trans-Resveratrol
[501-36-0]

Review of Toxicological Literature

March 2002

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Prepared for

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Executive Summary

Nomination

trans-Resveratrol was nominated for toxicology studies by the National Institute of Environmental Health Sciences (NIEHS) based on the widespread human exposure to resveratrol through natural dietary sources and dietary supplement use, and concern that it has not been sufficiently evaluated for potential toxicological effects.

Non-Toxicological Data

General Description: *trans*-Resveratrol is a polyphenol that occurs naturally in grapes, peanuts, and a number of other plants. It is found in foods/drinks made from grapes and peanuts, and also in a number of herbal remedies, both alone and as part of plant extracts.

Commercial Availability, Production, and Uses: *trans*-Resveratrol is produced commercially by several companies. A commercial extraction method involves using alcohol and water to produce *trans*-resveratrol from *Polygonum cuspidatum*. Resveratrol compounds may be produced or extracted for research purposes by treating cell suspension cultures of grapes with a natural substance from a fungus.

Resveratrol compounds have long been found in herbal medicines. Health claims of oral dietary supplements containing *trans*-resveratrol include protection from free-radical damage, inhibition of arthritic inflammation, inhibition of the cyclooxygenase-2 enzyme, protection of blood vessels, protection against cardiovascular disease and cancer, and alleviation of menopausal symptoms. A patent exists for the use of resveratrol to prevent and to treat restenosis after coronary disease treatment, and a patent application was filed for using resveratrol compounds with nucleoside analogs for treating HIV-1 infections.

Environmental Occurrence and Persistence: Plants that produce *trans*-resveratrol include grapes, peanuts, eucalyptus, spruce, lily, mulberries, groundnut, and members of the knotweed and hellebore genera. Plants synthesize *trans*-resveratrol when infected by microbes exposed to ultraviolet radiation, or when injured or subjected to stress; *trans*-resveratrol levels peak upon exposure to such stress.

Human Exposure: Human exposure to resveratrol compounds is mainly through ingestion, particularly of grapes, peanuts, and their products. Levels are higher in grapes and in grape products than in peanut products. The highest levels in grape products were found in red wine (≤0.02-13.4 mg/L [0.09-58.7 μM]). The highest levels in peanut products were found in boiled peanuts (0.02-1.79 μg/g [0.09-7.84 nmol/g]).

Exposure through dietary supplements is primarily oral, although one source provided information on a topical cream containing resveratrol. Recommended dosages for oral dietary supplements range from 2.495 mg to 1 g (0.01091 μmol to 4 mmol).

Regulatory Status: Manufacturers and distributors must notify the U.S. Food and Drug Administration (FDA) when they plan to market dietary supplements that contain "new dietary ingredients" (Section 413b of the Food, Drug, and Cosmetic Act [FDCA], 21 U.S.C. 350b). Other regulations that apply include 21CFR Section 190.6(b)(4), regarding safety; and Section 403(r)(6) of FDCA, 21, U.S.C. 343 (r)(6), regarding evaluation as a drug.

Toxicological Data

Note: When specified by the author(s), isomers were named. In most studies, "resveratrol" was used.

Human Studies: Adverse effects of resveratrol have not been reported; a recommended dosage of 5-10 mg (22-44 µmol) per day was stated to be "entirely safe." Recently, the National Cancer Institute (NCI) initiated preclinical toxicity studies on *trans*-resveratrol; clinical trials may also be conducted.

Chemical Disposition, Metabolism, and Toxicokinetics: In an isolated rat small intestine perfusion model, the majority of absorbed *trans*-resveratrol (administered doses of 28, 34, and 57 µM [6.4, 7.8, and 13 µg/mL]) was found in the luminal effluent (53.9%). Of this amount, free resveratrol was the dominant product (39.7%). At the vascular side, 20.5% of the administered resveratrol appeared, with the major product being the glucuronide (16.8%). Small amounts of unmetabolized resveratrol were absorbed across the enterocytes of the jejunum and ileum, while significant amounts of its glucuronide were found in the serosal fluid.

In human partially hepatectomized liver microsomes, the highest rate of *trans*-resveratrol glucuronidation (up to 1 mM [228 µg/mL] resveratrol and 1 mM uridine 5´-diphosphoglucuronic acid [UDPGA] in incubation mixture) occurred at neutral pH, and the resveratrol-glucuronide amount increased linearly with time up to 40 minutes. The reaction of resveratrol sulphation (up to 2 µM [0.5 µg/mL] resveratrol and 0.4 µM 3´-phosphoadenosine-5´-phosphosulphate [PAPS]) showed similar effects. The rates of resveratrol sulphation, similar in the human liver and duodenum, were inhibited by quercetin, fisetin, myricetin, kaempferol and apigenin; the inhibition was mixed and non-competitive. Flavonoids also inhibited resveratrol glucuronidation, but to a lesser extent. The addition of wine to the incubation mixture decreased both the rate of resveratrol sulphation and the rate of glucuronidation.

In human intestinal epithelial cell line Caco-2 cultured in Transwell, the permeability constant for resveratrol suggested that it could be orally absorbed.

In rats, resveratrol (single administration of 86 µg/kg [0.38 µmol/kg] or 43 µg/kg [0.19µmol/kg] for 15 days) in red wine was rapidly absorbed at the intestinal level, immediately entering the blood and reaching a maximum level around one hour after oral administration. The liver contained the highest concentrations (20.7 and 53.5 ng/g following single and repeated administration, respectively). Kinetic studies showed equilibrium between the absorbed resveratrol and the eliminated resveratrol. Significant cardiac bioavailability has also been observed. Given intraperitoneally (i.p.), *trans*-resveratrol (2 mg/kg [9 µmol/kg]) was rapidly absorbed and the concentration in rat blood declined in a "two-exponential" manner.

Short-term and Subchronic Exposure: In rats, daily oral administration of resveratrol (300, 1000, and 3000 mg/kg [1.31, 4.381, and 13.14 mmol/kg]) for 28 days produced nephrotoxicity, dehydration, labored breathing, hunched posture, decreased activity, rough coat, diarrhea, soft stool, and red material around the nose at the high dose. Males also had leukocytosis, and both sexes may have had anemia. Based on the results, the no observed adverse effect level (NOAEL) was 300 mg/kg/day.

In hypercholesterolemic rabbits, *trans*-resveratrol (0.06 mg/kg [0.3 µmol/kg] during days 1-5 and 1.0 mg/kg [4.4 µmol/kg] from days 6-60) promoted atherosclerosis.

Synergistic/Antagonistic Effects: Resveratrol produces a synergistic effect, as well as increased potency and availability, when combined with other antioxidants or compounds having antimutagenic or cardioprotective properties (e.g., anthocyanadins, indole-3-carbinol, and green tea extracts). A recent discovery is resveratrol's potential role in the control of HIV-1 (human immunodeficiency virus-1) replication; it may synergize with existing drugs, potentiating their antiviral effects.

In several mammary cancer cell lines, resveratrol showed mixed estrogen agonist/antagonist activities, whereas in the presence of 17β-estradiol, it was an antiestrogen. For example, in MCF-7 and S30 cells,

resveratrol alone showed weak estrogenic response, but when combined with estradiol (1 nM), a dose-dependent antagonism occurred. In addition, progesterone receptor (PR) protein expression was induced with the compound alone, but when combined with estradiol, the expression was suppressed. Administered at pharmacological doses, resveratrol (52-74 µM [12-17 µg/mL]) suppressed the growth of estrogen receptor (ER)-positive breast cancer cells (KPL-1 and MCF-7) and ER-negative breast cancer cells (MKL-F) stimulated by linoleic acid. Resveratrol (1 pM-1 µM [2.28 x 10^{-7}-0.2 µg/mL]) was also an agonist of steroid receptors. In MCF-7 and T47-D cells, it interacted with estradiol (at the nanomolar range) simultaneously with PRs (at the picomolar range). A significant increase in the growth of MCF-7 cells also occurred with *cis*-resveratrol (10 and 25 µM [2.3 and 5.7 µg/mL]). In MVLN cells, *trans*-resveratrol (10 and 25 µM) and *cis*-resveratrol (25 µM) significantly increased luciferase activity compared to estradiol. In the presence of estradiol, both isomers at the same doses functioned as superagonists of estradiol. In the MCF-7 and MVLN cell lines, *cis*-resveratrol was less effective than *trans*-resveratrol. Resveratrol also exhibited estradiol antagonist activity for ER-α with select estrogen response elements and no such activity with ER-β.

In contrast to *in vitro* tests, results of an *in vivo* study using weanling rats suggested that resveratrol (oral; 1, 4, 10, 40, and 100 µg [0.004, 0.02, 0.044, 0.18, and 0.438 µmol] per day for six days) was not an agonist at the ER (e.g., it had no effect on bone formation and mineralization rates versus the estrogen 17β-estradiol). However, when resveratrol and 17β-estradiol were administered in combination (1000 and 100 µg [4.381 and 0.438 µmol], respectively), a synergistic effect was observed—i.e., a significant decrease in cholesterol levels was seen in the animals. Oral or subcutaneous (s.c.) administered of *trans*-resveratrol (0.03-575 mg/kg [0.1 µmol/kg - 2.5 mmol/kg]) produced no estrogenic response in the uterine tissue of the animals.

Cytotoxicity: In bovine capillary endothelial (BCE) cells stimulated with fibroblast growth factor-2 (FGF-2), resveratrol inhibited capillary endothelial cell growth in a dose-dependent manner (1-10,000 nM [0.0002-2.2825 µg/mL]), the phosphorylation of mitogen-activated protein kinases (MAPKs) (10 and 20 µM [2.3 and 4.6 µg/mL]), and FGF-2 and vascular endothelial growth factor (VEGF)-induced proliferation of porcine aortic cell lines expressing PAE/FGFR-1 and PAE/VEGFR-2, respectively, in a dose-dependent manner (0.5-10 µM [0.1-2.3 µg/mL]). In human gingival epithelial Smulow-Glickman (S-G) cells, toxicity leveled off between day 2 and 3 for a 3-day continuous exposure to resveratrol (5-150 µM [1-34.2 µg/mL]). At concentrations >75 µM (17 µg/mL), irreversible damage to cell proliferation occurred, and the presence of an hepatic S9 microsomal fraction did not potentiate or improve the cytotoxicity. Additionally, the cytotoxicity of hydrogen peroxide or nitrogen oxide to S-G cells was not affected by resveratrol.

In mice with skin wounds, resveratrol (5.7 µg/mL [25 µM]) was an angiogenesis inhibitor. In corneal micropockets of the animals, resveratrol (oral; 0.4 µg/mL [2 µg/mL] given three days before growth factor implantation and for 15 days after surgery) significantly inhibited VEGF- and FGF-2-induced corneal neovascularization compared with controls.

In HL-60 cells, resveratrol (2.5, 5, 10, 20, 40, and 80 µg/L [0.011, 0.02, 0.044, 0.088, 0.18, and 0.35 µM]) dose-dependently inhibited [^{3}H]thymidine incorporation into DNA (by 30, 56, 67, 81, 83, and 87%, respectively) and [^{3}H]uridine incorporation into RNA (by 43, 54, 72, 85, 90, and 93%, respectively).

Reproductive and Teratological Effects: In developing white Leghorn chick embryos, resveratrol (1, 10, 25, 50, and 100 µg/disk [0.004, 0.044, 0.11, 0.22, and 0.438 µmol/disk] incubated for 48-72 hours) induced vascular zones in the developing chorioallantoic membrane.

Initiation/Promotion Studies: Resveratrol and 2-amino-1-methyl-6-phenylimidazo[4,5-b]pyridine (PhIP) were observed to equally antagonize toxicity when combined together. Resveratrol (10 µM [2.3 µg/mL])

was toxic to Chinese hamster V79MZ cells (nonmetabolically competent); coincubation with PhIP (100 µM) inhibited this effect. In contrast, resveratrol inhibited PhIP-induced mutation in V79MZh1A2 (expresses human CYP1A2) cells. Resveratrol (10 µM) in combination with PhIP (100 µM) increased the colony survival of V79MZh1B1 (expresses human CYP1B1) cells, whereas alone, neither compound was toxic.

Anticarcinogenicity: Using the mouse mammary gland organ culture model, resveratrol (1-10 µM [0.2-2.3 µg/mL]) inhibited formation of estrogen-dependent preneoplastic ductal lesions induced by 7,12-dimethylbenz[a]anthracene (DMBA).

In human breast cancer cell lines (KPL-1, MCF-7, MKL-F, T47-D, and MDA-MB-231), resveratrol (1 pM-180 µM [2 x 10^{-7}-40 µg/mL]) inhibited the growth of cell lines in a time- and/or dose-dependent manner. In addition, resveratrol (1 pM-1 µM [2 x 10^{-7}-0.2 µg/mL]) produced inhibition in the growth of prostate cancer cell lines PC3 and DU145. In LNCaP prostate cancer cells, resveratrol (100 µM [22.8 µg/mL]) inhibited cell growth in the presence of androgens.

In mice, oral administration of resveratrol (5.7 µg/mL [25 µM]; 1 mg/kg/day) significantly inhibited the growth of T241 fibrosarcomas. In rats, resveratrol (200 µg/kg [0.876 µmol/kg] body weight per day for 100 days) inhibited the number of azoxymethane (AOM)-induced aberrant crypt foci (ACF) and their multiplicity. When rats were treated with resveratrol (100 mg/kg [0.438 mmol/kg] body weight 5 days/week for >120 days) before *N*-methyl-*N*-nitrosourea (NMU) administration, a delay in tumorigenesis occurred; resveratrol increased tumor latency by 28 days. Additionally, the multiplicity of tumors and the total number of tumors were decreased compared to controls.

