from *V. jatamansi*, were tested for cytotoxic potential in human A549, PC-3M (metastatic prostate), HCT-8 (colon cancer), and Bel7402 (hepatoma) cells. The newly identified acylated iridoids were named jatamanvaltrates A-M and all but two were cytotoxic to the PC-3 cells (IC_{50s} = 1.4-6.3 μ M). Five of the nine valpotriates, didrovaltrate acetoxy hydrin, IVHD-valtrate, 5-hydroxydidrovaltrate, valtrate, and acevaltrate were cytotoxic in all cell lines (IC_{50s} = 1.0-7.4 μ M); acevaltrate was the most toxic compound evaluated (Lin et al., 2009 [PMID:19245261]).

9.2 Reproductive and Teratological Effects

Ten pregnant Sprague–Dawley rats were administered 2.79 g/kg/day valerian extract (containing 45% ethanol and 500 mg/mL valerian) by oral gavage either on gestation day (GD) 1-8 or GD 8-15. On GD 20, pregnant rats were euthanized and organs removed for weight and evaluation. All fetuses were examined. No external signs of maternal toxicity were noted in either group. Additionally, no significant difference in mean liver or kidney weights was noted when compared to control animals. No significant differences in the mean number of implantations per dam, corpora lutea per dam, live fetuses per litter or in total number of resorptions per dam, percentage pre-implantation loss, and percentage of runts between treated and control animals. The placental weight was significantly smaller in each group when compared to the respective ethanol control animals. Fetuses from 29 litters were examined and no external malformations in either group were found. The number of ossified metacarpals in fetuses of the GD 1-8 valerian group was significantly lower compared to the water, but not ethanol, controls. Comparatively, the number of ossified metacarpals in fetuses of the GD 8-15 valerian group was significantly

higher compared to the water controls. The number of ossified metacarpals from GD 1-8 fetuses was lower were compared to fetuses from GD 8-15 (Yao et al., 2007 [PMID:17611059]).

Male Swiss albino mice (6-8 weeks, 25-28 g) were administered 125, 250, or 500 mg/kg aqueous suspensions of commercially available valerian capsules (containing 800 mg valerian root and 220 mg valerian dried extract) daily for 90 days by gastric intubation. Significant increases in the weight of the caudae epididymis and seminal vesicles were observed at the highest dose tested. Additionally, a significant increase in sperm count was observed at 250 and 500 mg/kg. Cytogenetic analysis showed that the highest dose tested significantly increased the frequency of aneuploids, sex-univalents, and polyploids in evaluated testis chromosomes, and all doses increased the total percent of aberrations in testis chromosomes. None of the doses tested significantly affected the morphology of spermatozoa or the rate of pregnancy (Al-Majed, 2007).

In an earlier study, the effects of aqueous suspensions of commercially available valerian capsules (800 mg valerian root and 220 mg valerian dried extract, standardized to 0.8% valerenic acid) administered daily at 500, 1000, or 2000 mg/kg for 7 days via gastric intubation were evaluated in male Swiss albino mice. A dose-dependent increase in aneuploid frequency was observed in the testis. The frequency of sex-univalents at 1000 and 2000 mg/kg and polyploids at 2000 mg/kg also were significantly increased. Morphological alterations (i.e., amorphous and triangular head) of the spermatozoa were increased at 1000 and 2000 mg/kg. Total spermatozoa abnormalities were increased at all doses (Al-Majed et al., 2006 [PMID:16879905]).

A mixture of three valerian components (80% didrovaltrate:15% valtrate:5%acevaltrate) was orally administered to non-pregnant female rats for 30 days and to pregnant rats on GD 1-19 at doses of 6, 12 or 24 mg/kg. [Note: Article notes that dihydrovaltrate was administered with valtrate and acevaltrate. Based on references cited by the article, the information indicates that the administered substance was didrovaltrate.] The average length of estrus and number of estruses phases was not affected during the 30 day study period. No increased risk in fetotoxicity, external malformations, or developmental changes in offspring of pregnant rats was noted. A significant increase in the number of fetuses with retarded ossification was observed in the 12 and 24 mg/kg dose groups (Tufik et al., 1994 [PMID:8170157]).

9.3 Carcinogenicity

No data were available.

9.4 Initiation/Promotion Studies

No data were available.

9.5 Genotoxicity

DNA damage was measured by the Comet assay in human epithelial ECV304 cells treated with dichloromethane extracts of valerian (13.7% valepotriates: baldrinal, homobaldrinal, valtroxal, and didrovaltrate) *in vitro*. Damage was induced at the two highest concentrations (40 and 60 µg/mL) but not at lower concentrations (5, 10, and 20 µg/mL). Addition of vitamin E and vitamin C to the incubation produced a biphasic effect. At lower vitamin concentrations extract-induced damage was antagonized, indicating the DNA damage was caused by oxidative stress,

and at higher vitamin concentrations the damage increased (Hui-lian et al., 2003 [PMID:12668120]).

Valepotriates (i.e., didrovaltrate and isomer mixture valtrate/isovaltrate) were mutagenic in *Salmonella typhimurium* TA100 and *Escherichia coli* WP2 and WP2 uvrA- in the presence of S9 at concentrations up to 1 µmol/plate. [Note: Didrovaltrate was identified as dihydrovaltrate in the article.] The chemicals were toxic at higher concentrations. The valepotriates also showed alkylating activity against 4-(*p*-nitrobenzyl)-pyridine; however, valtrate/isovaltrate was more efficacious than didrovaltrate (von der Hude et al., 1985 [PMID:3994511]). Similar results were observed in the SOS-chromotest in which valepotriates were mutagenic in the presence of S9. Comparatively, baldrinol and homobaldrinol were mutagenic in *S. typhimurium* and the SOS-chromotest in the absence and presence of S9 (von der Hude et al., 1986 [PMID:3511364]). Studies by Glatt and colleagues (1983 [PMID:6355833]) showed that valtrate, didrovaltrate, and acevaltrate were not mutagenic in *S. typhimurium* strains TA98 and TA100. [Note: Valtrate, didrovaltrate, and acevaltrate were identified as valtratum, didovaltratum, and acevaltratum in the abstract.]

