

# Risks and safety of polyphenol consumption<sup>1–3</sup>

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## ABSTRACT

This article gives an overview of the potential hazards of polyphenol consumption, as reported during the round-table discussion at the 1st International Conference on Polyphenols and Health, held in Vichy, France, November 2003. Adverse effects of polyphenols have been evaluated primarily in experimental studies. It is known, for example, that certain polyphenols may have carcinogenic/genotoxic effects or may interfere with thyroid hormone biosynthesis. Isoflavones are of particular interest because of their estrogenic activity, for which beneficial as well as detrimental effects have been observed. Furthermore, consumption of polyphenols inhibits nonheme iron absorption and may lead to iron depletion in populations with marginal iron stores. Finally, polyphenols may interact with certain pharmaceutical agents and enhance their biologic effects. It is important to consider the doses at which these effects occur, in relation to the concentrations that naturally occur in the human body. Future studies evaluating either beneficial or adverse effects should therefore include relevant forms and doses of polyphenols and, before the development of fortified foods or supplements with pharmacologic doses, safety assessments of the applied doses should be performed. *Am J Clin Nutr* 2005;81(suppl):326S–9S.

**KEY WORDS** Risk, safety, polyphenols

## INTRODUCTION

In the past few decades, accumulating data have shown potential beneficial effects of polyphenols (1, 2). This has sometimes led to overestimation of the current knowledge regarding their effects, with disregard for the fact that some polyphenol-rich foods were previously considered to be inedible (soy, for example). These studies have stimulated additional research, focusing on the health effects of polyphenol-rich foods, specific phenolic compounds, or supplementation with a combination of several types of polyphenols. When extensive food composition tables for polyphenols become available, thorough observational epidemiologic studies can be carried out, potentially confirming the encouraging results of the mainly experimental data reported to date. Small-scale human intervention trials may even be planned to verify effects on surrogate endpoints of disease. Before we enter that stage, however, we must examine the potential adverse effects of polyphenols. With the disappointing results of the intervention trials with  $\beta$ -carotene supplementation (3) in mind, we need to consider the fact that polyphenols may, in specific populations, have effects opposite those we desire. In other words, the safety of elevated intakes cannot be assumed.

## INTAKE

In the recommendations made by companies selling various nutritional supplements rich in polyphenols, some recommend the consumption of 50 mg/d isoflavones or 100–300 mg/d grape seed extracts rich in proanthocyanidins. These intake levels are close to those derived from the consumption of soy products in Japan or of grapes or wine in some European countries (4, 5). However, some supplement manufacturers recommend intakes far higher than those currently associated with the diet. Tablets or capsules containing 300 mg quercetin, 1 g citrus flavonoids, or 20 mg resveratrol, with suggested use of 1–6 tablets or capsules per day, are commonly found on the Internet. This would result in intakes  $\sim$ 100 times higher than the common intakes in a Western diet.

Furthermore, some of these supplements may appear safe when isolated from food plants, but the method of extraction used to produce the supplements may influence the nature of the compounds ingested and thus the safety of the product. This occurred with a hydroalcoholic extract of tea buds, sold as a slimming supplement, which was withdrawn from the market because of severe cases of liver toxicity (6).

## RISK ASSESSMENT AND SAFETY EVALUATION

This takes us directly to the problem of risk assessment and safety evaluation. Hazard, risk, and safety are different issues, each of which should be considered (**Table 1**). A thorough risk assessment for polyphenols is complicated, not only because so many different compounds exist but also because not all necessary tools are currently available. Although hazards may be identified and characterized, no exposure assessment (ie, known/proposed intake) can be made, because of missing food composition data. Assessment of exposure through the measurement of biomarkers has also proved difficult, because metabolic

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**TABLE 1**  
Terms used in risk assessments and safety evaluations

Term	Definition
Hazard	Potential for causing adverse effects
Risk	Probability that adverse effects will occur at a specified dose/level
Safety	Practical certainty that no adverse effects will be observed

specificity among populations and individuals may exist and techniques for simple measurements of such biomarkers and corresponding validity data are mostly lacking. It is therefore extremely difficult to know whether proposed intakes are safe or what the likely risks are with those intakes. Several undesirable effects of different phenolic compounds have been observed and are described here, as an example of hazard identification (**Table 2**). These were also discussed during the round-table discussion at the 1st International Conference on Polyphenols and Health, but the list of effects is not exhaustive.