Genotoxicity: In the presence and absence of metabolic activation, *trans*-resveratrol (0.02-5000 µg/plate [0.09 nmol/plate – 21.91 µmol/plate) was not mutagenic in *Salmonella typhimurium* strains TA98 and TA100 and in *Escherichia coli* strain WP2*uvr*A. In the Chinese hamster lung, structural chromosome aberrations (CAs) (mainly chromatid breaks and exchanges) were induced dose-dependently at 2.5-20 µg/mL (11-88 µM). Furthermore, resveratrol (same doses) induced micronuclei (MN), polynuclei (PN), and karyorrhectic cells after a 48-hour treatment and sister chromatid exchanges (SCEs) in a dose-dependent manner at concentrations up to 10 µg/mL. Cell cycle analysis showed that resveratrol caused S phase arrest and induced apoptosis after a 48-hour treatment.

trans-Resveratrol (1, 5, 10, 25, 50, and 100 µM [0.2, 1, 2.3, 5.7, 11, and 22.8 µg/mL]) strongly cleaved plasmid DNA (i.e., strand excision or relaxation of pBR322) in the presence of Cu^{2+} at neutral pH and under aerobic conditions. Under anaerobic conditions, however, increasing the concentration of resveratrol failed to enhance the efficiency of DNA cleavage. Resveratrol was also found to be capable of binding to DNA. In the presence of ascorbic acid or glutathione, resveratrol (0.1 mM) lost its ability to promote hydroxyl-radical (•OH) formation by DNA-bound Cu^{2+} and was instead a powerful antioxidant. Resveratrol (10 µM [2.3 µg/mL]) significantly stimulated DNA strand breaks induced by adenosine 5´-diphosphate (ADP)-Fe^{3+} in the presence of hydrogen peroxide. By reducing ADP-Fe^{3+}, resveratrol acted as a prooxidant of DNA.

Other Data: In CD2F1 mice, *cis*- and *trans*-resveratrol (oral; 1000 µg/kg [4.381 µmol/kg] per day for five or ten days) caused almost complete inhibition of 7-ethoxyresorufin-*o*-dealkylation (EROD) activity (CYP1A2). No effect was observed on ethoxycoumarin-*o*-deethylation (ECOD) activity (CYP1A2/2E1) or benzo[a]pyrene metabolism. It was an effective inhibitor of recombinant human estrogen sulfotransferase (EST) (IC_{50} = 1.6 µM) and recombinant human P form phenolsulfotransferase (PST), an enzyme involved in carcinogen bioactivation (IC_{50} = 0.2 µM). In intact human hepatoma Hep G2 cells, inhibition of P-PST decreased fourfold (IC_{50} = 0.8 µM).

In rats orally administered resveratrol (8 mg/kg [0.04 mmol/kg]), CYP2E1 (chlorzoxazone 6-hydroxylation) and protein level in liver microsomes were significantly reduced 24 hours after administration. In human microsomes incubated with resveratrol (low micromolar levels), CYP1A2 (methoxyresorufin *O*-demethylation) and CYP3A4 (erythromycin demethylation) were inhibited, while CYP2E1 activity was moderately increased. Resveratrol also induced Phase 2 biotransformation.

Resveratrol (6-100 µM [1-22.8 µg/mL]) inhibited the growth and tube formation of bovine aorta endothelial (BAE) cells in a dose-dependent manner. In addition, DMBA metabolism by liver microsomes was inhibited *in vitro* in a dose-dependent manner by the compound.

Structure-Activity Relationships

Several compounds show structural similarities to *trans*-resveratrol. Kaempferol, for example, has a 4´-hydroxyl group in the B-ring and a 2,3-double bond in the C-ring, which allows conjugation across the A-ring containing the meta dihydroxy structure. *trans*-Resveratrol is also structurally similar to the synthetic estrogenic agent diethylstilbestrol (DES). In contrast to resveratrol, DES induced polyploidy *in vitro*. Like resveratrol, DES strongly inhibited nicotinamide adenine dinucleotide phosphate (NADPH)- and ADP-Fe^{3+}-dependent microsomal lipid peroxidation; an IC_{50} of 1.1 µM was obtained versus 4.8 µM for resveratrol. Both compounds strongly inhibited the reaction at the initiation and propagation stages. Other flavonoids, including quercetin, are very effective inhibitors of iron-dependent lipid peroxidation; their extent of reduction of ADP-Fe^{3+}, however, was less than that of resveratrol. DES, on the other hand, caused no reduction of ADP-Fe^{3+} or EDTA-Fe^{3+}. It also had no effect on DNA damage.

In several chemical disposition and toxicokinetic studies, the activity or effect of resveratrol was compared to that of quercetin. In the human intestinal epithelial cell line Caco-2, the permeability constant for quercetin was similar to that of resveratrol. In addition, quercetin, like resveratrol, was a strong inhibitor of P-PST (IC_{50} = 0.1 µM). In intact human hepatoma Hep G2 cells, this decreased by 25-fold (IC_{50} = 2.5 µM); the hepatocyte had a greater metabolism of quercetin than of resveratrol.

Resorcinol produced Cu^{2+}-dependent DNA strand excision under oxidative conditions. Having the same structural elements as this compound, the DNA-cleaving ability of resveratrol has been studied.

The NTP has conducted short-term toxicity, carcinogenicity, and/or genotoxicity tests on the above three chemicals. Below is a summary of available tests and their results.

<u>Diethylstilbestrol (DES)</u>: In female mice, "continuous exposure" (duration not specified) to 50 ppb DES in feed produced decreases in the fertility index, the number of litters, the number of live pups, and the proportion of pups born alive per litter. In addition, females had almost a 30% increase in pituitary weight and a majority (>75%) had no clear estrous cycle. Males given the same dose also showed a significant increase in pituitary weight as well as decreases in the weight of the epididymis, cauda epididymis, and prostate.

Mice given 2.5-100 µg/kg DES daily on gestation days 9-16 showed a decreased corrected maternal body weight gain. At 5 µg/kg, an increase in skeletal malformations was observed. At ≥10 µg/kg, the number of corpora lutea per dam was decreased and the percent resorptions per litter was increased. At the high dose, gravid uterine weight and live litter size were decreased, while relative maternal liver weight and the incidence of malformation per litter were increased.

Short-term toxicity tests have been conducted in mice; no results were available.

<u>Resorcinol</u>: In 17-day gavage studies, rats given 27.5-450 mg/kg resorcinol all survived and had no chemical-related gross or microscopic lesions. Mice, however, dosed with 37.5-600 mg/kg, had one

death (male) at 300 mg/kg, and all females (5 of 5) and 4 of 5 males died at the high dose. In a 13-week gavage study, all female (10 of 10) and 8 of 10 male rats died given 520 mg/kg. For mice, a dose of 420 mg/kg resulted in 80% death for both sexes. Other short-term toxicity tests (e.g., 24-week topical study in mice and a 14-day gavage study in rats) have been conducted; no results were available.

In two-year studies, rats (males received 225 mg/kg five days per week; females received 150 mg/kg for 15 months) exhibited decreased mean body weights and survival compared to controls. For mice, only females (receiving 225 mg/kg five days per week) showed reduced mean body weights. In both species, effects on the central nervous system—ataxia, recumbency, and tremors—were observed.

There was no evidence of carcinogenic activity in rats or mice.

Resorcinol was not mutagenic in *S. typhimurium* strains TA98, TA100, TA1535, and TA1537 in the presence and absence of metabolic activation (S9). In mouse L5178Y lymphoma cells, it induced trifluorothymidine resistance in the absence of S9. With and without S9, resorcinol induced SCEs in Chinese hamster ovary (CHO) cells, and only with S9 did it induce CAs. In *Drosophila melanogaster*, no induction of sex-linked recessive lethal mutations was seen, but an equivocal response was observed when resorcinol was administered by injection. Positive results were obtained in the MN test.

Quercetin: Studies showed some evidence of carcinogenicity. Male rats given 100-40,000 ppm quercetin in feed for two years had an increased incidence of renal tubule hyperplasia and an increased severity of nephropathy. Parathyroid hyperplasia was also seen. At the high dose, renal tubule adenomas were found in three rsats and adenocarcinomas in one other rat.

In *S. typhimurium* strains TA98 and TA100, quercetin induced mutations with and without S9. In CHO cells, both SCEs and CAs were induced. For the dihydrate, negative results were obtained in the MN test.

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1.0 Basis for Nomination

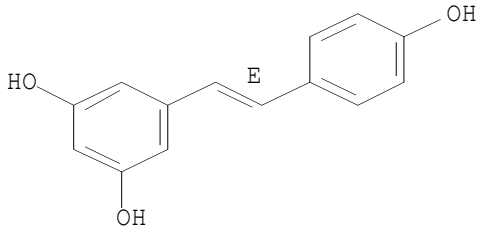
trans-Resveratrol was nominated for toxicology studies by the National Institute of Environmental Health Sciences (NIEHS) based on the widespread human exposure to resveratrol through natural dietary sources and dietary supplement use, and concern that it has not been sufficiently evaluated for potential toxicological effects.

2.0 Introduction

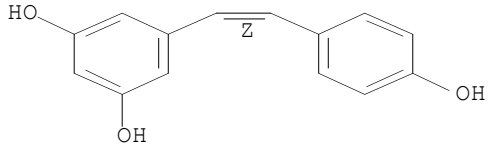
This report includes information on the *cis*-form of resveratrol, in addition to the *trans*-form, as well as *trans*-piceid (β-*D*-Glucopyranoside, 3-hydroxy-5-[(1*E*)-2-(4-hydroxyphenyl)ethenyl]-phenyl), a glucoside of *trans*-resveratrol. These compounds are often found in combination and are sometimes not identified specifically in the literature.

2.1 Chemical Identification and Analysis

trans-Resveratrol
[501-36-0]



cis-Resveratrol
[61434-67-1]



trans-Resveratrol ($C_{14}H_{12}O_3$; mol. wt. = 228.25) is also called:

1,3-Benzenediol, 5-[(1*E*)-2-(4-hydroxyphenyl)ethenyl] (9CI)
3, 5, 4′-Trihydroxystilbene
CA 1201
(*E*)-Resveratrol
3,4′, 5-Stilbenetriol (7CI, 8CI)
(*E*)-5-[2-(4-Hydroxyphenyl)ethenyl]-1,3-benzenediol
(*E*)-5-(*p*-Hydroxystyryl)resorcinol
Resveratrol (6CI)

cis-Resveratrol ($C_{14}H_{12}O_3$; mol. wt. = 228.25) is also called:
1,3-Benezenediol, 5[1*Z*]-2-(4-hydroxyphenyl)ethenyl (9CI)
1,3-Benzenediol, 5-[2-(4-hydroxyphenyl) ethenyl], (*Z*)-
(*Z*)-Resveratrol

Several methods have been used to extract resveratrol and related compounds from wine and to isolate the *trans*- and *cis*- isomers of resveratrol. They include high-performance liquid chromatography (HPLC) (Goldberg et al., 1997; Lamuela-Raventós et al., 1997; McMurtrey, 1997), liquid chromatography (LC) (McMurtrey et al., 1994; cited by McMurtrey, 1997), gas chromatography (GC), ([Barlass et al., 1987; Blache et al., 1997; both cited by Lin and Chen, 2001]; Goldberg et al., 1997), gas chromatography-mass spectrometry (GC-MS) (Soleas et al., 2001), and capillary electrophoresis (CE) ([Berzas Nevado et al., 1999; Cartoni et al., 1995; Gu et al., 1999; all cited by Lin and Chen, 2001]; Lin and Chen, 2001; Gu et al., 2000). High-speed counter-current chromatography—with the solvents chloroform, methanol, and water—was found to be an effective method for separating resveratrol from *Polygonum cuspidatum* Sieb. et Zucc.; this extraction method yields greater than 98% purity (as measured by HPLC) (Yang et al., 2001).

2.2 Physical-Chemical Properties of Resveratrol

Property	Information	Reference(s)
Physical State	Solid, powder	Budavari (1996)
Color	Off white	Budavari (1996)
Melting Point (^oC)	253-255	Budavari (1996)
Octanol-Water Partition Coefficient (LogP)	3.139±0.343	Registry (2001)
pKa (of the most acidic H-donor)	9.14±0.20	Registry (2001)
Solubility in Water (mol/L)	<0.01	Registry (2001)

2.3 Commercial Availability

Several companies produce *trans*-resveratrol commercially. Pharmascience of Montreal, Canada, produces a pure form of *trans*-resveratrol (PCT Gazette, 2001; Agriculture and Agri-Food Canada, undated). InterHealth of Concord, CA, (InterHealth, undated-a), produces a standardized extract of *trans*-resveratrol. Pharmascience calls its patented product Resverin® (PCT Gazette, 2001; Pharmascience, undated; Agriculture and Agri-Food Canada, undated; Food and Beverage America, 2000). InterHealth manufactures Protykin™, a standardized extract containing *trans*-resveratrol and emodin, also a polyphenol, from the dried rhizome of *P. cuspidatum* (InterHealth, undated-a,b,c,d). Laboratorio Italiano Biochimico Farmaceutical Lisapharma has patented a pharmaceutical composition of grape and wine polyphenols, particularly resveratrol, with yeast (Osterwalder, 1999). Other manufacturers of *trans*-resveratrol include TCI America of Portland, OR; LKT Laboratories of St. Paul, MN; and Samlong Chemical Co., Ltd. of China (Block, 2000; LKT Laboratories, Inc., undated; Samlong Chemical Co., Ltd., undated; TCI America, 1999). Moravek Biochemicals of Brea, CA produces radiolabeled resveratrol (Moravek Biochemicals, 2001).

Other companies incorporate Protykin™, Resverin®, and other formulations of resveratrol and related compounds or natural products containing it into dietary supplements (CCNow, undated; Enrich Corporation, 2000a, b; IHerb.com, undated; LaSasso, 2000; Life Extension Foundation,

2000; Mineral Connection, 2001). In dietary supplements, the isomer is not always specified; however, when the form is specified, it is typically *trans*-resveratrol.

3.0 Production Processes

Plants synthesize *trans*-resveratrol when infected by microbes or exposed to ultraviolet (UV) radiation ([Creasy and Coffee; 1988; Langcake and Pryce, 1976; Roggero and Garciaparilla, 1995; all cited by Daniel et al. 1999]; Deffieux et al., 2000; Stockley, 1996). It is also produced in response to injury and stress (Frémont, 2000; Nutrition for a Living Planet, undated). In response to these factors, plants synthesize one molecule of *trans*-resveratrol from one molecule *p*-coumaroyl-CoA and three molecules of malonyl-CoA (Daniel et al., 1999; Nutrition for a Living Planet, undated; Soleas et al., 1997).

Fresh grape skin contains 50 μg/g to 100 μg/g (0.22 μmol/g to 0.44 μmol/g) of *trans*-resveratrol (Hendler and Rorvik, 2001). As they ripen, grapes produce less resveratrol (Jeandet et al., 1995a; [Vrhovsek et al., 1995; cited by Daniel et al., 1999]).