Valtrate, didrovaltrate, and deoxy-didrovaltrate (obtained from *V. wallichii*) were shown to inhibit DNA and protein synthesis (as measured by thymidine and leucine incorporation) in rat hepatoma cells. Studies showed that valtrate was more potent than didrovaltrate or deoxy-didrovaltrate (Bounthanh et al., 1983 [PMID:17405036]). Additionally, valepotriates were shown to have alkylating potential (Braun et al., 1982; cited by Tortarolo et al., 1982).

The effects of aqueous suspensions of commercially available valerian capsules (800 mg valerian root and 220 mg valerian dried extract, standardized to 0.8% valerenic acid) administered daily at 500, 1000, or 2000 mg/kg for 7 days via gastric intubation were evaluated in male Swiss albino mice. A statistically significant ($p < 0.05$) increase in the frequency of micronucleated polychromatic erythrocytes (PCE) and a decrease in the PCE/normochromatic erythrocytes was reported at the highest dose (Al-Majed et al., 2006 [PMID:16879905]).

9.6 Cogenotoxicity

No data were available.

9.7 Immunotoxicity

No data were available.

9.8 Other Data

Neurological Effects

Over 60 *in vivo* and *in vitro* studies evaluated the neurological effects of valerian extracts and its components. The *in vivo* rodent studies generally showed that valerian and its constituents produced sedative, anxiolytic, and antidepressant effects (e.g., Hendriks et al., 1985 [PMID:17340394]; Holzl and Fink, 1984 [PMID:6538419]; Leuschner et al., 1993 [PMID:8352816]). Summaries of representative results from a few of the *in vivo* studies are provided below. Male Wistar rats administered valerian (a standard tincture of *V. officinalis* containing 10 g of valerian roots/100 mL ethanol) in the drinking water exhibited hypolocomotor and anxiolytic effects (Fachinnetto et al., 2007 [PMID:17669571]). These results were

corroborated by Hattesoehl and colleagues (2008 [PMID:18160026]) who showed two alcoholic extracts and a patented special extract phytofin Valerian 368 produced anxiolytic effects in female NMRI mice. Additionally, subchronic oral administration of phytofin Valerian 368 showed antidepressant activity in mice. Valerian also exhibited neuroprotective properties (Tang et al., 2008 [PMID:18334150]; Wang et al., 2003).

Overall, the evaluated *in vitro* studies suggest that the effects of valerian and its components may occur through modulation of a variety of neurotransmitter systems including GABA, adenosine, and serotonin systems. Valerian components and extracts may specifically bind to receptors and modulate neurotransmission (e.g., see Benke et al., 2009 [PMID:18602406]; Dietz et al., 2005 [PMID:15921820]; Ferreira et al., 1996; Lacher et al., 2007 [PMID:17097622]; Ortiz et al., 1999 [PMID:10555777]; Sichert et al., 2007 [PMID:17582590]; Trauner et al., 2008 [PMID:18095218]). Valerian extract may also protect against amyloid β peptide toxicity (Malva et al., 2004 [PMID:15325965]).

The ability of valeronic acid, acetoxyvaleronic acid, and hydroxyvaleronic acid to cross the blood-brain barrier (BBB) by passive diffusion was evaluated using a Transwell *in vitro* model based on ECV304 cells. The permeability rates of all three valerian components were significantly slower than the GABAergic modulator, diazepam. Further studies suggested that the components pass through the BBB through a transport mechanism (Neuhaus et al., 2008 [PMID:18704879]).

Anti-inflammatory Effects

Ethyl acetate extract of *V. officinalis* inhibited NF- κ B activity at 100 μ g/mL in HeLa cells (Jacobo-Herrera et al., 2006 [PMID:16909443]). Transforming growth factor β 1 expression was downregulated by *V. officinalis* var. *latifolia* in dietary-induced hypercholesterolemia in male Wistar rats (Si et al., 2003 [PMID:15015379]). Comparatively, a short-term *in vivo* study showed that research grade valerian had no effect on natural killer cell activity in Sprague-Dawley rats (Neill and Dixon, 2007 [PMID:17627197]). Polysaccharides isolated from *V. officinalis* were shown to exhibit mitogenic and co-mitogenic activity in rat thymocytes (Ebringerova et al., 2003 [PMID:12628395]).

Effect on Enzymes

Components of valerian and valerian extracts modulate a variety of enzyme activities. Components or valerian extracts inhibited glucuronidase activity and stimulated glutamic acid decarboxylase (Alkharfy and Frye, 2007 [PMID:17484515]; Awad et al., 2007 [PMID:18066140]). There were conflicting results reported for the effects of valerian on CYP activities (Hellum et al., 2009 [PMID:19371257]; Lefebvre et al., 2004 [PMID:15367385]; Strandell et al., 2004 [PMID:15070158]). For example, valerian inhibited baculovirus expressed CYP2D6-mediated metabolism of dextromethorphan but increased the activity of CYP2D6 (and CYP3A4) in cultured primary human hepatocytes (Hellum and Nilsen, 2007 [PMID:17910620]; Hellum et al., 2007 [PMID:17214607]).

Endocrine Activity

A petroleum ether extract of *V. officinalis* (root) exhibited affinity for the estrogen receptor β in MCF-7 cells (81% \pm 4% binding at 200 μ g/mL). The extract had much lower affinity for the α

receptor in these cells (43±11% at 200 µg/mL). Both a petroleum ether and dichloromethane extract showed induction of an estrogen-responsive element luciferase reporter construct in estrogen receptor α -positive cell line (7.2- and 5.9-fold induction; dimethylsulfoxide defined as 1.0) (Overk et al., 2008 [PMID:18473738]).

10.0 Structure-Activity Relationships

No data were identified that were directly applicable. (See Appendix C for the activity of some *V. officinalis* constituents.)

11.0 Online Databases and Secondary References Searched

11.1 Online Databases

National Library of Medicine Databases

PubMed

ChemIDplus – chemical information database that provides links to other databases such as CCRIS, DART, GENE-TOX, HSDB, IRIS, and TRI. A full list of databases and resources searched are available at <http://www.nlm.nih.gov/databases/>.