### HAZARD IDENTIFICATION FOR POLYPHENOLS

Most studies of polyphenols aimed to determine the protective effects of polyphenols against diseases or toxic drugs, and relatively few investigators have examined their possible toxicity. No acute toxicity was observed after oral administration of a grape seed proanthocyanidin extract at a dose of 0.5 or 2 g/kg body weight to rats or mice (7) or after administration of punicalagin (an ellagitannin present in pomegranate juice) at a dose of 60 g/kg diet to rats (8). However, chronic nephropathy was observed in rats when high doses of quercetin (2% or 4%) were added to their diet (9). No effect on survival times was observed in that study, whereas addition of quercetin (0.1%) to the diet of mice significantly reduced their life expectancy (10).

Some polyphenols may have carcinogenic or genotoxic effects at high doses or concentrations (11–13). Caffeic acid, for example, when present at a 2% level in the diet, induced forestomach and kidney tumors in rats and mice (14). Linear extrapolation of these data indicates appreciable risk at normal dietary levels. Furthermore, catecholestrogens are postulated to mediate induction of renal tumors by estradiol. Quercetin inhibits *O*-methylation of catecholestrogens and increases kidney concentrations of 2- and 4-hydroxyestrogen by 60–80%. This may result in enhanced redox cycling of catecholestrogens and estradiol-induced tumorigenesis (15, 16). It is possible that the genotoxic effects observed *in vitro* may be attributable to the high concentrations used, at which polyphenols may become prooxidants (17). The formation of glutathionyl quercetin adducts has been shown in tyrosinase-rich B16F-10 melanoma cells and in the myeloperoxidase-rich human HL-60 cell line, which provides important evidence for the prooxidative metabolism of quercetin in cellular *in vitro* models (H van der Woude, personal

**TABLE 2**  
Hazards related to polyphenols

Hazard
Carcinogenicity/genotoxicity
Thyroid toxicity
Estrogenic activity of isoflavones
Antinutritional effects
Interactions with pharmaceuticals

communication at the 1st International Conference on Polyphenols and Health, 2003) (18). This also suggests that tissues rich in oxidative enzymes may be particularly vulnerable to the prooxidant toxicity of quercetin. Finally, green tea catechins (1% or 0.1% of the diet) have been found to enhance tumor development in the colon of F344 male rats and, although quercetin may decrease cancer cell proliferation at high doses, it has been found to stimulate cell proliferation at low doses (1–5  $\mu\text{mol/L}$ ) (19, 20).

In common with synthetic antioxidants, several flavonoids can inhibit thyroid peroxidase and interfere with thyroid hormone biosynthesis (free radical iodination) (21, 22). When vitexin, a C-glycosylflavone abundant in millet, was administered to rats, it increased thyroid weight and decreased the plasma levels of thyroid hormones (23). This is thought to be one of the causes of endemic goiter in West Africa, where millet is a staple food. Furthermore, a reduction of thyroid peroxidase activity was observed in rats fed a diet supplemented with genistein (24, 25). These effects of genistein on thyroid function are more pronounced in cases of iodine deficiency. This is of particular concern for babies exposed to particularly high doses of isoflavones through soy feeding (26). Among adults, however, 2 clinical studies failed to show significant effects on thyroid hormones after consumption of isoflavone-containing soy proteins for 3–6 mo (27, 28).

Isoflavones are a family of polyphenols that are distinctive because of their estrogen-like activity. It is because of this activity that they may have beneficial as well as adverse effects (29, 30). Total plasma isoflavone levels are generally between 0.05 and 5  $\mu\text{mol/L}$  even in Asian populations, which represent consumers of large amounts of isoflavone-rich products such as soy. The intake from a Western diet is estimated as 0.2–5 mg/d, whereas a traditional Asian diet delivers 20–120 mg isoflavones/d (31, 32). These levels of intake were deemed safe in a comprehensive review, although sufficient data to draw conclusions regarding effects on cancer or neurologic diseases were lacking (33). High intakes have been associated with reduced fertility in animals and with anti-luteinizing hormone effects among premenopausal women (34–37). Furthermore, concerns have been expressed regarding sexual maturation of infants receiving very high levels of isoflavones in soy-based infant formula (38, 39). This is of particular importance for baby boys, who normally exhibit luteinizing hormone secretion between birth and 6 mo of age (40). It is therefore important to note that beneficial effects of isoflavones on the development of cancer through the inhibition of certain enzymes have been observed at levels that are all much higher (some >20 times higher) than those observed normally in human plasma (41–43). At these levels, isoflavones may have antiandrogenic effects, influence male and female fertility and sexual development *in utero* and after birth, and induce testicular atrophy (44–47).