Resveratrol forms are freed from the skin as wine is made ([Mattivi et al., 1995; Siemann and Creasy, 1992; both cited by Frémont, 2000]; Roggero, 1996). *cis*-Resveratrol is found in wine, but at lower levels than the *trans* isomer (Roggero and Garciaparilla, 1995; Romero-Perez et al., 1996; both cited by Daniel et al., 1999). These forms are probably created during the winemaking process (Goldberg et al., 1997; [Romero-Perez et al., 1996; Roggero and Garciaparilla, 1995; cited by Daniel et al., 1999]). *trans*- to *cis*-Resveratrol conversion occurs when the wine must (i.e., the juice from grapes) is exposed to light and oxygen (Cantos et al., 2000; Goldberg et al., 1997). The ratios of *cis*- to *trans*-resveratrol in wines vary by region (Goldberg et al., 1997).

Winemaking technique, the type of grape used, climate, and other factors all influence the levels of resveratrol found in wine. The most important factor is the length of time the skin is kept with the grape must during the winemaking process; longer times increase resveratrol concentration. In the case of white wine production, the skin is always removed prior to fermenting, giving these wines a lower resveratrol concentration than red wines. Rose wines (a combination of red and white wines) have an intermediate concentration (Frémont, 2000; Goldberg et al., 1997; Lamuela-Raventós et al., 1997; McMurtrey, 1997; Stockley, 1996; Roggero, 1996).

Commercial producers of resveratrol induce plants to produce greater quantities by adding aluminum chloride or aluminum sulfate to grape shoots and vines (Adrian et al., 1996; Jeandet et al., 2000). Production of resveratrol in harvested grapes increased twofold with irradiation by UVB light and threefold with irradiation by UVC light (Cantos et al., 2000).

Resveratrol has been produced by treating cell suspension cultures of grapes with Onozuka R-10, a cellulase derived from the fungus *Trichoderma viride* (Calderon et al., 1993). *trans*-Piceid, a glucoside of resveratrol, can be produced by growing grape plant cells in fermenters (Decendit et al., 1996). Also, resveratrol synthase genes have been isolated (Hain et al., 1996, 1997, 2000; Schroder et al., 1999) and inserted into plants, creating transgenic varieties of tobacco, grape, tomatoes, potatoes, rice, and alfalfa with higher *trans*-resveratrol concentrations (Stark-Lorenzen

et al., 1997; cited by Daniel et al., 1999; Hain et al., 1990; Paiva, 1999 abstr.; Soleas et al., 1997; Thomzik et al., 1997).

Grape plants excreted *trans*-resveratrol from leaves' wounds touching a cellulosic substratum, such as filter paper, soaked with inducers in aqueous solution. These inducers included monosaccharides, disaccharides, some polysaccharides, and Cu^{2+} ions. Alginate and mucic acid, a *Botrytis cinerea* metabolite, were the most potent inducers (Blaich and Bachmann, 1980). Resveratrol can be extracted from these plants with water and alcohol (InterHealth, undated-c), or with methanol and ethyl acetate (Vastano et al., 2000).

4.0 Production and Import Volumes

No data were available.

5.0 Uses

Traditional Asian medicine has long used the root of *P. cuspidatum,* a source of resveratrol, as a circulatory tonic, among other uses (Frémont, 2000; Hendler and Rorvik, 2001; Satchell, 2000). It is also a product of *Erythrophleum lasianthum*, a tree used in traditional medicine in South Africa (Orsini et al., 1997). Darakchasava, an herbal remedy containing resveratrol, is used as a heart tonic in Ayurvedic medicine (Hendler and Rorvik, 2001). Currently, several dietary supplements available in the United States contain resveratrol.

Health claims of supplements incorporating resveratrol include protection from free-radical damage, inhibition of inflammation such as in arthritis, inhibition of the cyclooxygenase-2 (COX-2) enzyme, enhancement of the elasticity and flexibility of muscles, relaxation and protection of blood vessels (Life Extension Foundation, 2000; Richards, 1999; Graves, 2000a; b; InterHealth, undated-b; Jarrow Formulas, 2001; Agriculture and Agri-Food Canada, undated; Natural Ways to Health, undated), improvement of cardiovascular health (Cosgrove, 2000; Enrich Corporation, 2000a; Howard, 2000 abstr.; InterHealth, undated-b), and reduction of the appearance of wrinkles (in a topically applied cream and in a form to be ingested) (Best Skin Care, undated; Healthy Living Intl.com, 2000). Other claims include preventing cancer (Natural Ways to Health, undated; Cosgrove, 2000), enhancing the immune system (Enrich Corporation, 2000a), and slowing the process of aging (Natural Ways to Health, undated). *trans*-Resveratrol is marketed as a phytoestrogen to maintain estrogen levels and help alleviate menopausal symptoms (Cosgrove, 2000; Inno-Vite, undated), as well as to promote healthy bone density (Inno-Vite, undated; Cosgrove, 2000).

Pharmascience has a patent for use of *trans*-resveratrol to prevent and to treat restenosis after coronary disease treatment (AML Information Services, 2000), and the Institute for Human Virology, funded by Pharmascience, has filed a patent application for the use of resveratrol with nucleoside analogs for treating HIV-1 infections (IHV, 2001a,b).

Many sources say resveratrol's benefits come primarily from their antioxidant effects or from their estrogenic effects (Hendler and Rorvik, 2001; Gehm et al., 1997; Agriculture and Agri-Food Canada, undated; Soleas et al., 1997; [Rice-Evans et al., 1997; cited by Frémont, 2000]; Howard, 2000 abstr.; Paiva, 1999 abstr.). In demonstrations of its antioxidant properties, *trans*-resveratrol is better at inhibiting oxidation of LDL (low density lipoprotein) than was

α-tocopherol (Frankel et al., 1993; Arichi et al., 1982; both cited by Soleas et al., 1997). In demonstrations of its estrogenic properties, resveratrol acts as a mixed agonist-antagonist for estrogen receptors α and β (ER-α and ER-β) (Hendler and Rorvik, 2001) and increased native-regulated gene expression and stimulated growth of estrogen-dependent breast cancer cells (Gehm et al., 1997).

6.0 Environmental Occurrence and Persistence

Resveratrol is a polyphenol that is found in more than 70 common plant species (Turner, 1999). Plants that contain *trans*-resveratrol include grapes, peanuts, eucalyptus, spruce, and lily ([Langcake and Pryce, 1976; cited by Daniel et al., 1999]; Sobolev and Cole, 1998 abstr.; McElderry, 1997), mulberries (Hendler and Rorvik, 2001), groundnut (Schroder et al., 1999; Hain et al., 1990), members of the knotweed and hellebore genera (*Polygonum* and *Helleborus*), and fescue grass (Budavari, 1996).

Resveratrol in grapes is found in lignified plant tissues, in leaves, and in berries (Langcake and Pryce, 1976; cited by Daniel et al., 1999). In *Vitis vinifera, trans*-resveratrol was detected in vines, and leaf tissues produced the compound when infected with fungi or when exposed to UV light (Langcake and Pryce, 1976; cited by Frémont, 2000). When a grape becomes infected with the fungus *B. cinerea*, known as gray mold, the concentration of resveratrol rises in nearby grapes (Sbaghi, 1994; Jeandet et al., 1995b). Stimulating a grape plant's production of resveratrol and other defense chemicals can increase its resistance to *B. cinerea*, enabling it to limit fungal infection (Jeandet et al., 1998). Once a plant has made resveratrol to defend itself, the concentration declines (Creasy and Creasy, 1998; Thomzik et al., 1997).

7.0 Human Exposure

Human exposure to resveratrol is mainly through ingestion, particularly of peanuts, grapes, and their products ([Langcake and Pryce, 1976; Goldberg, 1995; both cited by Daniel et al., 1999]; Sobolev and Cole, 1998 abstr.). In 1998, per-capita wine consumption in the United States was 7.88 L or 1.97 gallons (Wine Institute, 2000). Details about the levels of resveratrol in wines are in **Table 1**.

Resveratrol levels in peanuts and peanut products are lower than in grape products. Resveratrol concentrations were 0.055 μg/g (0.24 nmol/g) for roasted peanuts, 0.324 μg/g (1.42 nmol/g) for peanut butter, and 5.138 μg/g (22.51 nmol/g) for boiled peanuts (Sobolev and Cole, 1998 abstr.). Hendler and Rorvik (2001) reported the levels of *trans*-resveratrol in peanuts to be 0.02 -1.79 μg/g (0.09-7.84 nmol/g).

Exposure through dietary supplements is mostly oral. However, exposure would be dermal in the case of a resveratrol-containing cream (Best Skin Care, undated). For dietary supplements, amounts found in products and dosage recommendations vary. Information in a document from Protykin's™ manufacturer mentions that resveratrol supplements contain <1-10 mg (<4-44 μmol) resveratrol per tablet (InterHealth, 1998). An online article recommends a dosage of 200-600 μg (0.876-2.63 μmol) resveratrol per day for atherosclerosis or cancer prevention (Micromedex Thomson Health Care, 2000). Additional details about the concentrations of resveratrol in herbal products, as well as recommended dosages, are shown in **Table 2**.

Table 1. Concentration of Resveratrol in Wines

Wine Type (Grape Species Used)	Compound	Concentration Range	References
White (*V. vinifera*)	*trans*-Resveratrol	≤0.02 mg/L (0.09 μM)	McMurtrey et al. (1994); cited by McMurtrey (1997)
White (*V. rotundifolia*)	*trans*-Resveratrol	0.29-1.18 mg/L (1.3-5.17 μM)	McMurtrey (1997)
Spanish rosè (grape species n.p.)	*trans*- and *cis*-Isomers of resveratrol, piceid	~4.5-7.0 μM (1.0-1.6 μg/mL)	Lamuela-Raventós et al. (1997)
	trans-Resveratrol	~1.2-2.2 μM (0.27-0.50 μg/mL)	
Red (muscadine [where noted]; otherwise, species n.p.)	*trans*- and *cis*-Isomers of resveratrol, piceid	175 ng/L - 0.5 mg/L (0.77 nM - 2.2 μM)	[Roggero and Archier (1994); cited by Frémont (2000)]; Lamuela-Raventós et al. (1997)
	trans-Resveratrol	≤0.02-13.4 mg/L (0.09-58.7 μM) (upper concentration from muscadine grapes)	McMurtrey et al. (1994); Lamikanra et al. (1996); both cited by Frémont (2000)

Abbreviation: n.p.=not provided

Table 2. Concentration of Resveratrol in Various Herbal Products

Product	Resveratrol Concentration	Recommended Dosage	Source
Bio Vin Full Spectrum Grape Seed and Skin Extracts	463 ppm (23.2 μg [0.102 μmol]) resveratrol per 50 mg capsule	1 to 2 capsules daily in divided dosages	Life Extension Foundation (2000)
Biochem Olive Leaf Extract	5 mg (0.02 mmol) resveratrol per capsule	2 capsules daily	Mineral Connection (2001)
Cardio Cholestamax™	1.9% (1.9 mg [8.3 μmol]) resveratrol per 100 mg tablet	2 tablets daily	Organix-South, Inc. (undated)
ORAC+ Biosynergistic Super Fruit Powder	20% (1 g [4 mmol]) resveratrol in 5 g of powder	1 heaping teaspoon (~5 g)	Natural Ways to Health (undated)
ActiVin™ + Resveratrol	100 μg (0.438 μmol) *trans*-resveratrol[a]	1 tablet twice daily	InterHealth (undated-a)
Protykin®	5-10 mg (0.02-0.04 mmol) *trans*-resveratrol per 25-50 mg tablet	1 tablet daily	InterHealth (1998; undated-a)
	2.495 mg (0.01091 μmol) *trans*-resveratrol per 50 mg tablet	1 to 2 tablets daily	LaSasso (2000)
Resveratrol Synergy™	16 mg (70 μmol) resveratrol per tablet	1 to 2 tablets daily	Jarrow Formulas (2001)

Abbreviation: n.p.=not provided

[a] This product is also listed to contain 100 mg grape seed extract and 500 μg of *P. cuspidatum* root extract without indicating the quantity of resveratrol in these extracts.

8.0 Regulatory Status

Resveratrol available in dietary supplements is regulated under the U.S. Food, Drug, and Cosmetic Act (FDCA). Manufacturers and distributors must notify the Food and Drug Administration (FDA) when they plan to market dietary supplements that contain "new dietary ingredients" (Section 413b of the Act, 21 U.S.C. 350b)(FDA, 2001).

Solgar Vitamin & Herb filed a new dietary ingredient notification for resveratrol extract from *P. cuspidatum* on Sept. 13, 2000 (Docket #95S-0316) (FDA, 2001). Its product, however, was considered possibly adulterated under 21 U.S.C. 342 (f)(1)(B) because of inadequate information regarding reasonable expectation of its safety (21CFR Sec. 190.6(b)(4)). The submission contained contradictory information about the amount of *trans*-resveratrol in the supplement (Satchell, 2000; LaSasso, 2000). In March 2001, the company gave official notification to FDA that it would not market a product containing resveratrol (LaSasso, 2001).

An FDA regulatory letter informed Natural Balance, Inc. that it was not allowed to claim that its products containing *trans*-resveratrol treat inflammatory disorders of joint, back, and muscles. Under FDA regulation 21 U.S.C. 343(r)(6), manufacturers are not allowed to claim a dietary supplement can "diagnose, mitigate, treat, cure, or prevent a specific disease or class of diseases" (Graves, 2000a,b; Foret, 2000).

9.0 Toxicological Data

When specified by the author(s), isomers were named. In most instances, "resveratrol" was used.

9.1 General Toxicology

9.1.1 Human Data

Adverse effects of resveratrol in humans have not been reported. InterHealth (Concord, CA) reported that the recommended dosage of 5 to 10 mg per day was "entirely safe" (Turner, 1999). Recently, the National Cancer Institute (NCI) initiated preclinical toxicity studies on *trans*-resveratrol; clinical trials may follow (AIM, 2000).

9.1.2 Chemical Disposition, Metabolism, and Toxicokinetics

The details of the following studies, except where noted, are presented in **Table 3**.