STN International Files

AGRICOLA	FROSTI
BIOSIS	FSTA
BIOTECHNO	IPA
CABA	MEDLINE
EMBASE	Registry
ESBIOBASE	TOXCENTER

Information on the content, sources, file data, and producer of each of the searched STN International Files is available at <http://www.cas.org/support/stngen/dbss/index.html>.

Government Printing Office

Code of Federal Regulations (CFR)

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- Isovaltrate; CASRN: 31078-10-1
- Valerian; CASRN: 8008-88-6
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Acknowledgements

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Appendix A: Units and Abbreviations

°C = degrees Celsius

µg/L = microgram(s) per liter

µg/m³ = microgram(s) per cubic meter

µg/mL = microgram(s) per milliliter

µM = micromolar

ADHD = attention deficit hyperactivity disorder

BBB = blood brain barrier

CAM = complementary and alternative medicine

CFR = code of federal registry

CO₂ = carbon dioxide

CYP = cytochrome P450

DNA = deoxyribose nucleic acid

DSHEA = Dietary Supplement Health and Education Act of 1994

FDA = Food and Drug Administration

g = gram(s)

g/mL = gram(s) per milliliter

GABA = γ -aminobutyric acid

GC = gas chromatography

GD = gestation day

GI = gastrointestinal

GRAS = generally recognized as safe

HPLC = high performance liquid chromatography

IC₅₀ = inhibitory concentration for 50% of test animals

ID₅₀ = inhibitory dose for 50% of test animals

i.p. = intraperitoneal(ly)

i.v. = intravenous(ly)

kg = kilogram(s)

L = liter(s)

LD₅₀ = lethal dose for 50% of test animals

m/m = mass per mass

mg/kg = milligram(s) per kilogram

mg/m³ = milligram(s) per cubic meter

mg/mL = milligram(s) per milliliter

mL/kg = milliliter(s) per kilogram

mm = millimeter(s)

mM = millimolar

mmol = millimole(s)

mmol/kg = millimole(s) per kilogram

mol = mole(s)

mol. wt. = molecular weight

MS = mass spectrometry

n.d. = not detected

NF- κ B = nuclear factor of kappa light polypeptide gene enhancer in B-cells

NHIS = National Health Interview Survey

n.p. = not provided

PCE = polychromatic erythrocyte

PMID = PubMed identification

TLC = thin layer chromatography

U.S. = United States

WHO = World Health Organization

Appendix B: Description of Search Strategy and Results

Internet searching via Google and Google Scholar was limited and largely devoted to finding sources such as government reports indicated in the database searches or listed in the bibliographies of retrieved articles. Many relevant URLs had already been compiled by the Project Officer. Searches for commercially available products were done in Google Products.

STN International files MEDLINE, AGRICOLA, CABA, EMBASE, ESBIODBASE, BIOTECHNO, IPA, BIOSIS, TOXCENTER, FSTA, and FROSTI were searched simultaneously on September 12, 2008. Results of PubMed searches a day or two previously for valerian OR "*Valeriana officinalis*" had been manually searched for chemical constituents to serve as additional keywords. *Valeriana* species that were not the primary focus of the search were also noted. Many CAS Registry Numbers were found by searching ChemIDplus and/or the STN International REGISTRY file (also on September 12, 2008). The resulting 3075 titles were printed. Several duplicates were noted as the titles were examined offline. Answers that were selected for printing in full were assigned tentative subject codes relevant to appropriate sections of the toxicology review. Topics that were generally excluded from consideration included the following:

- Finding of a *V. officinalis* constituent in plants of other genres
- Structure elucidation and synthesis of constituents
- Therapeutic uses for specific conditions, aromatherapy
- Testing of mixtures or preparative methods for formulations
- Horticulture/cultivation/breeding/pests/plant morphology
- Multiple herb and foreign-language reviews
- Reports of secretion of the alkaloid actinidine by different insect species
- Sedative or sleep-inducing efficacy in humans, except in clinical trials or volunteer studies
- Genetics of the subspecies/morphological diversity
- Pesticidal effects
- Potential for interactions with anesthesia and other drugs
- Physiological effects of other species, except when compared with those of *V. officinalis*

Approximately 190 database records about the constituents and about 440 records about the other toxicological review topics were printed in full and later imported into EndNote. The database tallies for the other topics (or the constituents) were MEDLINE, 170 (49); EMBASE, 109 (34); BIOSIS, 66 (37); CABA, 26 (27); TOXCENTER, 26 (9); AGRICOLA, 24 (22); FSTA, 11 (0); IPA, 9 (12); and FROSTI, 9 (0).