Consumption of polyphenols may also have antinutritional effects. The inhibition of nonheme iron absorption attributable to simultaneous tea consumption is well known; high consumption of polyphenols may increase the risk of iron depletion in populations of individuals with marginal iron status (48). Important in this respect is the fact that major sources of polyphenols, such as coffee, tea, and wine, which are regularly consumed with meals, do not contain vitamin C, which is an enhancer of nonheme iron absorption (49). Furthermore, proanthocyanidins (condensed tannins) and ellagitannins have been considered antinutritional compounds, particularly in animal nutrition, because they are

able to interact with proteins and inhibit several enzymes. They affected growth and digestibility in rats when added to the diet at a high dose (10 g/kg diet) but not at a lower dose (50). Consumption of proanthocyanidin-rich fava beans by Egyptian boys reduced the net protein utilization, which was restored with dehulling of the beans (51). It should be noted that these particular effects are unlikely to occur with regular Western diets, which are characterized by a much lower tannin intake (52).

Finally, polyphenols may affect drug bioavailability and pharmacokinetics. Some drugs, such as benzodiazepines and terfenadine, show up to 3-fold increases in bioavailability with grapefruit juice (rich in naringenin), because of inhibition of CYP3A4 (53–55). These effects, which may be attributable in part to psoralens as well as naringenin, are clinically significant in the case of cyclosporine, because of a narrow therapeutic range (eg, when used after organ transplants).

Most of these effects have been shown in *in vitro* or animal studies, and it has not been proved that these effects also occur among humans. Intakes from habitual diets are usually lower than the doses used in these studies, and the food matrix may also influence the effects of polyphenols, which may explain why observational epidemiologic studies have not shown, for example, any carcinogenic effects of polyphenols to date (56) (although this is probably also attributable to lack of accurate exposure assessment and residual confounding). However, we must take the results of the experimental studies seriously, as seriously as we take the beneficial effects. Therefore, the known carcinogenic and endocrine system-disrupting effects of certain polyphenols in animals make human trials with high doses of these polyphenols unethical.

## CONCLUSIONS

It is clear from the aforementioned findings that, in evaluations of experimental studies, we must look carefully at the doses used. In the 17th century, Paracelsus said, "All substances are poisons, there is none which is not a poison. It is the dose that distinguishes a poison from a remedy." A dose that produces a beneficial effect in cell cultures may be poisonous when applied in a human setting. Alternatively, a dose used in an experimental study may never occur in a human setting, because consumption never reaches the same level, because the bioavailability is very low, or because the appropriate dose never reaches the target site. The form of the phenolic compound is also important, because phenolic compounds occur in food mainly as conjugated compounds and the substances occurring in plasma and tissues are mainly mammalian conjugates, except for certain isoflavones and flavonols. All of these aspects must be taken into account in the design of future experimental studies in the field of polyphenols; there is a need to try to model the human situation more closely, irrespective of whether studies are aimed at evaluating beneficial or adverse effects.

Finally, it must be pointed out that exposure levels depend on the mode of presentation of the polyphenols. The risk of consuming high doses of polyphenols from naturally polyphenol-rich foods is low, but we must take into account the negative effects of other ingredients in these foods, such as cholesterol-increasing fats in coffee, alcohol in wine, and fat in chocolate. Foods can be fortified with polyphenols, but we must be sure that they are consumed by the target populations for which they are designed and not by populations that are potentially at risk, such

as children and pregnant women. Dietary supplements that contain high (ie, pharmacologic) doses of polyphenols can be developed. The intake of polyphenols may then easily reach very high levels; in such cases, toxicologic testing may be required to ensure safe levels of intake. In this respect, a recent report on the assessment of the safety of botanicals and botanical preparations for use in food and food supplements might very well apply to the field of polyphenols (57). The type of safety evaluation would depend on the nature of the polyphenol-containing product (a food, a food extract, or a pure compound) and on the proposed use potentially leading to a significant increase in exposure.

Before human intervention trials are designed to evaluate the effects of polyphenols on chronic diseases, with the use of fortified foods or supplements (with either nutritional or pharmacologic doses of polyphenols), a safety assessment of the applied dose should be performed, to prevent unethical studies from being conducted. Before we reach that stage, however, we need to accumulate substantial data from *in vitro*, animal, and observational epidemiologic studies with only relevant forms and doses, to ascribe a potential beneficial effect to total or specific polyphenol intake. 

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