<u>*In Vitro* Assays</u>

In an isolated rat small intestine perfusion model, the majority of absorbed *trans*-resveratrol (administered doses of 28, 34, and 57 µM [6.4, 7.8, and 13 µg/mL]) was found in the luminal effluent (53.9%). Of this amount, free resveratrol was the dominant product (39.7%). At the vascular side, 20.5% of the administered resveratrol appeared, with the major product being the glucuronide (16.8%) (Andlauer et al., 2000). In a separate study, small amounts of unmetabolized resveratrol were absorbed across the enterocytes of the jejunum and ileum. In contrast, significant amounts of its glucuronide (1.19 nmol/cm jejunum and ~0.45 nmol/cm ileum [100 µM administered resveratrol]) were found in the serosal fluid (Kuhnle et al., 2000).

Table 3. Chemical Disposition, Metabolism, and Toxicokinetics of Resveratrol

Test System and/or Species, Strain, and Age, Number, and Sex of Animals	Chemical Form and Purity	Route, Dose, Duration, and Observation Period	Results/Comments	Reference
***In Vitro* Assays**				
Small intestine (Rats, Sprague-Dawley, age n.p., 6M [3 test, 3 controls])	*trans*-resveratrol, purity n.p.	single-pass perfusion for 60 min; 28, 34, and 57 µmol/L (6.4, 7.8, and 13 µg/mL) or 837.1, 1006.6, and 1704.4 nmol in 7 mL bolus of luminal media (flow rates of 5 mL/min vascularly and 0.5 mL/min luminally)	There were no significant differences in viability data (e.g., oxygen consumption and arterial pressure) between the test and control perfusion. In the luminal perfusate, resveratrol degradation was 16.0±3.8% after 2 h at 37 °C; in the vascular perfusate, no degradation occurred. The recoveries of resveratrol (mean±SD%) were as follows: free resveratrol / glucuronide / sulfate Luminal effluent 39.7±7.6 / 11.2±5.7 / 3.0±4.4 Vascular side 3.4±2.2 / 6.8±0.6 / 0.3±0.5 Intestinal tissue 1.5±1.4 / 0.1±0.1 / 0.3±0.3 Blood vessels 0.0±0.0 / 0.0±0.0 / 0.0±0.0 Total Recovery = 76.3±6.7	Andlauer et al. (2000)
Small intestine (Rats, Sprague-Dawley, age and number n.p., M)	resveratrol, purity n.p.	single-pass perfusion for 90 min; 100 µM (22.8 µg/mL)	Significant amounts of resveratrol glucuronide (1.19 nmol/cm; 96.5% ± 4.6 of the amount absorbed) were found on the serosal side of the enterocytes of the jejunum versus the amount of unmetabolized resveratrol (0.03 mol/cm). For the ileum, the combined transfer of resveratrol and its glucuronide was lower. In the serosal fluid, the amount of resveratrol glucuronide was ~38% of that transferred across the jejunum; the amount of unmetabolized resveratrol was undetectable.	Kuhnle et al. (2000)
Resveratrol Glucuronidation				
Partially hepatectomized liver microsomes (Humans, 41- to 71-yr-old, 7M and 3F)	*trans*-resveratrol, >99% pure	incubation for 30 min; 1 mM (228 µg/mL) in 50 µL incubation mixture (1 mM UDPGA)	The highest rate of resveratrol glucuronidation occurred at pH 7. At pH 7.4, the resveratrol-glucuronide amount increased linearly with time up to 40 min and 0.2 mg/mL protein concentration. The coefficients of intra- and interassays variabilities were 1.0 and 1.5%, respectively. The rate of resveratrol glucuronidation ranged from 0.23 to 1.2 nmol/min/mg (mean = 0.69±0.34; median = 0.80); it did not correlate with age or sex.	De Santi et al. (2000a)

Table 3. Chemical Disposition, Metabolism, and Toxicokinetics of Resveratrol (Continued)

Species, Strain, and Age, Number, and Sex of Animals	Chemical Form and Purity	Route, Dose, Duration, and Observation Period	Results/Comments	Reference
Partially hepatectomized liver microsomes (Humans, 47- to 71-yr-old, 3M and 2F)	*trans*-resveratrol, >99% pure	incubation for 30 min; 0.0625, 0.125, 0.25, 0.5, and 1 mM (14.3, 28.5, 57, 114, and 228 µg/mL) in incubation mixture (1 mM UDPGA)	Glucuronosyl transferase toward resveratrol followed Michaelis-Menten kinetics. mean K_m = 0.15±0.09 mM mean V_{max} = 1.3±0.3 nmol/min/mg intrinsic clearance = 11±0.004 mL/min/mg	De Santi et al. (2000a)
Partially hepatectomized liver microsomes (Humans, 47- to 71-yr-old, 2M and 1F)	*trans*-resveratrol, >99% pure	incubation for 30 min; 0.0625, 0.125, 0.25, 0.5, and 1 mM (14.3, 28.5, 57, 114, and 228 µg/mL) in incubation mixture (1 mM UDPGA) with 0, 1.25, 2.5, 5, 10, 20, and 40 µM quercetin	Quercetin effectively inhibited resveratrol glucuronidation; the mean IC_{50} value was 10±1 µM. mean K_i = 10±4 µM mean K_{ies} = 9±2 µM mean K_m = 0.15±0.09 mM (control), 0.06±0.04 mM (5 µM quercetin), and 0.13±0.06 mM (10 µM quercetin) V_{max} = 1.3±0.3 nmol/min/mg (control), 0.73±0.07 (5 µM quercetin), and 0.46±0.23 (10 µM quercetin) The inhibition was mixed, non-competitive.	De Santi et al. (2000a)
Partially hepatectomized liver microsomes (Humans, 47- to 71-yr-old, 2M and 1F)	*trans*-resveratrol, >99% pure	incubation for 30 min; 1 mM (228 µg/mL) in incubation mixture with 20 µM myricetin, catechin, kaempferol, fisetin, or apigenin	The flavonoids inhibited resveratrol glucuronidation; the percents of control value were 50±3, 46±2, 55±13, 72±14, and 66±8, respectively.	De Santi et al. (2000a)
Partially hepatectomized liver microsomes (Humans, 47- to 71-yr-old, 2M and 1F)	*trans*-resveratrol, >99% pure	incubation for 30 min; 1 mM (228 µg/mL) in incubation mixture with 4 µL red Chianti wine (1998 year, 12% [v/v] alcohol, pH 6)	The rate of resveratrol glucuronidation decreased to 65.3% of the control value.	De Santi et al. (2000a)
Resveratrol Sulphation				
Partially hepatectomized liver microsomes (Humans, 47- to 71-yr-old, 3M and 1F)	*trans*-resveratrol, >99% pure	incubation for 20 min; 2 µM (0.5 µg/mL) in 150 µL incubation mixture (0.4 µM PAPS); reaction linear up to at least 40 min	The mean rate of resveratrol sulphation was 80±22 pmol/min/mg.	De Santi et al. (2000b)

Table 3. Chemical Disposition, Metabolism, and Toxicokinetics of Resveratrol (Continued)

Species, Strain, and Age, Number, and Sex of Animals	Chemical Form and Purity	Route, Dose, Duration, and Observation Period	Results/Comments	Reference
Partially hepatectomized liver microsomes (Humans, 60- to 71-yr-old, 3M and 2F)	*trans*-resveratrol, >99% pure	incubation for 20 min; 0.12, 0.25, 0.5, 1, and 2 µM (0.027, 0.057, 0.1, 0.2, and 0.5 µg/mL) in incubation mixture (0.4 µM PAPS)	mean V_{max} = 125±31 pmol/min/mg cytosolic protein mean K_m = 0.60±0.08 µM The rate of resveratrol sulphation did not correlate with the activity of phenol sulphotransferase or of catechol sulphotransferase.	De Santi et al. (2000c)
Partially hepatectomized liver microsomes (Humans; age, number, and sex n.p.)	*trans*-resveratrol, >99% pure	incubation for 20 min; 2 µM (0.5 µg/mL) in incubation mixture (0.4 µM PAPS) with the following inhibitors: 3.1, 6.2, 12.5, 25, and 50 pM quercetin; 0.62, 1.2, 2.5, 5, and 10 µM kaempferol or apigenin; or 0.31, 0.62, 1.2, 2.5, and 5 µM fisetin or myricetin	The following IC_{50} values were obtained: quercetin 12±2 pm fisetin 1.0±0.04 µM myricetin 1.4±0.1 µM kaempferol 2.2±0.1 µM apigenin 2.8±0.2 µM	De Santi et al. (2000b)
Partially hepatectomized liver microsomes (Humans, 47- to 71-yr-old, 2M and 1F)	*trans*-resveratrol, >99% pure	incubation for 20 min; 0.12, 0.25, 0.5, 1, and 2 µM (0.027, 0.057, 0.1, 0.2, and 0.5 µg/mL) in incubation mixture with 0, 5, and 20 pM quercetin	Inhibition of resveratrol sulphation was mixed and non-competitive. mean K_i = 3.7±1.8 pM mean K_{ies} = 12.1±1.7 pM mean K_m = 0.23±0.07 µM (control), 0.40±0.08 µM (5 pM quercetin), and 0.56±0.09 µM (10 pM quercetin) V_{max} = 99±11 pmol/min/mg (control), 73±15 pmol/min/mg (5 pM quercetin), and 57±10 pmol/min/mg (10 pM quercetin)	De Santi et al. (2000b)
Partially hepatectomized liver microsomes (Humans, 47- to 71-yr-old, 2M and 1F)	*trans*-resveratrol, >99% pure	incubation for 20 min; 2 µM (0.5 µg/mL) in incubation mixture (0.4 µM PAPS) with the following inhibitors: 3.1, 6.2, 12.5, 25, and 50 pM quercetin; 7.8, 15.6, 31.2, 62.5, and 125 nM mefenamic acid; or 12, 25, 50, 100, and 200 µM salicylic acid	The following IC_{50} values were obtained. quercetin 12.4±2 pM mefenamic acid 24±3 nM salicylic acid 53±9 µM	De Santi et al. (2000c)

Table 3. Chemical Disposition, Metabolism, and Toxicokinetics of Resveratrol (Continued)

Species, Strain, and Age, Number, and Sex of Animals	Chemical Form and Purity	Route, Dose, Duration, and Observation Period	Results/Comments	Reference
Partially hepatectomized liver microsomes (Humans; age, number, and sex n.p.)	*trans*-resveratrol, >99% pure	incubation for 20 min; 2 µM (0.5 µg/mL) in incubation mixture with 2, 4, and 8 µL red Chianti wine (1998 year, 11.5% [v/v] alcohol, pH 6)	The rate of resveratrol sulphation was decreased to 47±9% with the low dose, 26±7% with the mid dose, and 9±0.4% with the high dose of the control value.	De Santi et al. (2000b)
Duodenal samples (Humans; age, number, and sex n.p.)	*trans*-resveratrol, >99% pure	incubation for 20 min; 2 µM (0.5 µg/mL) in incubation mixture with the following inhibitors: 3.1, 6.2, 12.5, 25, and 50 pM quercetin; 0.62, 1.25, 2.5, 5, and 10 µM kaempferol or myricetin; or 0.31, 0.62, 1.2, 2.5, and 5 µM fisetin or apigenin	The following IC_{50} values were obtained: quercetin 15±2 pM fisetin 1.3±0.5 µM myricetin 2.5±0.3 µM kaempferol 2.3±0.1 µM apigenin 1.3±0.1 µM	De Santi et al. (2000b)
Duodenal samples (Humans, 67- to 68-yr-old, 1M and 2F)	*trans*-resveratrol, >99% pure	incubation for 20 min; 2 µM (0.5 µg/mL) in incubation mixture (0.4 µM PAPS) with the following inhibitors: 3.1, 6.2, 12.5, 25, and 50 pM quercetin; 1.9, 3.9, 7.8, 15.6, and 31.2 nM mefenamic acid; or 12, 25, 50, 100, and 200 µM salicylic acid	The following IC_{50} values were obtained: quercetin 15.2±2 pM mefenamic acid 11±0.6 nM salicylic acid 66±4 µM	De Santi et al. (2000c)
Duodenal samples (Humans; age, number, and sex n.p.)	*trans*-resveratrol, >99% pure	incubation for 20 min; 2 µM (0.5 µg/mL) in incubation mixture with 2, 4, and 8 µL red Chianti wine (1998 year, 11.5% [v/v] alcohol, pH 6)	The rate of resveratrol sulphation was decreased to 32.2±1% with the low dose, 16.5±1% with the mid dose, and 10±1% with the high dose.	De Santi et al. (2000b)

Table 3. Chemical Disposition, Metabolism, and Toxicokinetics of Resveratrol (Continued)

Species, Strain, and Age, Number, and Sex of Animals	Chemical Form and Purity	Route, Dose, Duration, and Observation Period	Results/Comments	Reference
***In Vivo* Assays**				
Rats, Wistar, age n.p., 42M (36 test, 6 control)	Cabernet Sauvignon red wine (from central Italy) containing 6.5 mg/L resveratrol, purity n.p.	gastric intubation; single dose of 4 mL red wine, corresponding to 86 µg/kg (0.38 µmol/kg) resveratrol; rats sacrificed before wine administration (controls) and after 30 min and 1, 2, 4, 8, and 12 h	Maximum resveratrol concentration was reached ~1 h after administration in plasma (20.2±1.55 ng/mL). Maximum resveratrol concentrations in tissues were as follows: 20.7±1.61 ng/g in the liver, 2.2±0.5 ng/g in the heart, and 20±1.15 ng/g in the kidney.	Bertelli et al. (1998a)
Rats, Wistar, age n.p., 42M (36 test, 6 control)	Cabernet Sauvignon red wine (from central Italy) containing 6.5 mg/L resveratrol, purity n.p.	gastric intubation; 2 mL red wine, corresponding to 43 µg/kg (0.19 µmol/kg) resveratrol, for 15 days; rats sacrificed after 15 days	Maximum resveratrol concentrations were as follows: 7.6±0.55 ng/mL in plasma, 53.5±1.46 ng/g in the liver, 3.1±0.3 ng/g in the heart, and 44.1±1.52 ng/g in the kidney. Kinetic studies showed that an equilibrium was reached between the absorbed resveratrol and the eliminated resveratrol.	Bertelli et al. (1998a)
Rats, Wistar, age n.p., 42M (36 test, 6 control)	Cabernet Sauvignon red wine (from central Italy) containing 7.06 mg/L resveratrol (*trans* and *cis*), purity n.p.	gastric intubation; 4 mL red wine corresponding to 28.24 µg (0.1237 µmol) resveratrol; rats sacrificed before wine administration (controls) and after 30 min and 1, 2, 4, 6, and 12 h	Plasma resveratrol concentrations were measured only at 30 min, 1 h, and 2 h, and data were, therefore, analyzed using a one-compartment model. The following values were obtained: clearance = 739 mL/h, V_1 = 533 mL, and K_a = 1.46/h. Analysis of plasma and tissue (heart, kidney, and liver) concentration data used a two-compartment model. From the plasma+kidneys model, the following results were obtained: half-life of absorption = 0.46 h half-life of distribution, α= 0.48 h half-life of elimination from kidneys = 0.50 h half-life of elimination from plasma = 0.50 h half-life of terminal plasma, β (last time point where authors were able to detect resveratrol in the plasma) = 25 h Tissue bioavailability of resveratrol was higher in the kidneys and liver (295 and 218% AUC plasma) and lower in the heart (24.7% AUC plasma) compared to plasma.	Bertelli et al. (1998b)