The history of the STN International online session on September 12, 2008, is reproduced below:

```
L1          11 S ACETOXYVALERANONE
L2          50 S ACETOXYVALERENIC ACID
L3          129 S ACETOXYVALTRATE? OR ACEVALTRATE? OR ACETOVALTRATE? OR ACETYLOXY(W)
           VALEPOTRIATE? OR 25161-41-5
L4          117 S ACEVALTRATE
L5          114 S ACTINIDINE OR 524-03-8 OR 32115-42-7 OR 11010-93-8
L6          0 S 15524-83-1
L7          73 S BALDRINAL? OR 18234-46-3
L8          0 S CHATARINE
L9          3 S CHATININE OR 1390-84-7
L10         3 S DESISOVALEROYL(2A)ACETYLVALTRATE
L11         236 S DIDROVALTRAT? OR DIHYDROVALTRAT? OR DIHYDROISOVALTRAT? OR
           DIHYDROISOVALEPOTRIATE? OR 18296-45-2
L12         16 S EPOXYVALERENIC(W)ACID OR EUGENYLISOVALERATE OR EUGENYL(W)ISOVALERATE
           OR 61114-24-7
L13         52 S HOMOALDRINAL OR 67910-07-0
L14         22 S HOMOVALTRAT? OR 58523-20-9
L15         60 S (HYDROXYVALERENIC OR VALERENOLIC)(W)ACID OR 1619-16-5
L16         7625 S IRIDOID(W)ESTER? OR IRIDOID?
L17         497 S L1-L15
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L18 9 S ISOEUGENYL(W)ISOVALERATE OR 61114-23-6
 L19 9 S DESOXYIDODIDROVALTRATE OR 18296-46-3 OR ISODIDROVALTRAT? OR 58560-51-3
 L20 13 S HOMOISOVALTRAT? OR 96681-64-0 OR HOMOACEVALTRATE OR 58523-21-0 OR
 480988-94-5
 L21 3 S DEACETYLIISOVALTRAT? OR DIHOMOISOVALTRAT? OR 96681-65-1
 L22 2 S ISOHOMOACEVALTRAT? OR 72432-16-7
 L23 15 S HOMODIDROVALTRAT? OR 18361-41-6 OR HOMODIHYDROISOVALEPOTRIATE? OR
 HOMODIHYDROISOVALTRAT?
 L24 21 S ISOVALEROXYHYDROXYDIDROVALTRAT? OR ISOVALEROHYDROXYDIHYDROVALTRAT?
 OR 28325-56-6 OR 56585-34-3
 L25 129 S ISOVALTRAT? OR 31078-10-1
 L26 2 S NAPHTHYRIDYLMETHYLKETONE OR NAPHTHYRIDYL(W)METHYL(W)KETONE
 L27 142 S OLIVIL
 L28 8 S L27 AND VALERIAN?
 L29 170 S L18-L26
 L30 542 S L17 OR L29
 L31 801 S VALEPOTRIATE? OR VALERANE OR 5050-72-6 OR VALERANAL
 L32 126 S VALERANONE OR JATAMANSONE OR 55528-90-0 OR 1803-39-0 OR 5090-54-0
 L33 72 S VALERENAL OR 4176-16-3 OR VALERENOL OR 101628-22-2
 L34 265 S VALERENIC(W)ACID OR 3569-10-6
 L35 1 S VALERIANIE
 L36 3 S VALERIANINE OR 30768-38-1 OR 30625-42-4 OR 30625-43-5
 L37 9 S VALERINE OR VALERNYL(W)ACETATE
 L38 4 S VALERACYL OR VALIRACIL OR 109617-17-6
 L39 340 S VALTRATE? OR ISOVALTRATE?
 L40 32 S VALMANE
 L41 163 S 78769-65-0
 L42 307 S 18296-44-1
 L43 665 S L31 AND VALERIAN?
 L44 1195 S L31-L42
 L45 3280 S VALERIAN OR 8008-88-6 OR 8057-47-6 OR 97927-02-1
 L46 1367 S L30 OR L44
 L47 101 S VALERIANAE(2A)RADIX
 L48 1725 S VALERIANA(W)OFFICINALIS
 L49 1799 S L47 OR L48
 L50 9394 S JATAMANSI OR WALLICHII OR AMURENSIS OR SORBIFOLIA OR ADSCENDENS OR
 HARDWICKII OR FAURIEI
 L51 49679 S PROCERA OR EDULIS OR LAXIFLORA OR PRIONOPHYLLA OR GLECHOMIFOLIA
 OR ITALICA OR TUBEROSA
 L52 11762 S ALTERNIFOLIA OR GLECHOMIFOLIA OR MICROPHYLLA OR ALLIARIIFOLIA
 OR SITCHENSIS
 L53 11972 S THALICTROIDES OR KILIMANDASCHARICA OR NITIDA OR EXALTATA OR
 PROCURENS OR STOLONIFERA
 L54 526 S STUBENDORFI OR PYROLAEOFOLIA OR KILIMANDASCHARICA OR DISCOIDEA
 OR GLECHOMIFOLIA
 L55 12305 S JAVANICA OR ALLIARIIFOLIA OR PRIONOPHYLLA
 L56 3059 S L45 NOT (L50 OR L51 OR L52 OR L53 OR L54 OR L55)
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 L58 4776 L46 OR L57
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 374 ANSWERS '804-1177' FROM FILE CABA
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 9 ANSWERS '2136-2144' FROM FILE ESBIODBASE
 113 ANSWERS '2145-2257' FROM FILE IPA
 541 ANSWERS '2258-2798' FROM FILE BIOSIS
 172 ANSWERS '2799-2970' FROM FILE TOXCENTER
 19 ANSWERS '2971-2989' FROM FILE FSTA
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Update on Valerian – September 2009

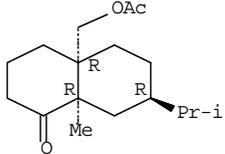
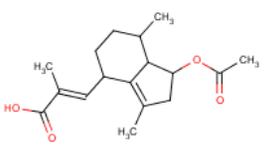
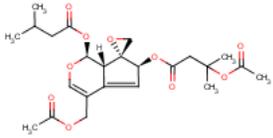
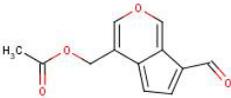
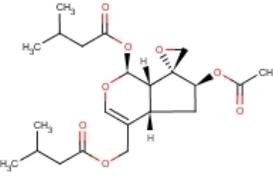
