Hormesis is a concept of biphasic dose–response to different toxicological and pharmacological stimuli. According to this concept, a noxious agent at a small dose can exert a beneficial action. Among the known hormetic agents are pro-oxidants, heavy metals, heat, radiation, exercise, food restriction1,2 and different kinds of stress.3 All these agents are present in the environment so that the hormetic effect can be explained from the evolutionary viewpoint as living organisms have adapted to a certain level of the impact. For antibiotics,2 hormetic effects develop secondarily along with the positive selection of resistant microorganisms. Another example is that the adaptation of certain human populations to ethanol for over 1000 years apparently resulted in hormesis; moderate alcohol consumption was reported to be associated with a reduced risk of coronary heart disease and other health benefits.4 However, the data on hormetic effects of ethanol originated mainly from more developed countries, that is, populations historically adapted to alcohol; and it is questionable whether hormetic effects would be pronounced in people with no historic experience of alcohol consumption. In the author’s opinion, hormesis as a general principle is conceivable only for the factors that are present in the environment, having induced adaptation of living organisms, so that a deviation in either direction from an optimum would be harmful. It is the case, for example, for light or atmospheric pressure, ionizing radiation5,6 as well as for many chemical substances and elements. There are no general grounds to expect hormetic dose–responses for factors absent in the natural environment. Discussed explanations for hormetic effects, for example, the homeostasis overshoot hypothesis assuming an excess of repair mechanisms in response to mild damage,7 or proposed existence of two different receptor types (small numbers of high-affinity receptors and large numbers of low-affinity receptors)8,9 appear to be neither sufficiently proven nor universal. Some reported hormetic effects can be questionable because of the difficulties of differentiation complex low-level hormetic responses from the placebo effect,10 suboptimal design of some studies and so on.

Hormesis has been generalized and used, more or less directly, as a theoretic support for homeopathy.11,12 Homeopathy claims a curative reaction from a small dose of a drug, of which high doses cause symptoms similar to those from which the patient is suffering.12 Homeopathy originated in the vacuum of medical knowledge of the 19th century, prior to the acceptance of the germ and gene bases of disease; it was never grounded on empirical scientific evidence.13 Some publications generalizing hormesis11,14 can be cited in support of homeopathy and placebo treatments in gerontology and other fields of medicine, being suitable for endorsement of official registration of drugs and dietary supplements. Suggestions that homeopathy is based on hormesis create an illusion that homeopathy employs a scientific method. There is a well-founded opinion that without supporting evidence for the efficacy or purported mechanisms of homeopathy, the term hormesis should not be linked with it in any way.13 If homeopaths have useful empirical knowledge, it should be discussed in the professional literature and tested by scientific methods.

In some works by Edward Calabrese,11 the concept of hormesis tends to be treated as a postulate. The question “Is hormesis likely to occur for all types of

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drugs?” was responded “There are sufficient data to conclude that the hormetic dose response is common, reproducible, and a biological expectation in the vast majority of biological systems, end points measured, and chemical classes tested.”11 The question “May drugs be acting hormetically even though the experimental data appear inconsistent with this interpretation?” was answered “The hormesis concept establishes a biological context for some of the key ‘rules’ of pharmacology and toxicology.”11 These statements can make an impression that hormesis is a general biological principle. However, generalizations, according to which “hormetic-like biphasic dose responses may represent a general biological dose–response pattern or strategy”11 are not sufficiently supported by scientific evidence.15,16 Moreover, hormesis merely further defines one response; but most toxicoses have many responses.10 Some noxious agents can have a cumulative effect or act synergistically with other harmful factors, for example, on the cells with a limited or no potential for cellular regeneration such as cardiomyocytes or neurons. It can be of particular importance in conditions when such cells are pre-damaged, for example, by ischemia so that even a mild damaging impact would act according to the no-threshold pattern without hormesis. In conditions when a cell, tissue, or organ is close to a decompensation, even minimal additional damage can be fatal. Under such circumstances, which are not uncommon especially in gerontology, the hormesis concept can be dangerous if used in clinical thinking. For example, it would hardly be indicated to apply small doses of ethanol, a known hormetic agent, in hepatic failure.

Considering the above, the statement ‘The hormesis concept is a fundamental dose response, highly conserved, and set in an evolutionary framework’11 might be relevant only for the factors that have induced evolutionary adaptation. If even hormesis was observed in studies of substances that are absent in the environment such as certain drugs,9,17 there is still no reason to conclude that “hormetic dose responses are broadly generalizable, being independent of biological model, endpoint measured, and stressor agent, and represent a basic feature of biological responsiveness to chemical and physical stressors.”11 The article11 can be cited in support of homeopathy and placebo treatments, in gerontology and other fields of medicine, also to endorse official registration of drugs without specific effect or efficacy not exceeding that of placebo, which is regarded inadmissible.18 It can pave the way for homeopathy and placebos instead of evidence-based medications, as an inexpensive substitute, especially for elderly patients. There are many examples of marketed compounds without scientifically demonstrated efficacy18 in Russia often in the guise of evidence-based medications, while artificial theoretic concepts are sometimes created to promote them.19

In conclusion, hormesis as a general principle has no proven theoretic basis for factors that are absent in the environment, thus having induced no evolutionary adaptation in living organisms. If an agent is present in the natural environment, existence of an optimal level of its impact, corresponding to the current environmental level or some average of historic levels, can be assumed. This general principle does not exclude a possibility that some agents, if even present in the natural environment, can be noxious at a low dose level or can exert a synergistic harmful action together with other factors. Low-level noxious impacts may be associated with higher risks in a state of subcompensation or in the senile age. Accordingly, hormesis should not be accepted as a default approach in health risk assessment20 especially for the factors that are absent in the natural environment. All clinically significant effects, hormetic or not, should be tested according to the principles of evidence-based medicine.

References
explanation for the molecular mechanisms that underlie the benefits of mild stress. *Dose Response* 2012; 11: 413–430.