Table 3. Chemical Disposition, Metabolism, and Toxicokinetics of Resveratrol (Continued)

Species, Strain, and Age, Number, and Sex of Animals	Chemical Form and Purity	Route, Dose, Duration, and Observation Period	Results/Comments	Reference
Rats, Sprague-Dawley, age n.p., 3, sex n.p.	*trans*-resveratrol, purity n.p.	i.p.; single dose of 2 mg/kg (9 µmol/kg); Rats were connected to sterile tubing on the Culex™ and then dosed with resveratrol; blood concentration measured up to 300 min post-dosing	Resveratrol was rapidly absorbed. Blood concentration declined following a "two-exponential" pathway. The elimination rate constant for phase 1 (k_{e1}) was 0.185/min. The half-life ($t_{1/2}$) was 3.74 min, and the AUC was 9917 min-ng/mL.	Zhu et al. (2000)

Abbreviations: AUC = area under curve (time concentration curves); EROD = 7-ethoxyresorufin-*o*-dealkylation; F= female(s); h = hour(s); IC_{50} = 50% inhibitory concentration; i.p. = intraperitoneal(ly); K_a = absorption rate; K_i = ([E]x[I])/[EI], where [E] = concentration of enzyme, [I] = concentration of inhibitor, and [EI] = concentration of enzyme-inhibitor complex; K_{ies} = ([ES]x[I])/[EIS], where [ES] = concentration of enzyme-substrate complex and [EIS] = concentration of enzyme-inhibitor-substrate complex; K_m = Michaelis constant; M = male(s); min = minute(s); n.p. = not provided; PAPS = 3´-phosphoadenosine-5´-phosphosulphate-[^{35}S]; SD = standard deviation; UDPGA = uridine 5´-diphosphoglucuronic acid; V_1 = central volume; V_{max} = maximum reaction velocity; wk = week(s); yr = year(s)

In human partially hepatectomized liver microsomes, the highest rate of *trans*-resveratrol glucuronidation (up to 1 mM [228 µg/mL] resveratrol and 1 mM uridine 5´-diphosphoglucuronic acid [UDPGA] in incubation mixture) occurred at neutral pH, and the resveratrol-glucuronide amount increased linearly with time up to 40 minutes. The reaction of resveratrol sulphation (up to 2 µM [0.5 µg/mL] resveratrol and 0.4 µM 3´-phosphoadenosine-5´-phosphosulphate [PAPS]) was also linear up to at least 40 minutes. The rates of resveratrol sulphation, similar in the human liver and duodenum, were inhibited by quercetin, fisetin, myricetin, kaempferol and apigenin; quercetin was the most effective inhibitor. The inhibition was mixed and noncompetitive. Flavonoids also inhibited resveratrol glucuronidation, but the extent of inhibition was less than that for sulphation. The addition of wine to the incubation mixture decreased both the rate of resveratrol sulphation and the rate of glucuronidation (De Santi et al., 2000a,b,c).

In human intestinal epithelial cell line Caco-2 cultured in Transwell, resveratrol had a permeability constant of 7.4 x 10^{-6} cm/s, suggesting that it could be orally absorbed (study details, including dose, not provided) (Walle et al., 1998 abstr.).

<u>*In Vivo* Assays</u>
In rats, resveratrol (single administration of 86 µg/kg [0.38 µmol/kg] or 43 µg/kg [0.19µmol/kg] for 15 days) in red wine was rapidly absorbed at the intestinal level, immediately entering the blood and reaching a maximum level around one hour after oral administration. The liver contained the highest concentrations (20.7 and 53.5 ng/g following single and repeated administration, respectively), while the "main excretion pathways appear to be renal." Kinetic studies showed an equilibrium between the absorbed resveratrol and the eliminated resveratrol (Bertelli et al., 1998a). In a separate study, significant cardiac bioavailability was observed, as well as a strong affinity for the liver and kidneys (Bertelli et al., 1998b). Given intraperitoneally (i.p.), *trans*-resveratrol (2 mg/kg [9 µmol/kg]) was rapidly absorbed and the concentration in rat blood declined in a "two-exponential" manner (Zhu et al., 2000).

9.1.3 Acute Exposure
No data were available.

9.1.4 Short-term and Subchronic Exposure
The details of the following two studies are presented in **Table 4**.

In rats, daily oral administration of resveratrol (300, 1000, and 3000 mg/kg [1.31, 4.381, and 13.14 mmol/kg]) for 28 days produced nephrotoxicity, dehydration, labored breathing, hunched posture, decreased activity, rough coat, diarrhea, soft stool, and red material around the nose at the high dose. Males also had leukocytosis, and both sexes may have had anemia. Based on the results, the no observed adverse effect level (NOAEL) was 300 mg/kg/day (Korytko et al., 2002). [The same test was carried out on dogs; no results, however, were available (CRISP, 2002).]

In hypercholesterolemic rabbits, *trans*-resveratrol (0.06 mg/kg [0.3 µmol/kg] during days 1-5 and 1.0 mg/kg [4.4 µmol/kg] from days 6-60) promoted atherosclerosis. On day 60, the percentage area of stained aortic surface was ~67% in treated animals compared to ~41% in controls (95% ethanol only) (Wilson et al., 1996).

Table 4. Short-term and Subchronic Exposure to Resveratrol

Species, Strain, and Age, Number, and Sex of Animals (If Given)	Chemical Form and Purity	Route, Dose, Duration, and Observation Period	Results/Comments	Reference
Rats, strain and age n.p., 20M and 20F/group	resveratrol, purity n.p.	gavage; 300, 1000, and 3000 mg/kg (1.31, 4.381, 13.14 mmol/kg) daily for 28 days	At the high dose, nephrotoxicity (elevated serum BUN and creatinine levels, increased kidney weights, and gross and microscopic renal lesions) and dehydration (reduced bw gain and hyperalbuminemia) were observed. The animals also exhibited labored breathing, hunched posture, decreased activity, a rough coat, diarrhea, soft stool, and red material around the nose. M rats had leukocytosis. Anemia in F and possibly M may have been a direct effect on red blood cells (increased total bilirubin) or secondary to renal injury (decreased erythropoietin synthesis). Mild liver toxicity, indicated by increased serum ALT, ALKP, and possibly total bilirubin, was not seen histologically. Liver QR, GST, UGT, and 2E1 were increased, while 1A1 was slightly decreased. At the mid dose, dehydration, labored breathing, and reduced bw gains were seen in all rats. Additionally, M had an increased white blood cell count. (NOAEL = 300 mg/kg/day)	Korytko et al. (2002)
Rabbits, New Zealand white (specific-pathogen-free), 72-days-old, 18M	resveratrol, purity n.p.	oral; 0.06 mg/kg [0.3 µmol/kg] during days 1-5 and 1.0 mg/kg [4.4 µmol/kg] from days 6-60). (Rabbits were first fed a cholesterol-supplemented diet that contained 0.5% cholesterol by weight for 60 days after 7-day acclimatization period.) Blood samples and plasma lipoproteins and triglycerides were collected and observed on days 0, 40, and 60.	No adverse effects on health were observed other than the promotion of atherosclerosis. The largest increase in cholesterol concentration occurred between days 0 to 40. On day 60, Sudan-IV dye showed that the percentage area of stained aortic surface was 66.87±18.92% in treated animals compared to 40.81±24.63% in controls (95% ethanol only).	Wilson et al. (1996)

Abbreviations: ALKP = alkaline phosphatase; ALT = alanine aminotransaminase; BUN = blood urea nitrogen; bw = body weight; F = female(s); GST = glutathione-*S*-transferase; M = male(s); n.p. = not provided; QR = quinone reductase; UGT = uridyl diphosphate (UDP)-glucuronyltransferase

9.1.5 Chronic Exposure

No data were available.

9.1.6 Synergistic/Antagonistic Effects

Resveratrol produces a synergistic effect, as well as increased potency and availability, when combined with other antioxidants or compounds having antimutagenic or cardioprotective properties (e.g., anthocyanadins, indole-3-carbinol, and green tea extracts) (Turner, 1999). A recent discovery is resveratrol's potential role in the control of HIV-1 (human immunodeficiency virus-1) replication; the compound may synergize with existing drugs, potentiating their antiviral effects (IHV, 2000).

Resveratrol and 2-amino-1-methyl-6-phenylimidazo[4,5-b]pyridine (PhIP) were observed to equally antagonize toxicity when combined together. Resveratrol (10 µM [2.3 µg/mL]) was toxic to Chinese hamster V79MZ cells (nonmetabolically competent); coincubation with PhIP (100 µM) inhibited this effect. In contrast, resveratrol inhibited PhIP-induced mutation in V79MZh1A2 (expresses human CYP1A2) cells. Resveratrol (10 µM) in combination with PhIP (100 µM) increased the colony survival of V79MZh1B1 (expresses human CYP1B1) cells, whereas alone, neither compound was toxic (Boyce et al., 2000 abstr.).

In some mammary cancer cell lines, resveratrol showed mixed estrogen agonist/antagonist activities, whereas in the presence of 17β-estradiol, it was an antiestrogen (Bhat et al., 2001; Gehm et al., 1997). For example, in MCF-7 and S30 cells, resveratrol alone showed weak estrogenic response, but when combined with estradiol (1 nM), a dose-dependent antagonism occurred. In addition, progesterone receptor (PR) protein expression was induced with the compound alone, but when combined with estradiol, the expression was suppressed. In T47-D and LY2 cells, resveratrol was a pure estrogen antagonist, and it significantly down-regulated steady-state and estradiol-induced PR protein levels. With LY2 and S30 cells, presnelin 2 protein expression was down-regulated (Bhat et al., 2001). [Resveratrol competes with 17β-estradiol to bind to the human estrogen receptor (ER) (Calabrese, 1999).]

Resveratrol, administered at pharmacological doses (52-74 µM [12-17 µg/mL]), was able to suppress the growth of ER-positive breast cancer cells (KPL-1 and MCF-7) and ER-negative breast cancer cells (MKL-F) stimulated by linoleic acid, a potent stimulator of these cells (Nakagawa et al., 2001). Resveratrol (1 pM-1 µM [2.28×10^{-7}-0.2 µg/mL]) was also an agonist of steroid receptors. In the MCF-7 cells, resveratrol interacted with estradiol (at the nanomolar range) simultaneously with PRs (at the picomolar range). In T47-D cells (hormone-sensitive breast cancer cell line), the same interactions were seen but to a lesser extent; both occurred at the nanomolar range. In MDA-MB-231 cells (hormone-independent breast cancer cell line), no steroid binding was observed (Damianaki et al., 2000).

In a study of both isomers, *trans*- and *cis*-resveratrol (10 and 25 µM [2.3 and 5.7 µg/mL]) significantly increased the growth of MCF-7 cells. At a high dose of 50 µM (11 µg/mL), cell growth was decreased, and this concentration was determined to be cytotoxic. In the presence of estradiol and at 25 and 50 µM *trans*-resveratrol and 50 µM *cis*-resveratrol, significant reduction in cell proliferation was observed. In MVLN cells, *trans*-resveratrol (10 and 25 µM) and *cis*-resveratrol (25 µM) significantly increased luciferase activity compared to estradiol. In the

presence of estradiol, both isomers at the same doses functioned as superagonists of estradiol. In both cell lines, *cis*-resveratrol was less effective than *trans*-resveratrol (Basly et al., 2000).

Resveratrol was observed to exhibit estradiol antagonist activity for ER-α with select estrogen response elements and no such activity with ER-β (Bowers et al., 2000). For example, in human endometrial adenocarcinoma (Ishikawa) cells at concentrations as high as 10 µM (2.3 µg/mL), it mediated antiestrogenic effects by selective down-regulation of ER-α but no ER-β (Bhat and Pezzuto, 2001).

In contrast to *in vitro* tests, an *in vivo* study using weanling rats suggested that resveratrol (oral; 1, 4, 10, 40, and 100 µg [0.004, 0.02, 0.044, 0.18, and 0.438 µmol] per day for six days) was not an agonist at the ER (e.g., it had no effect on bone formation and mineralization rates versus the estrogen 17β-estradiol). But when resveratrol and 17β-estradiol were given together (1000 and 100 µg [4.381 and 0.438 µmol], respectively), a synergistic effect was observed—i.e., a significant decrease in cholesterol levels was seen in the animals. The inability of low doses (1 and 10 µg [0.004 and 0.044 µmol], respectively) to lower serum cholesterol levels suggested antagonism by resveratrol at the ER (Turner et al., 1999). In rats orally or subcutaneously administered *trans*-resveratrol (0.03-575 mg/kg [0.1 µmol/kg - 2.5 mmol/kg]), no estrogenic response was observed in uterine tissue (Ashby et al., 1999; Freyberger et al., 2000 abstr.).

9.1.7 Cytotoxicity

The details of the following studies are presented in **Table 5**.

<u>*In Vitro* Assays</u>

In bovine capillary endothelial (BCE) cells stimulated with fibroblast growth factor-2 (FGF-2), resveratrol inhibited capillary endothelial cell growth in a dose-dependent manner (1-10,000 nM [0.0002-2.2825 µg/mL]), the phosphorylation of mitogen-activated protein kinases (MAPKs) (10 and 20 µM [2.3 and 4.6 µg/mL]), and FGF-2 and vascular endothelial growth factor (VEGF)-induced proliferation of porcine aortic cell lines expressing PAE/FGFR-1 and PAE/VEGFR-2, respectively, in a dose-dependent manner (0.5-10 µM [0.1-2.3 µg/mL]) (Bråkenhielm et al., 2001).