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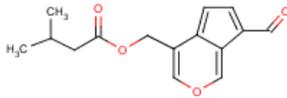
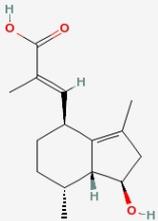
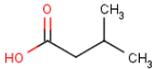
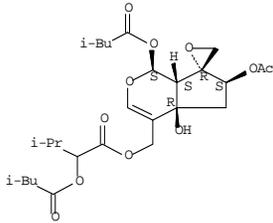
showing the actual search strategy is shown below. A total of 272 titles were identified, 88 of which were duplicates. Of the remaining 184 citations, 42 records were selected for further review.

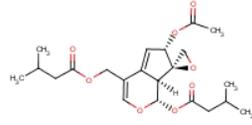
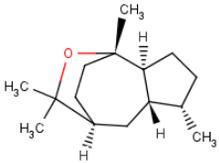
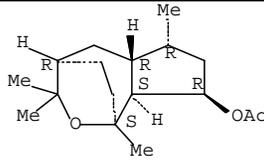
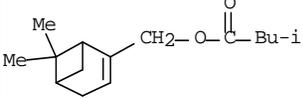
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VALEPOTRIATE? OR 25161-41-5
L4 122 S ACEVALTRATE
L5 121 S ACTINIDINE OR 524-03-8 OR 32115-42-7 OR 11010-93-8
L6 0 S 15524-83-1
L7 74 S BALDRINAL? OR 18234-46-3
L8 0 S CHATARINE
L9 3 S CHATININE OR 1390-84-7
L10 3 S DESISOVALEROYL(2A)ACETYLVALTRATE
L11 247 S DIDROVALTRAT? OR DIHYDROVALTRAT? OR DIHYDROISOVALTRAT? OR
DIHYDROISOVALEPOTRIATE? OR 18296-45-2
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OR 61114-24-7
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HOMODIHYDROISOVALTRAT?
L23 23 S ISOVALEROXYHYDROXYDIDROVALTRAT? OR ISOVALEROHYDROXYDIHYDROVAL
OR 28325-56-6 OR 56585-34-3
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L40 45 S (L28-L39) AND (2009/PY OR 20080901-20081231/UP)
L41 188 S (VALERIAN OR 8008-88-6 OR 8057-47-6 OR 97927-02-1) AND (2009/PY OR
20080901-20081231/UP)
L42 52 S L27 OR L40
L43 114 S VALERIANAE(2A)RADIX
L44 1897 S VALERIANA(W)OFFICINALIS
L45 141 S (L43 OR L44) AND (2009/PY OR 20080901-20081231/UP)
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HARDWICKII OR FAURIEI
L47 53328 S PROCERA OR EDULIS OR LAXIFLORA OR PRIONOPHYLLA OR GLECHOMIFOLIA
OR ITALICA OR TUBEROSA
L48 12421 S ALTERNIFOLIA OR GLECHOMIFOLIA OR MICROPHYLLA OR ALLIARIIFOLIA
OR SITCHENSIS
L49 12810 S THALICTROIDES OR KILIMANDASCHARICA OR NITIDA OR EXALTATA OR
PROCURENS OR STOLONIFERA
L50 550 S STUBENDORFI OR PYROLAEOFOLIA OR KILIMANDASCHARICA OR DISCOIDEA
OR GLECHOMIFOLIA
L51 13532 S JAVANICA OR ALLIARIIFOLIA OR PRIONOPHYLLA
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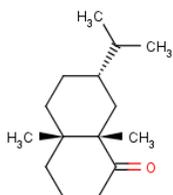
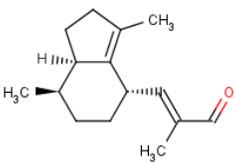
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         5 ANSWERS '112-116' FROM FILE IPA
        20 ANSWERS '117-136' FROM FILE BIOSIS
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         1 ANSWER '180' FROM FILE FSTA
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Appendix C: Selected Constituents of *V. officinalis* Extracts and Essential Oil

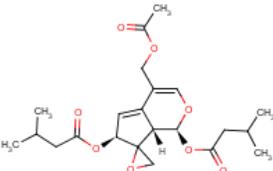
Constituent and Synonyms	CAS No.	PubChem CID	Structure ^a	Commercial Products	Other Extracts (%)	Essential Oil, (%) ^{b,c}	Comments and References
Acetoxyvaleranone; 15-Acetoxyvaleranone; Kanokonyl acetate; 1(2 <i>H</i>)-Naphthalenone, 4a-[(acetyloxy)methyl]-octahydro-8a-methyl-7-(1-methylethyl)-, (4 <i>aR</i> ,7 <i>R</i> ,8 <i>aR</i>)-rel- (CA INDEX NAME)	3429-29-6					5.6-9.6 (7.6)	Safaralie et al. (2008 [PMID:18164718]). Structure shown is from only specific acetoxyvaleranone found in the literature for <i>Valeriana</i> spp. (Fokialakis et al., 2002).
Acetoxyvalerenic acid; Acetylvalerenolic acid; 2-Propenoic acid, 3-[1-(acetyloxy)-2,4,5,6,7,7a-hexahydro-3,7-dimethyl-1 <i>H</i> -inden-4-yl]-2-methyl- (CA INDEX NAME)	81397-67-3	6537490		See total valerenic acids	0.299 (based on the root)		Extracts: Roots from 60 <i>V. officinalis</i> provenances (Stahn and Bomme, 1998)
Acetoxyvaltrate; Acevaltrate	25161-41-5	65717					Toxicity discussed in this report.
Baldrinal	18234-46-3	159846		See total baldrinals			Toxicity discussed in this report.
Didrovaltrate (INN); Dihydrovaltrate; Dihydroisovaltrate; Didrovaltratum; Dihydroisovalepotriate; Butanoic acid, 3-methyl-, (1 <i>S</i> ,2' <i>R</i> ,4 <i>aS</i> ,6 <i>S</i> ,7 <i>aS</i>)-6-(acetyloxy)-4 <i>a</i> ,5,6,7 <i>a</i> -tetrahydro-4-[(3-methyl-1-oxobutoxy)methyl]spiro[cyclopenta[<i>c</i>]pyran-7(1 <i>H</i>),2'-oxiran]-1-yl ester (CA INDEX NAME)	18296-45-2	65689					Toxicity discussed in this report.

