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Too much of a good thing?

To the editor:

The boosted antioxidant activity of transgenic tomatoes containing up to 78-fold enhanced levels of the peel flavonol rutin, reported in the May issue (*Nat. Biotechnol.* **19**, 470–474, 2001), was touted to confer health promoting effects against coronary heart disease and certain forms of cancer. However, as the celebrated physician Paracelsus noted: "All substances are poisons…The right dose differentiates a poison from a remedy." In this context, while flavonols and related polyphenols can be beneficial, they can also have potentially harmful effects.

For example, for several years quercetin, the aglycone of rutin found in red wine, has been recognized as a mutagen. Indeed, studies with mice have indicated that quercetin may have tumorigenic activity[1]. The protective beneficial properties of flavonols and other dietary polyphenols are believed to result from their ability to serve as antioxidants. By donating electrons to free radicals, which might otherwise induce biomolecular damage, polyphenols are converted to phenoxyl radicals ($Ph(OH)_nO^{\cdot}$), which are poorly reactive. However, the very properties that confer polyphenols with the ability to quench free radicals are also responsible for the ease with which they undergo iron- and copper-catalyzed autooxidation, resulting in formation of mutagenic hydroxyl radicals ($^{\cdot}OH$):

$$Ph(OH)_nOH + Cu^{2+} \rightarrow Ph(OH)_nO^{\cdot} + Cu^{+} + H^{+}$$
$$2Cu^{+} + O_2 + 2H^{+} \rightarrow H_2O_2 + 2Cu^{2+}$$
$$Cu^{+} + H_2O_2 \rightarrow Cu^{2+} + {}^{\cdot}OH + OH^{-}$$

Model studies have shown that simple combinations of quercetin and copper ions, which may occur naturally in chromosomes, can induce hydroxyl-radical-mediated oxidative damage to DNA, thereby providing a mechanism for mutation[2].

It should be no surprise that molecules possessing antioxidant properties can also behave as pro-oxidants; a prerequisite of both phenomena is the ability to undergo facile one-electron oxidation. Similar reactions are known for ascorbic acid, glutathione, and NAD(P)H. The fine line that divides anti- and pro-oxidant behavior is exemplified by *trans*-resveratrol, a polyphenolic believed to be responsible for some of the health *benefits* of red wine. This compound can damage DNA by the above mechanisms. However in the presence of the cellular thiol glutathione, which suppresses $^{\cdot}OH$ generation through its stabilization of Cu^{+} ions, the polyphenol displays antioxidant behavior. This involves its sparing of glutathione from Cu^{2+}-mediated oxidation[3].

A potentially important metal-ion independent mechanism through which dietary polyphenols may exert toxicity involves their initial oxidation to phenoxyl radicals by peroxidases (e.g., myeloperoxidase and lactoperoxidase). Generally speaking, such radicals are not sufficiently reactive to propagate lipid peroxidation and DNA damage, but they can oxidize glutathione to its thiyl radical ($GS^{\cdot}$). The glutathionyl radical then combines with the parent thiolate anion (GS^{-}), forming the glutathione disulfide radical anion ($GSSG^{\cdot-}$), which is an extremely powerful one-electron reductant, activating molecular oxygen to potentially harmful species ($O_2^{\cdot-}$ and H_2O_2).

Indeed, several flavonols have been shown to activate large amounts of oxygen by this mechanism in the presence of only catalytic amounts of a peroxidase. Because the flavonol also acts as a catalyst (its phenoxyl radical is repaired by glutathione), relatively small quantities have the potential to induce severe toxicity[4].

Not wishing to diminish the importance of novel dietary antioxidants, or the potential benefits that may be derived from a diet artificially enriched in flavonols, it is hoped the preceding comments highlight the need for studies into the fundamental, free-radical chemistry of novel antioxidants to keep pace with progress in food technology.

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In defense of the precautionary principle

To the editor:

As representatives of one of the civil society organizations mentioned in Miller and Conko's Commentary on the precautionary principle (*Nat. Biotechnol.* **19**, 302–303, 2001), we would like to respond by clarifying both our position and the current status of the precautionary principle in environmental and public health policy.

The precautionary principle was first established as a concept of environmental law in the 1970s. Since that time, precaution has been invoked in numerous international environmental agreements, including the 1992 Rio Declaration on Environment and Development, and more recently the Cartagena Protocol on Biosafety which regulates international movement of genetically modified (GM) organisms. The precautionary principle is also stated explicitly in the environmental policies of several countries (e.g., Canada, Australia, and Sweden) and in the Maastricht Treaty of the European Union. The US Department of Agriculture (Washington, DC) and Food and Drug Administration (FDA, Rockville, MD) adamantly claim that US food safety policies are firmly grounded in a precautionary approach, but stop short of acknowledging precaution as a *principle* of law[1]. Precaution, therefore, is a widely recognized and adopted foundation for making wise decisions under uncertain conditions.

Although there are differences in wording, three core elements are present in all statements of the precautionary principle: if there is reason to believe that a technology or activity may result in harm and there is scientific uncertainty regarding the nature and extent of that harm, then measures to anticipate and prevent harm are necessary and justifiable.

The precautionary principle is necessary and justifiable because, simply stated, our ability to predict, calculate, and control the impacts of technologies such as GM organisms is limited. The novelty and complexity associated with inserting isolated gene constructs into organisms, and releasing those organisms on a global scale demand that we acknowledge uncertainties, accept responsibility, and exercise due caution. This is recognized by the international adoption of the Protocol on Biosafety and by independent scientific bodies in the US, EU, and Canada among others[2,3].

Although there is consistency among definitions, no uniform, global recipe exists for implementing the precautionary principle. It is a general *principle*, not a set of rules, and it must remain responsive to social and ecological context. Nonetheless, it is possible and important to set procedural guidelines such that implementation is not arbitrary. We advocate the following six steps:

- Set broad social, environmental, and economic policies that outline clear, long-term goals. For example, how can we achieve environmentally, economically, and socially sustainable agriculture?

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