Using the neutral red uptake (NRU) assay, the following sequence of sensitivity to resveratrol (doses up to 500 µM [114 µg/mL]) was determined: tongue squamous carcinoma SCC-25 cells > Smulow-Glickman (S-G) human gingival epithelial cells > RHEK-1 keratinocytes >> fibroblasts (i.e., gingival, periodontal ligament, and pulp). In S-G cells, toxicity was found to level off between day 2 and 3 for a 3-day continuous exposure to resveratrol (5-150 µM [1-34.2 µg/mL]). At concentrations >75 µM (17 µg/mL), irreversible damage to cell proliferation occurred, and the presence of an hepatic S9 microsomal fraction did not potentiate or improve the cytotoxicity. Additionally, the cytotoxicity of hydrogen peroxide or nitrogen oxide to S-G cells was not affected by resveratrol. Other cytotoxicity endpoints were noted (see table) (Babich et al., 2000).

In HL-60 cells, resveratrol (2.5, 5, 10, 20, 40, and 80 µg/L [0.011, 0.02, 0.044, 0.088, 0.18, and 0.35 µM]) inhibited [^{3}H]thymidine incorporation into DNA (by 30, 56, 67, 81, 83, and 87%, respectively) and [^{3}H]uridine incorporation into RNA (by 43, 54, 72, 85, 90, and 93%, respectively) in a dose-dependent manner (Dubash et al., 1999).

Table 5. Cytotoxicity Studies of Resveratrol

Test System or Species, Strain, Age, Number, and Sex	Chemical Form and Purity	Route, Dose, and Duration	Results/Comments		Reference
***In Vitro* Assays**					
BCE cells stimulated with FGF-2 (1 ng/mL)	resveratrol, >99% pure	incubation with 1, 10, 100, 1000, and 10,000 nM (0.2, 2.3, 22.8, 228, 2282.5 ng/mL) for 72 h	Resveratrol inhibited capillary endothelial cell growth in a dose-dependent manner. [EC_{50} value was 10x lower compared with several other tumor cell lines (e.g., murine B16 melanoma cells, T241 fibrosarcoma cells, and Lewis lung carcinoma cells).]		Bråkenhielm et al. (2001)
BCE cells stimulated with FGF-2 (1 ng/mL)	resveratrol, >99% pure	incubation with 10 and 20 µM (2.3 and 4.6 µg/mL)	Resveratrol inhibited FGF-2-induced phosphorylation of $MAPK^{p42}$ and $MAPK^{p44}$.		Bråkenhielm et al. (2001)
BCE cells stimulated with FGF-2 (1 ng/mL)	resveratrol, >99% pure	incubation with 0.5, 1, 2.5, 5, and 10 µM (0.1, 0.2, 0.57, 1, and 2.3 µg/mL) for 72 h	Resveratrol inhibited the FGF-2 and VEGF-induced proliferation of PAE/FGFR-1 and PAE/VEGFR-2 cells, respectively, in a dose-dependent manner. At 1 µM, significant inhibition of the VEGF-induced PAE/VEGFR-2 endothelial cell migration was observed.		Bråkenhielm et al. (2001)
S-G human gingival epithelial cell line	resveratrol solubilized in ethanol, purity n.p.	incubation with up to 500 µM (114 µg/mL) for 24 h	Initial toxicity (µM) 100	NRU_{50} (µM) 206	Babich et al. (2000)
periodontal ligament fibroblasts			200	457	
dental pulp fibroblasts			400	432	
normal human gingival GN56 fibroblasts			400	462	
nontumorigenic human epidermal RHEK-1 keratinocytes			150	216	
human tongue squamous carcinoma SCC-25 cells			25	154	

Table 5. Cytotoxicity Studies of Resveratrol (Continued)

Test System or Species, Strain, Age, Number, and Sex	Chemical Form and Purity	Route, Dose, and Duration	Results/Comments	Reference
S-G human gingival epithelial cell line, seeded at a density of $1.5x10^4$ cells/well	resveratrol solubilized in ethanol, purity n.p.	*NRU assay*: incubation with 10, 25, 50, 75, 100 and 150 µM (2.3, 5.7, 11, 17, 22.8, and 34.2 µg/mL) continuously for 3 days	The toxicity of resveratrol gradually increased to day 2 of exposure and leveled off between day 2 and 3. NRU_{50} values were 154 µM for a 1-day exposure, 93 µM for a 2-day exposure, and 94 for a 3-day exposure.	Babich et al. (2000)
S-G human gingival epithelial cell line, seeded at a density of $1.5x10^4$ cells/well	resveratrol solubilized in ethanol, purity n.p.	*NRU assay*: incubation with 5-150 µM (1-34.2 µg/mL) for 2 days, refed with recovery medium (without resveratrol), and incubated for an additional 3 days	At doses up to 50 µM resveratrol, cells resumed normal growth kinetics during the recovery period. Concentrations between 75-150 µM caused a steady decrease in cell numbers during the period, possibly indicating irreversible damage.	Babich et al. (2000)
S-G human gingival epithelial cell line, seeded at a density of $1.5x10^4$ cells/well	resveratrol solubilized in ethanol, purity n.p.	*Bioactivation assay*: incubation with 100, 150, and 200 µM (22.8, 34.2, and 45.7 µg/mL) in the presence of an hepatic S9 microsomal fraction, derived from Aroclor-induced rats, for 24 h	Cytotoxicity was not potentiated or improved.	Babich et al. (2000)
S-G human gingival epithelial cell line, seeded at a density of $1.5x10^4$ cells/well	resveratrol solubilized in ethanol, purity n.p.	*AlamarBlue reduction assay*: incubation with up to 400 µM (91.3 µg/mL) for 24 h, followed by refeeding with phenol red-free medium containing 10% Alamar Blue solution and incubation for 3 h	Initial toxicity occurred with 100 µM resveratrol, and the NRU_{50} value at 24 h was 256 µM.	Babich et al. (2000)
S-G human gingival epithelial cell line, seeded at a density of $1.5x10^4$ cells/well	resveratrol solubilized in ethanol, purity n.p.	*WST-1 assay*: incubation with up to 400 µM (91.3 µg/mL) for 24 h, followed by washing with PBS, refeeding with exposure medium containing 4% WST-1 reagent, and incubation for 20 min	Initial toxicity occurred with 150 µM resveratrol, and the NRU_{50} at 24 h was 282 µM.	Babich et al. (2000)
S-G human gingival epithelial cell line, seeded at a density of $1.5x10^4$ cells/well	resveratrol solubilized in ethanol, purity n.p.	*BrdU ELISA assay*: incubation with 0.01-100 µM (0.002-22.8 µg/mL) for 24 h, followed by treatment with BrdU for 4 h	Inhibition of DNA synthesis was initially detected at 50 µM resveratrol, and the NRU_{50} was 100 µM.	Babich et al. (2000)

Table 5. Cytotoxicity Studies of Resveratrol (Continued)

Test System or Species, Strain, Age, Number, and Sex	Chemical Form and Purity	Route, Dose, and Duration	Results/Comments	Reference
S-G human gingival epithelial cell line, seeded at a density of $1.5x10^4$ cells/well	resveratrol solubilized in ethanol, purity n.p.	incubation with or without 25 µM and either H_2O_2 or NO for 24 h	Resveratrol had no effect on the toxicity of H_2O_2 or NO to the cells.	Babich et al. (2000)
human promyelocytic HL-60 cells	resveratrol, purity n.p.	incubation with 2.5, 5, 10, 20, 40, and 80 µg/L (0.011, 0.02, 0.044, 0.088, 0.18, and 0.35 µM) for 90 min	In a dose-dependent fashion, [^{3}H]thymidine incorporation into DNA was inhibited by 30, 56, 67, 81, 83, and 87%, respectively, and [^{3}H]uridine incorporation into RNA was inhibited by 43, 54, 72, 85, 90, and 93%, respectively. [Stilbenes and piceid (at the same doses) also inhibited both processes dose-dependently.]	Dubash et al. (1999)
***In Vivo* Assays**				
Mice, C57B16/J, having full thickness skin wounds created by surgery on the backs, 5- to 6-wk-old, 6F/group	resveratrol, >99% pure	oral; 5.7 µg/mL (25 µM) in 1% ethanol in drinking water 2 days before the operation and for 15 days after surgery	Resveratrol significantly delayed wound healing. Wound sizes were significantly larger from day 2 and throughout the experiment in test animals.	Bråkenhielm et al. (2001)
Corneal micropockets (Mice, C57B16/J, 6- to 7-wk-old, 5/group, sex n.p.)	resveratrol, >99% pure	oral; 0.4 µg/mL (2 µM) in 1% ethanol (final amount of 1.2 µg/mouse/day [48 µg/kg]) given 3 days before growth factor implantation and "throughout the experiment" (duration n.p.). Animals were examined on day 5 after pellet implantation.	Resveratrol significantly inhibited corneal neovascularization induced by VEGF and FGF-2 compared with controls (ethanol). Vessel density was significantly reduced in the FGF-2-implanted corneas.	Bråkenhielm et al. (2001)

Abbreviations: BCE = bovine capillary endothelial; BrdU = 5-bromo-2´-deoxyuridine; DNA = 2´-deoxy-5´-ribonucleic acid; EC_{50} = concentration needed to reach 50% inhibition; FGF-2 = fibroblast growth factor-2; h = hour(s); H_2O_2 = hydrogen peroxide; MAPK = mitogen-activated protein kinase; min = minute(s); NO = nitric oxide; NRU = neutral red uptake; NRU_{50} = midpoint cytotoxicity, NRU=neutral red uptake; PAE/VEGFR-2 and PAE/FGFR-1 = porcine aortic cell lines expressing VEGFR-2 and FGFR-1, respectively; PBS = phosphate buffer solution; RNA = ribonucleic acid ;S-G = Smulow-Glickman; VEGF = vascular endothelial growth factor; wk = week(s); WST-1 = 4-[3-(4-iodophenyl)-2-(4-nitrophenyl)-2H-5-tetrazolio]-1,3-benzene disulfonate

In Vivo Assays
In mice with skin wounds, resveratrol (5.7 µg/mL [25 µM]) was an angiogenesis inhibitor. In corneal micropockets of the animals, resveratrol (oral; 0.4 µg/mL [2 µg/mL] given three days before growth factor implantation and throughout the experiment) significantly inhibited VEGF- and FGF-2-induced corneal neovascularization compared with controls (Bråkenhielm et al., 2001).

9.2 Reproductive and Teratological Effects
In developing chick embryos of white Leghorn, resveratrol (1, 10, 25, 50, and 100 µg/disk [0.004, 0.044, 0.11, 0.22, and 0.438 µmol/disk] incubated for 48-72 hours) induced vascular zones in the developing chorioallantoic membrane (Bråkenhielm et al., 2001).

9.3 Carcinogenicity
No data were available.

9.4 Initiation/Promotion Studies
No data were available.

9.5 Anticarcinogenicity
Studies have shown the blocking ability of resveratrol on the process of multistep carcinogenesis—that is, tumor initiation, promotion, and progression via mitotic signal transduction blockade, removal of reactive oxygen species by resveratrol, etc. (Lin and Tsai, 1999). The anticancer activity of resveratrol and its molecular mechanisms have been recently reviewed (Gusman et al., 2001).

The details of the following studies are presented in **Table 6**.

In Vitro Assays
Using the mouse mammary gland organ culture model, resveratrol (1-10 µM [0.2-2.3 µg/mL]) inhibited formation of estrogen-dependent preneoplastic ductal lesions induced by 7,12-dimethylbenz[a]anthracene (DMBA) (Bhat et al., 2001).

In human breast cancer cell lines (KPL-1, MCF-7, MKL-F, T47-D, and MDA-MB-231), resveratrol (1 pM-180 µM [2 x 10^{-7}-40 µg/mL]) inhibited the growth of cell lines in a time- and/or dose-dependent manner (Damianaki et al, 2000; Nakagawa et al., 2001). In addition, resveratrol (1 pM-1 µM [2 x 10^{-7}-0.2 µg/mL]) inhibited growth of prostate cancer cell lines PC3 and DU145 (Kampa et al., 2000). In LNCaP prostate cancer cells, resveratrol (100 µM [22.8 µg/mL]) inhibited cell growth in the presence of androgens (Mitchell et al., 1999).

In Vivo Assays
In mice, oral administration of resveratrol (5.7 µg/mL [25 µM]; 1 mg/kg/day) significantly inhibited the growth of T241 fibrosarcomas (Bråkenhielm et al., 2001).