Constituent and Synonyms	CAS No.	PubChem CID	Structure ^a	Commercial Products	Other Extracts (%)	Essential Oil, (%) ^{b,c}	Comments and References
Homobaldrinal	67910-07-0	49999		See total baldrinals			Toxicity discussed in this report.
Hydroxyvalerenic acid; 2-Propenoic acid, 3-[(1 <i>R</i> ,4 <i>S</i> ,7 <i>R</i> ,7 <i>aR</i>)-2,4,5,6,7,7 <i>a</i> -hexahydro-1 <i>H</i> -hydroxy-3,7- dimethyl-1 <i>H</i> -inden-4-yl]-2-methyl-, (2 <i>E</i>)- (CA INDEX NAME)	1619-16-5	6537505		See total valerenic acids	0.012 (based on the root)	0.012 (based on the root)	Sedative action Oils: From 60 <i>V. officinalis</i> provenances (Stahn and Bomme, 1998)
Isovaleric acid; 3-Methylbutanoic acid	503-74-2	10430				0.2 (fresh roots) and 13.0 (dried roots); 0-2.1 (mean 0.82); 18.7-41.8 (only CO ₂ extract)	Skin irritant. Max. no-effect in rat diet was 5% (HSDB, 2003); Oils: Roots of British Columbian plants. Enzymatic hydrolysis during drying may increase concentrations (Lopes et al., 2005). Other oils: Raal et al. (2007); Safaralie et al. (2008 [PMID:18164718])
Isovaleroxyhydroxy-didrovaltrate; Isovaleroxyhydroxy-didrovaltratum; Isovaleroxyhydroxy-dihydrovaltrate; Butanoic acid, 3-methyl-2-(3-methyl-1-oxobutoxy)-, [(1 <i>S</i> ,2' <i>R</i> ,4 <i>aR</i> ,6 <i>S</i> ,7 <i>aS</i>)-6-(acetyloxy)-4 <i>a</i> ,5,6,7 <i>a</i> -tetrahydro-4 <i>a</i> -hydroxy-1-(3-methyl-1-oxobutoxy)spiro[cyclopenta[<i>c</i>]pyran-7(1 <i>H</i>),2'-oxiran]-4-yl]methyl ester (CA INDEX NAME)	28325-56-6						

Constituent and Synonyms	CAS No.	PubChem CID	Structure ^a	Commercial Products	Other Extracts (%)	Essential Oil, (%) ^{b,c}	Comments and References
Isovaltrate; Isovaltratum; Butanoic acid, 3-methyl-, (1 <i>S</i> ,2' <i>R</i> ,6 <i>S</i> ,7 <i>aS</i>)-6-(acetyloxy)-6,7 <i>a</i> -dihydro-4-[(3-methyl-1-oxobutoxy)methyl]-spiro[cyclopenta[<i>c</i>]-pyran-7(1 <i>H</i>),2'-oxiran]-1-yl ester (CA INDEX NAME)	31078-10-1	92275					Toxicity discussed in this report.
Kessane	3321-66-2	6451544				0.2-3.8 (0.7-8.2); 0-1.5 (mean 0.80); 0.3-0.8 (CO ₂ only)	No toxicity studies found. Oils: Bos et al. (1997); Raal et al. (2007); Safaralie et al. (2008 [PMID:18164718])
Kessyl acetate; α -Kessyl acetate; 1,4-Ethano-1 <i>H</i> -cyclopent[<i>c</i>]oxepin-8-ol, octahydro-1,3,3,6-tetramethyl-, 8-acetate, (1 <i>S</i> ,4 <i>R</i> ,5 <i>aR</i> ,6 <i>R</i> ,8 <i>R</i> ,8 <i>aS</i>)- (CA INDEX NAME)	3925-77-7	6428681 23305099				0.1-12.6 (ND-2.1); 0.4-2.3 (mean 1.2)	No toxicity studies found. Kessyl acetate, kessyl glycol, and the glycol mono- and diacetates have sedative action and are present in the essential oil at $\leq 0.1\%$ (Takeuchi et al., 2001). Oils: Bos et al. (1997); Raal et al. (2007)
Myrtenyl isovalerate; 2-Pinen-10-yl isovalerate; Butanoic acid, 3-methyl-, (6,6-dimethylbicyclo[3.1.1]-hept-2-en-2-yl)methyl ester (CA INDEX NAME)	33900-84-4					1.6-10.5 (0.5-3.3); 1.1-2.5 (mean 1.52)	No toxicity studies found. Oils: Bos et al. (1997); Raal et al. (2007)
Total other isovalerates (13 at individual concns. $\leq 3.8\%$ [Bos et al., 1997] or 7 with individual concns. $< 5\%$ [Raal et al. (2007)])						1.9-11.1 (ND-12.9); 1.0-7.2 (sum of means 3.41)	Oils: Isovalerates included <i>cis</i> - and <i>trans</i> -valerenyl isovalerates (Bos et al., 1997; Raal et al., 2007)
Total baldrinals				$\leq 0.988\text{mg/dose}$ (standardized to valepotriates concentration)			Braun (1982, cited by WHO, 1999)

Constituent and Synonyms	CAS No.	PubChem CID	Structure ^a	Commercial Products	Other Extracts (%)	Essential Oil, (%) ^{b,c}	Comments and References
Total valepotriates (valtrates)					≤4.5 (5.53 in rhizomes, 3.5 in roots); 1.0-3.3; 0.092-0.367	1.1-1.4	Extracts from: dried underground parts (Konovalova et al., 1983); rhizomes and roots grown in Moscow from seeds of Russia, Czechoslovakia, Hungary, Austria, Sweden, and the Netherlands (Konovalova et al., 1991); roots and rhizomes from Swedish cultivars (Gao and Björk, 2000 [PMID:11449465]) Oils: Plants grown in The Netherlands (Bos et al., 1996)