Table 6. Anticarcinogenicity Studies of Resveratrol

Test System or Species, Strain, and Age, Number, and Sex of Animals	Chemical Form and Purity	Route, Dose, Duration, and Observation Period	Results/Comments	Reference
***In Vitro* Assays**				
Mammary glands of mice, BALB/c, 3- to 4-wk-old, number n.p., F	resveratrol, purity n.p.	incubation with 1, 2.5, 5, and 10 µM (0.2, 0.57, 1, and 2.3 µg/mL) for the first 10 days of 14-day culture (Ductal lesions were induced with 2 µg/mL DMBA on day 3 for 24 h.)	The incidence of hyperplastic and aggressive ductal lesions induced by DMBA was reduced by resveratrol in a dose-dependent manner (IC_{50} ~3 µM).	Bhat et al. (2001)
Human breast cancer cell lines: ER-positive KPL-1 and MCF-7 and ER-negative MKL-F	*trans*-resveratrol, 99.8% pure	incubation with 0.01-40 µg/mL (0.04-180 µM) for 24, 48, 72, and 96 h	At ≥44 µM, the growth of all cell lines was inhibited in time- and dose-dependent manners. The IC_{50} for the 72-h treatment ranged from 105 to 149 µM. At lower concentrations of resveratrol, moderate inhibition of the growth of MKL-F and stimulation of KPL-1 and MCF-7 in a time-dependent manner were seen. At 72 h, the cells were stimulated by up to 132 and 115% of control level, respectively.	Nakagawa et al. (2001)
Human breast cancer cell lines: hormone-sensitive MCF-7 and T47-D and hormone-resistant MDA-MB-231	(+)-resveratrol, >99% pure	incubation with 10^{-12}-10^{-6} M (1 pM-1 µM [2 x 10^{-7}-0.2 µg/mL]) for a total of 6 days; applied on day 2 (one cell cycle) and day 5 (three cell cycles)	Cell proliferation was inhibited in a dose-dependent manner in all cell lines; the effect after day 5 was more apparent than at day 2. The IC_{50} and maximum inhibition of resveratrol were as follows: IC_{50} (pM) / Inhibition MCF-7: 13.7±8.3 / 0.42 T47-D: 0.1±1.2 / 0.56 MDA-MB-231: 5.2±9.1 / 0.30	Damianaki et al. (2000)
Prostate cancer cell lines: hormone-sensitive LNCaP, PC3, and DU145	(+)-resveratrol, >99% pure	incubation with 10^{-12}-10^{-6} M (1 pM-1 µM [2 x 10^{-7}-0.2 µg/mL]) given one day after seeding (day 0) and cultured for 6 days	Resveratrol had no effect in LNCaP cells (IC_{50} = >10^{-6} M). At >10^{-7} M, resveratrol produced partial inhibition of growth in the PC3 cell line (IC_{50} = 0.11±1.23 x 10^{-6} M; maximum inhibition at 0.48). In DU145 cells, it was a potent inhibitor of cell growth, which was time- and dose-dependent (IC_{50} = 0.57±0.58 x 10^{-12} M; maximum inhibition at 0.82). In LNCaP cells, resveratrol was a very weak competitor of androgen binding.	Kampa et al. (2000)
Prostate cancer cell line LNCaP	resveratrol, purity n.p.	incubation with up to 200 µM (45.7 µg/mL) for 24 or 32 h with or without Mib 2 days after cells were seeded	At 100 µM, Mib-stimulated cell growth was inhibited and very little apoptosis was observed. At 200 µM, massive apoptotic cell death was seen.	Mitchell et al. (1999)

Table 6. Anticarcinogenicity Studies of Resveratrol (Continued)

Test System or Species, Strain, and Age, Number, and Sex of Animals	Chemical Form and Purity	Route, Dose, Duration, and Observation Period	Results/Comments	Reference
***In Vivo* Assays**				
Mice, C57B16/J (implanted s.c. with a murine T241 fibrosarcoma in the middle dorsum [tumors visible after 72 h]), 5- to 6-wk-old, 6-7M/ group	resveratrol, >99% pure	oral; 5.7 µg/mL (25 µM) or 1 mg/kg/day in absolute ethanol added to drinking water for 25 days	Resveratrol significantly inhibited the growth of T241 fibrosarcomas in the animals.	Bråkenhielm et al. (2001)
Rats, F344, 2-mo-old, 10M/group	resveratrol, purity n.p.	oral; 200 µg/kg (0.876 µmol/kg) bw/day in drinking water for 100 days beginning 10 days before s.c. injection of 2 doses of 15 mg/kg AOM 1 wk apart	The number of ACF in the colorectal mucosa (25.7±3.6 vs. 39.4±3.3 in controls) and mean multiplicity (2.7±0.3 vs. 4.9±0.6 in controls) were significantly reduced. Resveratrol also reduced the number of small and medium ACF and stopped the development of large ACF. Compared to controls, *bax* was significantly expressed in ACF of treated rats (53±1.3% and 57±1.3%, respectively) but not in the surrounding mucosa. In addition, *p21* was expressed in ACF of treated rats but to a lower degree compared to controls (1.5±0.1% and 2.2±0.1%, respectively) but not in the normal mucosa.	Tessitore et al. (2000)
Rats, Sprague-Dawley, 42-days-old, 20F/group	resveratrol, purity n.p.	intragastric; 10 and 100 mg/kg (0.044 and 0.438 mmol/kg) bw 5 days/wk starting 7 days before NMU administration and terminating 120 days after administration of NMU	By day 21, tumors were palpable in the control group after NMU administration. By day 111, 100% incidence was reached. The high dose of resveratrol delayed tumorigenesis: on day 40, 0% incidence was observed versus 42% incidence in the control group; the median time for appearance of the first tumor was 79.5 days in the treated group versus 51.5 days in the control group; at termination, the multiplicity of tumors was 3.9 versus 6.0 in control animals. There was also a decrease in the total number of tumors. Morphologically, there was an increase in differentiated alveolar structures among tumor parenchyma, focal reduction of cell layers and numerous luminal openings within alveolar structures, and necrosis and apoptotic cells in small areas of some tumors.	Bhat et al. (2001)

Abbreviations: ACF = aberrant crypt foci; AOM = azoxymethane; bw = body weight; DMBA = 7,12-dimethylbenz[a]anthracene; ER = estrogen receptor; h = hour(s); IC_{50} = inhibitory concentration for 50% of cells; M = male(s); Mib = anti-hormone blockade (nonmetabolizable, synthetic androgen); NMU = *N*-methyl-*N*-nitrosourea; mo = month(s); n.p. = not provided; s.c. = subcutaneous(ly); wk = week(s)

In rats, resveratrol (200 µg/kg [0.876 µmol/kg] body weight per day for 100 days) inhibited the number of azoxymethane (AOM)-induced aberrant crypt foci (ACF) and their multiplicity, suggesting a protective role in colon carcinogenesis. In ACF but not the surrounding mucosa, *bax* and *p21* were expressed (Tessitore et al., 2000). When rats were treated with resveratrol (100 mg/kg [0.438 mmol/kg] body weight 5 days/week for >120 days) before *N*-methyl-*N*-nitrosourea (NMU) administration, a delay in tumorigenesis occurred; resveratrol increased tumor latency by 28 days. Additionally, the multiplicity of tumors and the total number of tumors were decreased compared to controls (Bhat et al., 2001).

9.6 Genotoxicity

The details of the following studies by Matsuoka et al. (2001) are presented in **Table 7**. In the presence and absence of metabolic activation, *trans*-resveratrol (0.02-5000 µg/plate [0.09 nmol/plate – 21.91 µmol/plate) was nonmutagenic in *Salmonella typhimurium* strains TA98 and TA100 and *Escherichia coli* strain WP2*uvr*A. In the Chinese hamster lung, structural chromosome aberrations (CAs) (mainly chromatid breaks and exchanges) were induced dose-dependently at 2.5-20 µg/mL (11-88 µM); in addition, weak aneuploidy induction was observed. Furthermore, resveratrol (same doses) induced micronucleus (MN), polynuclear (PN), and karyorrhectic cells after a 48-hour treatment and sister chromatid exchanges (SCEs) in a dose-dependent manner at concentrations up to 10 µg/mL. Cell cycle analysis showed that resveratrol caused S phase arrest and induced apoptosis after a 48-hour treatment.

trans-Resveratrol (1, 5, 10, 25, 50, and 100 µM [0.2, 1, 2.3, 5.7, 11, and 22.8 µg/mL]) strongly cleaved plasmid DNA (i.e., strand excision or relaxation of pBR322) in the presence of Cu^{2+} at neutral pH and under aerobic conditions. Under anaerobic conditions, however, increasing the concentration of resveratrol failed to enhance the efficiency of DNA cleavage, suggesting the cleavage to be "absolutely" dependent on the presence of both Cu^{2+} and oxygen. Resveratrol was also found to be capable of binding to DNA (Fukuhara and Miyata, 1998). Studying the mechanism of the DNA-damaging properties of *trans*-resveratrol, the compound's effects were found to be of no importance under physiological conditions. In the presence of ascorbic acid or glutathione, resveratrol (0.1 mM) lost its ability to promote hydroxyl-radical (•OH) formation by DNA-bound Cu^{2+} and was instead a powerful antioxidant (Burkitt and Duncan, 2000).

In addition, resveratrol (10 µM [2.3 µg/mL]) significantly stimulated DNA strand breaks induced by adenosine 5´-diphosphate (ADP)-Fe^{3+} in the presence of hydrogen peroxide. By reducing ADP-Fe^{3+}, resveratrol acted as a prooxidant of DNA (Miura et al., 2000).

9.7 Cogenotoxicity

No data were available.

9.8 Antigenotoxicity

No data were available.

9.9 Immunotoxicity

No data were available.

Table 7. Genotoxicity Studies of Resveratrol

Test System	Biological Endpoint	Chemical Form and Purity	Dose and Duration	Comments	Reference
Salmonella typhimurium strains TA98 and TA100 and *Escherichia coli* strain WP2*uvr*A	bacterial reverse mutation	*trans*-resveratrol, purity n.p.	incubation with 0.02 to 5000 µg/plate (0.09 nmol/plate – 21.91 µmol/plate) for 20 min	Resveratrol was negative in all strains.	Matsuoka et al. (2001)
Chinese hamster lung cells	cytotoxicity		cells seeded at 1.5 x 10^5/plate incubated for 17 h and then treated with 2.5, 5, 10, and 20 µg/mL (11, 22, 44, and 99 µM) for 24, 29, 36, 48, 54, or 72 h	Cell survival decreased with dose with both the 24- and 48-h treatments. Survival calculations were greater for cell density than for cell count. Cytotoxicity was observed at the high dose.	
	CA			Structural CAs (chromatid breaks and exchanges [majority], chromatid and chromosome gaps, and chromosome breaks) were induced dose-dependently. The modal chromosome number of 25 in 80% of control cells was reduced to ~60% and aneuploid cells increased at 10 µg/mL with the 48-h treatment and at 5.0 and 10 µg/mL with the 72-h treatment.	
	MN and/or PN			A slight increase in MN occurred with the 24-h treatment and a dose-dependent increase in MN, PN, and karyorrhectic cells occurred with the 48-h treatment up to the 10 µg/mL dose. Mitotic cells did not increase significantly with either time of treatment and had ~2% tripolar anaphase cells at 10 µg/mL with the 48-h treatment. At 24 h, almost all control cells had reached the second metaphase, while cells given 5 and 10 µg/mL reached the first metaphase. At 48 h, control cells had passed through the fifth metaphase, while cells treated at 10 µg/mL reached the second metaphase. At 54 h, cells given 20 µg/mL were still in the first metaphase.	
	SCE			SCEs were induced dose-dependently. At 10 µg/mL, peak frequency of SCEs per cell was 71.6±21.79 versus 10.36±3.52 at baseline.	
	S phase arrest			The number of cells in G1 phase was decreased, while the number in S phase was increased, particularly early to mid-S phase. At high concentrations, apoptosis was induced with the 48-h treatment.	

Abbreviations: CA = chromosome aberration; h = hour(s); min = minute(s); MN = mononuclei; n.p. = not provided; PN = polynuclei; SCE = sister chromatid exchange

9.10 Other Data

Modulation of Enzyme Activity

In CD2F1 mice (four- to six-weeks-old), *cis*- and *trans*-resveratrol (oral; 1000 µg/kg [4.381 µmol/kg] per day for five or ten days) caused almost complete inhibition of 7-ethoxyresorufin-*o*-dealkylation (EROD) activity (CYP1A2). No effect was observed on ethoxycoumarin-*o*-deethylation (ECOD) activity (CYP1A2/2E1) or benzo[a]pyrene metabolism (Boyce and Gooderham, 2000 abstr.).

Resveratrol was an effective inhibitor of recombinant human estrogen sulfotransferase (EST); the IC_{50} was 1.6 µM. In intact cultured human mammary epithelial cells, a more physiologically relevant condition, the inhibition (1.3 µM) was similar to that with EST (Otake et al., 2000). In recombinant human P form phenolsulfotransferase (PST), an enzyme involved in carcinogen bioactivation, resveratrol was a potent inhibitor; its IC_{50} was 0.2 µM. In intact human hepatoma Hep G2 cells, inhibition of P-PST decreased fourfold (IC_{50} = 0.8 µM) (Walle et al., 1998 abstr.).

Phase 1 (Cytochrome P450) Enzymes

In rats orally administered resveratrol (8 mg/kg [0.04 mmol/kg]), CYP2E1 (chlorzoxazone 6-hydroxylation) and protein level in liver microsomes were significantly reduced 24 hours after administration. In human microsomes incubated with resveratrol (low micromolar levels), CYP1A2 (methoxyresorufin *O*-demethylation) and CYP3A4 (erythromycin demethylation) were inhibited, while CYP2E1 activity was moderately increased. Resveratrol also induced Phase 2 biotransformation (Delaporte and Wilkinson, 1998 abstr.).

Miscellaneous Studies

Resveratrol (6-100 µM [1-22.8 µg/mL]) inhibited the growth and tube formation of bovine aorta endothelial (BAE) cells in a dose-dependent manner (Igura et al., 2001). In addition, DMBA metabolism by liver microsomes was inhibited *in vitro* in a dose-dependent manner; at 10, 20, 40, and 80 µg/mL, resveratrol produced inhibitory effects of 37, 48, 61, and 69%, respectively (Dubash et al., 1999).

10.0 Structure-Activity Relationships

Several compounds show structural similarities to *trans*-resveratrol. Kaempferol (3,5,7-trihydroxy-2-(2-hydroxyphenyl)-4*H*-1-benzopyran-4-one), for example, has a 4′-hydroxyl group in the B-ring and a 2,3-double bond in the C-ring, which allows conjugation across the A-ring containing the meta dihydroxy structure (Kuhnle et al., 2000). The bioavailability of resveratrol and other polyphenols, such as enterodiol, isoflavone, and anthocyanidin, has been reviewed (Scalbert and Williamson, 2000). Comparative studies regarding beneficial effects and mechanism of resveratrol commonly use the compounds below. A table summarizing studies conducted by the National Toxicology Program (NTP) occurs at the end of this section.

Diethylstilbestrol

trans-Resveratrol is structurally similar to the synthetic estrogenic agent diethylstilbestrol (DES), also called α,α′-diethylstilbenediol. In contrast to resveratrol, DES induced polyploidy *in vitro* (Sawada and Ishidate, 1978; Sofuni, 1998; both cited by Matsuoka et al., 2001).

Like resveratrol, DES strongly inhibited nicotinamide adenine dinucleotide phosphate (NADPH)- and ADP-Fe^{3+}-dependent microsomal lipid peroxidation; an IC_{50} of 1.1 µM was

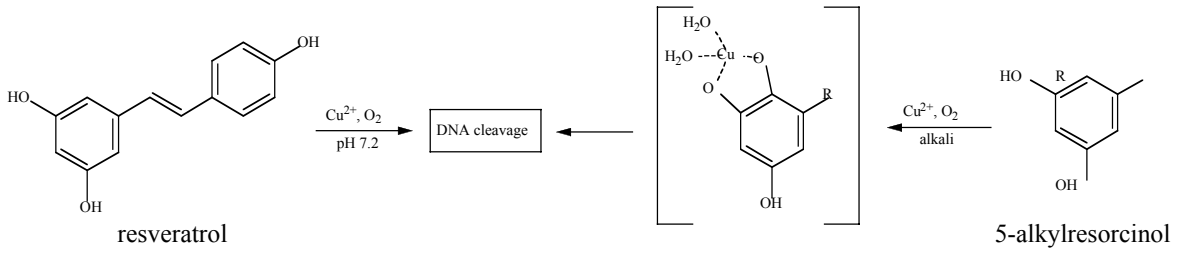
obtained versus 4.8 µM for resveratrol. In addition, both compounds strongly inhibited the reaction at the initiation and propagation stages (Miura et al., 2000). Other flavonoids, including quercetin (see below), are very effective inhibitors of iron-dependent lipid peroxidation; their extent of reduction of ADP-Fe^{3+}, however, was less than that of resveratrol. DES, on the other hand, caused no reduction of ADP-Fe^{3+} or EDTA-Fe^{3+}. It also had no effect on DNA damage (Afanas'ev et al., 1989; cited by Miura et al., 2000).

Quercetin

In several studies, the activity or effect of resveratrol was compared to that of quercetin (2-(3,4-dihydroxyphenyl)-3,5,7-trihydroxy-4*H*-1-benzopyran-4-one) (e.g., see Section 9.1.2). In the human intestinal epithelial cell line Caco-2, the permeability constant for quercetin was similar to that of resveratrol. In addition, quercetin, like resveratrol, was a strong inhibitor of P-PST (IC_{50} = 0.1 µM). In intact human hepatoma Hep G2 cells, this decreased by 25-fold (IC_{50} = 2.5 µM); the hepatocyte had a greater metabolism of quercetin than of resveratrol (Walle et al., 1998 abstr.).

Resorcinol

Resorcinol (*m*-dihydroxybenzene) produced Cu^{2+}-dependent DNA strand excision under oxidative conditions (Barr et al., 1988; Scannell et al., 1988; Hecht, 1989; Lytollis et al., 1995; all cited by Fukuhara and Miyata, 2001). Having the same structural elements as this compound, resveratrol was then studied for its DNA-cleaving ability (see Section 9.6) (Fukuhara and Miyata, 2001).



Other Stilbene Analogs

Many other compounds containing a stilbene moiety have been tested for estrogenicity. These include 4,4′-stilbenediol and 4-stilbenol; 1,1,2-triphenylbut-1-ene derivatives such as tamoxifen, droloxifene, nafoxidine, and clomiphene; and 2-phenylindene derivatives (in which the moiety is part of a fused ring structure) (Fang et al., 2001). [An ILS project A086-003 report with test results will be published on the ICCVAM/NICEATM web site.]

Table 8. NTP Studies of Chemicals Structurally Related to Resveratrol

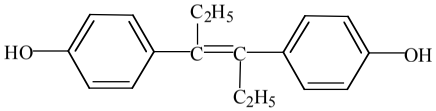
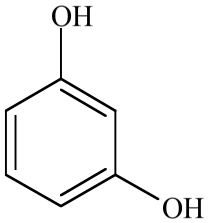
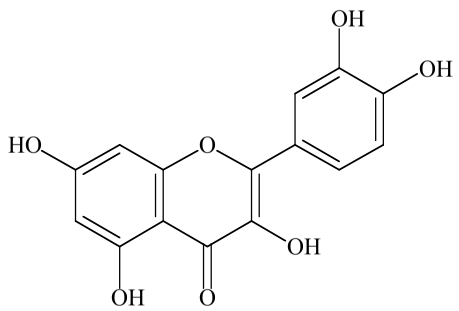
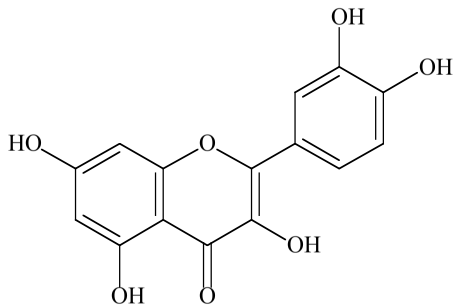
Chemical Name and [CASRN]	Structure	Toxicity Tests*	Reference(s)
Diethylstilbestrol (DES) [56-53-1]		*Short-term carcinogenicity (transgenic models)*: 24- and 26-wk topical [Tg.AC], 25-wk s.c. [p53$^{+/-}$] and 26-wk gavage [Tg.AC] studies have been conducted in transgenic mice; results were not available.	NTP (2002d)
		Reproductive Toxicity: [mice: 1, 10, and 50 ppb in feed] At the high dose, continuous exposure (duration not specified) produced decreases in the fertility index, the number of litters, the number of live pups, and the proportion of pups born alive per litter in F mice.	NTP (1983)
		At the high dose, F had almost a 30% increase in pituitary weight and >75% had no clear estrous cycle (versus 25% of controls). In M, a significant increase in pituitary weight (~15%) and 13-18% reductions in the weight of the epididymis, cauda epididymis, and prostate were observed.	NTP (1984)
		Teratology: [mice: s.c.; 2.5, 5, 10, or 100 µg/kg/day in corn oil on gd 9-16] Corrected maternal bw gain was decreased in all dose groups. At 5 µg/kg/day, there was an increase in skeletal malformations (scrambled sternebrae, perforated sternum, and fused ribs [which have not been shown to be DES-treatment specified]). At ≥10 µg/kg/day, the number of corpora lutea per dam was decreased, and the percent resorptions per litter was increased. At the high dose, gravid uterine weight and live litter size were decreased, while relative maternal liver weight and the incidence of malformation per litter (F more severely affected than M) were increased. LOAEL = 10 µg/kg/day; NOAEL = 5 µg/kg/day Comparison test: 100 µg/kg/day DES in trioctanoin had similar effects.	NTP (1994)
Resorcinol [108-46-3]		***Short-term or Subchronic Toxicity***: 17-day gavage studies [M and F rats: 27.5, 55, 110, 225, or 450 mg/kg; M and F mice: 37.5, 75, 100, 300, or 600 mg/kg] No rats died, and no chemical-related gross or microscopic lesions were found. For mice, 1/5 M from the 300 mg/kg group died, and all F (5/5) and 4/5 M from the high-dose group died. 13-wk gavage studies [M and F rats: 32, 65, 130, 260, or 520 mg/kg; M and F mice: 28, 56, 112, 225, or 420 mg/kg] All F rats (10/10) and 8/10 M rats from the high-dose group died. For mice, 8/10 M and 8/10 F from the high-dose group died.	NTP (1992b)
		Short-term carcinogenicity (transgenic models): 24-wk topical [Tg.AC] or gavage [p53$^{+/-}$] and 26-wk gavage [rasH2]) studies have been conducted in transgenic mice; results were not available.	NTP (2002c,e)

Table 8. NTP Studies of Chemicals Structurally Related to Resveratrol (Continued)

Chemical Name and [CASRN]	Structure	Toxicity Tests*	Reference(s)
Resorcinol [108-46-3] (continued)	(See above row.)	***Chronic Toxicity***: [M rats: 112 or 225 mg/kg 5 days/wk for 2 yr; F rats: 50, 100, or 150 mg/kg for 15 mo; M and F mice: 112 or 225 mg/kg 5 days/wk for 2 yr] At the high dose, mean body weights of rats were decreased compared to those of controls (10-15% lower in M from wk 87 to study termination and 11-14% lower in F from wk 95 to study termination). Additionally, survival was significantly lower than controls. For mice, mean body weights of F were 10-15% lower compared to controls from wk 85 to study termination. In both rats and mice, effects on the CNS were observed—ataxia, recumbency, and tremors.	NTP (1992b)
		Carcinogenicity: [M rats: 112 or 225 mg/kg 5 days/wk for 2 yr; F rats: 50, 100, or 150 mg/kg for 15 mo; M and F mice: 112 or 225 mg/kg 5 days/wk for 2 yr] Studies showed no evidence of carcinogenicity in rats and mice. There were no treatment-related increased incidences of neoplasms or nonneoplastic lesions in the animals. In all F rats, significantly reduced incidences of mammary gland fibroadenomas were seen. In high-dose M mice, the incidence of s.c. fibroma or sarcoma was significantly reduced compared to controls.	
		Genotoxicity: In *S. typhimurium* strains TA98, TA100, TA1535, and TA1537, no mutagenic activity was seen in the presence and absence of S9. In the absence of S9, induction of trifluorothymidine resistance in mouse L5178Y lymphoma cells was seen; no tests were done with S9. With and without S9, resorcinol induced SCEs in CHO cells. Induction of CAs was seen in CHO cells with S9; an equivocal response was found in the absence of S9. In *Drosophila melanogaster*, no induction of sex-linked recessive lethal mutations was seen, but an equivocal response was observed when resorcinol was administered by injection.	
		Positive results were obtained in the MN test.	NTP (2002b)

Table 8. NTP Studies of Chemicals Structurally Related to Resveratrol (Continued)

Chemical Name and [CASRN]	Structure	Toxicity Tests*	Reference(s)
Quercetin [117-39-5]		***Carcinogenicity***: [F344/N M rats: 1000, 10,000, and 40,000 ppm in feed for 2 yr] Studies showed some evidence of carcinogenicity: incidence of renal tubule hyperplasia and severity of nephropathy were increased. Parathyroid hyperplasia (indicative of renal secondary hyperparathyroidism) was also observed. At the high dose, renal tubule adenomas were found in three rats and adenocarcinomas in one other rat. In addition, there was accumulation of yellow-brown granular pigment adsorbed to or absorbed by the epithelial cells of the glandular stomach, ileum, jejunum, duodenum, and colon. ***Genotoxicity***: In *S. typhimurium* strains TA98 and TA100, mutations were induced with and without S9. In CHO cells, SCEs and CAs were induced.	NTP (1992a)
Quercetin dihydrate [6151-25-3]	 $\bullet 2H_2O$	***Genotoxicity***: Negative results were obtained in the MN test.	NTP (2002a)

* Study details (e.g., dose of compound) have been reported if provided in the NTP abstract/report.

Abbreviations: bw = body weight; CA = chromosome aberration; CHO = Chinese hamster ovary; CNS = central nervous system; F = female(s); gd = gestation day(s); LOAEL = lowest observed adverse effect level; M = male(s); MN = micronucleus; mo = month(s); NOAEL = no observed adverse effect level; s.c. = subcutaneous; SCE = sister chromatic exchange; wk = week(s); yr = year(s)

11.0 Online Databases and Secondary References

11.1 Online Databases

Dialog Files
DIOGENES
Chemical Economics Handbook

STN International Files

AGRICOLA	LIFESCI
BIOSIS	MEDLINE
CA	NIOSHTIC
CABA	PROMT
CANCERLIT	Registry
CAPLUS	RTECS
EMBASE	TOXLINE

TOXLINE includes the following subfiles:

Toxicity Bibliography	TOXBIB
International Labor Office	CIS
Hazardous Materials Technical Center	HMTC
Environmental Mutagen Information Center File	EMIC
Environmental Teratology Information Center File (continued after 1989 by DART)	ETIC
Toxicology Document and Data Depository	NTIS
Toxicological Research Projects	CRISP
NIOSHTIC®	NIOSH
Pesticides Abstracts	PESTAB
Poisonous Plants Bibliography	PPBIB
Aneuploidy	ANEUPL
Epidemiology Information System	EPIDEM
Toxic Substances Control Act Test Submissions	TSCATS
Toxicological Aspects of Environmental Health	BIOSIS
International Pharmaceutical Abstracts	IPA
Federal Research in Progress	FEDRIP
Developmental and Reproductive Toxicology	DART

Databases Available on the Internet
CFR (Code of Federal Regulations, National Archives and Records Administration)
CRISP (Computer Retrieval of Information on Scientific Projects)

In-House Databases
Current Contents on Diskette®
The Merck Index, 1996, on CD-ROM

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Appendix: Units and Abbreviations
°C = degrees Celsius
μg/L = microgram(s) per liter
μg/mL = microgram(s) per milliliter
μM = micromolar
BCE = bovine capillary endothelial
bw = body weight
CA = chromosome aberration
DNA = 2′-deoxy-5′-ribonucleic acid
ER = estrogen receptor
EROD = 7-ethoxyresorufin-*o*-dealkylation
F = female(s)
FDA = Food and Drug Administration
FDCA = Federal Drug and Cosmetics Act
FGF-2 = fibroblast growth factor-2
g = gram(s)
g/mL = gram(s) per milliliter
h = hour(s)
IC_{50} = inhibitory concentration for 50% of cells
i.p. = intraperitoneal(ly)
IHV = Institute for Human Virology
kg = kilogram(s)
L = liter(s)
LC = liquid chromatography
LC_{50} = lethal concentration for 50% of test animals
LD_{50} = lethal dose for 50% of test animals
LOD = limit of detection
M = male(s)
mg/kg = milligram(s) per kilogram
mg/m^3 = milligram(s) per cubic meter
mg/mL = milligram(s) per milliliter
min = minute(s)
mL/kg = milliliter(s) per kilogram
mM = millimolar
mmol = millimole(s)
mmol/kg = millimoles per kilogram
mo = month(s)
mol = mole(s)0
mol. wt. = molecular weight

NIEHS = National Institute of Environmental Health Sciences
NOAEL = no observed adverse effect level
n.p. = not provided
NRU = neutral red uptake
NRU_{50} = midpoint cytotoxicity, NRU assay
PhIP = 2-amino-1-methyl-6-phenylimidazo[4,5-b]pyridine
ppb = parts per billion
ppm = parts per million
p.o. = peroral(ly), *per os*
PR = progesterone receptor
RNA = ribonucleic acid
s = second(s)
s.c. = subcutaneous(ly)
SCE = sister chromatid exchange
S-G = Smulow-Glickman
VEGF = vascular endothelial growth factor
wk = week(s)
yr = year(s)