Total valerenic acids				<u>U.S. mkt.</u> : 0.4-0.9% (daily doses 0.6-4.0 mg) (8 that met label claims, but 2 had 0.98-1.0 µg Cd/capsule); 5 had 50-82% of label claim and 3 had <20% (<1%, 5%, and 17%) (daily doses 0.008-1.96 mg) (one had 2.09 µg Pb/capsule)	0.630 (based on the root)		16 U.S. products; 8 powdered extracts (4 in capsule and 4 in tablet form) met label claims for total valerenic acid and its hydroxy and acetoxy derivatives. The remaining 8 were: 3 capsules, 2 tablets, and 3 liquid exts. (ConsumerLab.com, 2006a,b,c). Extracts from roots of 60 <i>V. officinalis</i> provenances (oil content: 0.13-0.52% v/v) (Stahn and Bomme, 1998)
Valeranone; (±)-Valeranone; 1(2 <i>H</i>)-Naphthalenone, octahydro-4a,8a-dimethyl-7-(1-methylethyl)-, (4 <i>aR</i> ,7 <i>S</i> ,8 <i>aS</i>)-rel- (CA INDEX NAME)	55528-90-0	171455				0.5-8.2 (0.2-10.4); 0.5-9.4 (mean 4.22)	Toxicity discussed in this report. Possible sedative or muscle-relaxant activity (TOXLINE, undated-b). Oils: Bos et al. (1997); Raal et al. (2007)
Valerenal; 2-Propenal, 3-(2,4,5,6,7,7 <i>a</i> -hexahydro-3,7-dimethyl-1 <i>H</i> -inden-4-yl)-2-methyl-, [4 <i>S</i> -(4 <i>α</i> (<i>E</i>),7 <i>β</i> ,7 <i>α</i>)]-	4176-16-3	6440942			0.002-0.264 (based on the root)	0.4-12.4 (0.3-3.8); 0-14.7 (mean 9.38)	Possible sedative or muscle-relaxant activity; may affect dopamine activity in the brain of rats (PubMed, undated ; TOXLINE, undated-c). Extracts: Roots of plants from southern Germany (Noller, 1989 diss.). Oils: Bos et al. (1997); Raal et al. (2007)

Constituent and Synonyms	CAS No.	PubChem CID	Structure ^a	Commercial Products	Other Extracts (%)	Essential Oil, (%) ^{b,c}	Comments and References
Valerenol; 2-Propen-1-ol, 3-[(4 <i>S</i> ,7 <i>R</i> ,7 <i>aR</i>)-2,4,5,6,7,7 <i>a</i> -hexahydro-3,7-dimethyl-1 <i>H</i> -inden-4-yl]-2-methyl-, (2 <i>E</i>)- (CA INDEX NAME)	101628-22-2					0.0-0.8 (mean 0.26); 3.7-5.2 (CO ₂ extract)	Potent anxiolytic activity in mice (Benke et al., 2009 [PMID:18602406]). No toxicity studies found. Oils: Raal et al. (2007); Safaralie et al. (2008 [PMID:18164718])
Valerenic acid; 2-Propenoic acid, 3-[(4 <i>S</i> ,7 <i>R</i> ,7 <i>aR</i>)-2,4,5,6,7,7 <i>a</i> -hexahydro-3,7-dimethyl-1 <i>H</i> -inden-4-yl]-2-methyl-, (2 <i>E</i>)- (CA INDEX NAME)	3569-10-6	6440940			0.301-1.234; 0.331; 0.002-0.559 (all based on the root)	0.3-2.8 (0.1-4.7); 0.0-0.9 (mean 0.28); 8.2-11.8 (8.0); 0.8-0.9	Sedative action. Toxicity discussed in this report. Extracts from rhizomes and roots grown in Moscow from seeds of Russia, Czechoslovakia, Hungary, Austria, Sweden, and the Netherlands (Konovalova et al., 1991). Roots from sources (Stahn and Bomme, 1998). Roots from southern Germany (Noller, 1989 diss.). Oils: Bos et al. (1997); Raal et al. (2007); Safaralie et al. (2008 [PMID:18164718]). Plants grown in The Netherlands (Bos et al., 1996)
(<i>Z</i>)- or <i>cis</i> -Valerenyl acetate; 2-Propen-1-ol, 3-[(4 <i>S</i> ,7 <i>R</i> ,7 <i>aR</i>)-2,4,5,6,7,7 <i>a</i> -hexahydro-3,7-dimethyl-1 <i>H</i> -inden-4-yl]-2-methyl-, 1-acetate, (2 <i>Z</i>)- (CA INDEX NAME)	101527-78-0					0.2-0.8 (ND-0.6); 0.0-1.6 (mean 0.94); 4.5-6.5 (7.9)	Oils: Bos et al. (1997); Raal et al. (2007); Safaralie et al. (2008 [PMID:18164718])
Valerianol; 2-[(2 <i>R</i> ,8 <i>aR</i>)-8,8 <i>a</i> -dimethyl-2,3,4,6,7,8-hexahydro-1 <i>H</i> -naphthalen-2-yl]propan-2-ol (IUPAC name)	20489-45-6	5315163				0.3-16.7 (mean 3.86)	Oils: Raal et al. (2007)

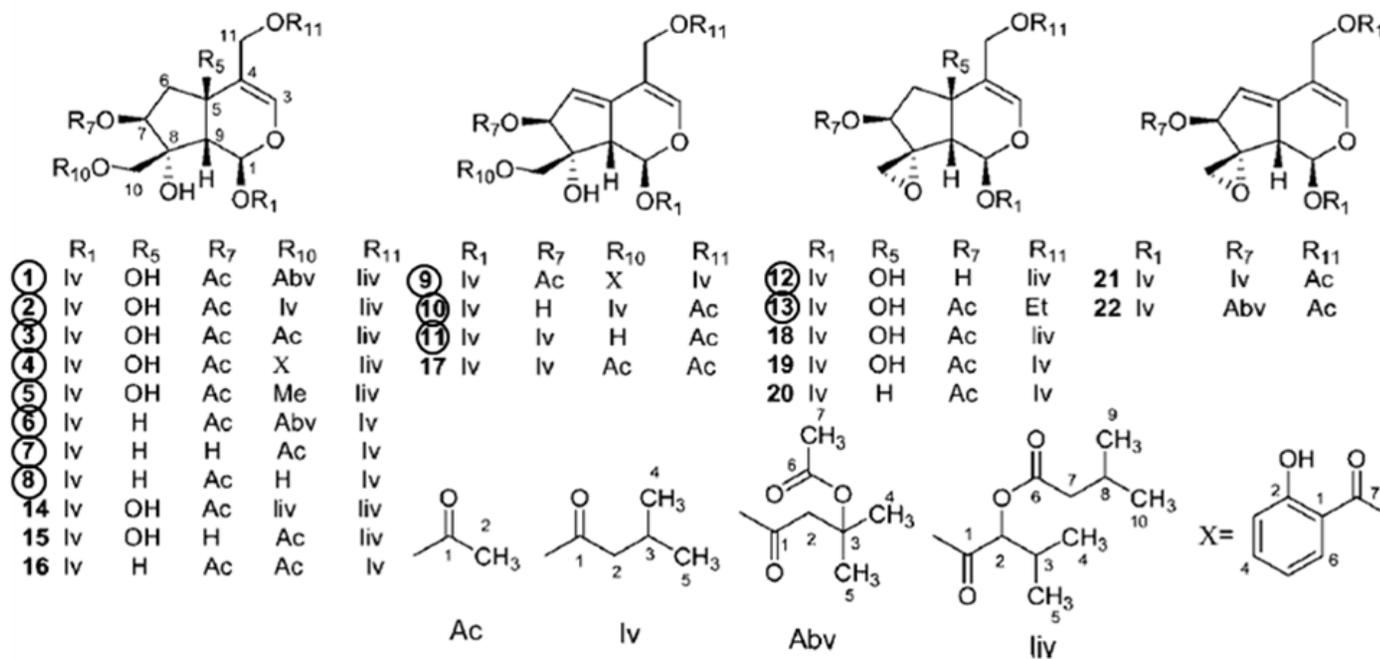
Constituent and Synonyms	CAS No.	PubChem CID	Structure ^a	Commercial Products	Other Extracts (%)	Essential Oil, (%) ^{b,c}	Comments and References
Valtrate; Valepotriate; Valtratam; Butanoic acid, 3-methyl-, 1,1'-[(1 <i>S</i> ,2' <i>R</i> ,6 <i>S</i> ,7 <i>aS</i>)-4-[(acetyloxy)methyl]-6,7a-dihydrospiro[cyclopenta[<i>c</i>]pyran-7(1 <i>H</i>),2'-oxirane]-1,6-diyl] ester (CA INDEX NAME)	18296-44-1	493850					Toxicity reviewed in this report.
Unidentified oxidized sesquiterpenes (2), C ₁₅ H ₂₄ O (includes only those with at least one concn. ≥5%)						1.4-13.8 (ND) and 0.9-6.1 (ND-4.9)	Oils: Bos et al. (1997)
Unidentified oxidized sesquiterpenes (3), C ₁₅ H ₂₆ O (includes only those with at least one concn. ≥5%)						0.2-9.7 (ND-0.7) and 14.5-15.3 (ND-19.5) and 4.1-5.4 (ND-0.4)	Oils: Bos et al. (1997)
Unknown						0.3-10.9 (ND-0.6)	Oils: Bos et al. (1997)
Unidentified sesquiterpene acetate, C ₁₇ H ₂₆ O ₂						tr-10.2 (0.2-13.8)	Oils: Bos et al. (1997)
Unidentified sesquiterpene acetate, C ₁₇ H ₂₈ O ₂						1.3-7.1 (ND-0.5); 0.0-0.6 (mean 0.20)	Oils: Bos et al. (1997); Raal et al. (2007)

^a Structures, where available, obtained from PubChem, ChemIDplus, and Registry files.

^bThe root essential oils of Bos et al. (1997) (16 from *V. officinalis* subspecies *officinalis* and 10 from three other subspecies, from various European sources) and Raal et al. (2007) (Estonian plants) and those of Safaralie et al. (2008 [PMID:18164718]) with values shown in parenthesis were prepared by hydrodistillation. Other essential oils from Iranian *V. officinalis* roots prepared by Safaralie et al. (2008 [PMID:18164718]) were extracted by supercritical carbon dioxide (the first values given in the table for this reference).

^c *V. officinalis* essential oils contained several nonunique terpenes in concentrations of >5%, at least in some samples. These included the most common major constituent, bornyl acetate (PubChem Compound ID [CID]: 6448), a compound with a sedative action in mice (TOXLINE, undated-d), at concentrations of 2.3-35.5%. Others were *allo*-aromadendrene (CID: 91354), 0.3-7.6% (mean 4.42%); camphene (CID: 6616), 0.1-8.1%; (*E*)-caryophyllene [β - or *trans*-caryophyllene] (CID: 5281515), 1.2-5.1%; eudesma-2,6,8-triene (not found in PubChem), 0.5-7.6%; β -eudesmol (CID:91457), ND-8.3%; α -fenchene (CID:28930), 0.6-5.8%; and myrtenyl acetate (CID:61262) [toxicology review in TOXLINE, undated-e], trace-9.1% (Bos et al., 1997; Raal et al., 2007; Safaralie et al., 2008 [PMID:18164718]). Other studies have reported other compounds as major constituents in essential oils, e.g. 3-thujene, β -pinene, sabinol (Wu et al., 1999 [Korean]); spathulenol (4.1-5.2%), (-)-valerena-4,7(11)-diene (4.6-7.2%) in subspecies *collina* (Bos et al., 2000); 5-isocedranol (21.7%), *cis,cis*-farnesol (15%); guaiol (7.7%), and cubenol in an Iranian oil prepared by hydrodistillation (Ashnagar et al., 2006; possibly some confusion with *Nardostachys jatamansi*).

Eight newly identified constituents of *Valeriana jatamansi* are shown in the diagram below (circled numbers) that was published in a study described by Lin et al. (2009 [PMID:19245261]). These compounds were isolated from the ethanolic extract of the whole plant. The chemicals were classified as acylated iridoids and referred to as jatamanvaltrates A-M. The remaining chemicals shown in the diagram are known valepotriates that also were isolated from the plant extract.



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- Acetoxyvaltrate; CID: 65717. Internet address: <http://pubchem.ncbi.nlm.nih.gov/summary/summary.cgi?cid=65717>.
- Baldrinal; CID: 159846. Internet address: <http://pubchem.ncbi.nlm.nih.gov/summary/summary.cgi?cid=159846>.
- Didrovaltratum; CID: 65689. Internet address: <http://pubchem.ncbi.nlm.nih.gov/summary/summary.cgi?cid=65689>.
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- Isovaleric acid; CID: 10430. Internet address: <http://pubchem.ncbi.nlm.nih.gov/summary/summary.cgi?cid=10430>.
- Isovaltrate; CID: 92275. Internet address: <http://pubchem.ncbi.nlm.nih.gov/summary/summary.cgi?cid=92275>.
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