

NON-LINEARITY AND STATISTICS - IMPLICATIONS OF HORMESIS ON DOSE-RESPONSE ANALYSIS

There is no such thing as good science with bad statistics
- John C. Bailar III

*Statistics is like a bikini swim suit -
it exposes a lot but not the most important...*
-Anonymous

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In medical applications of statistics, such as drug testing or risk assessment, most investigators usually expects linear dose-response pattern and is rather surprised finding that the effects on some individuals are even opposite than those expected from the assumption of linearity. We provide several examples of the non-linear dose-response pattern, the phenomenon called *hormesis*, both chemical and radiation hormesis. We also discuss possible explanation of hormesis based on cybernetic regulation mechanism or on chaotic attractor hypothesis, as well as consequences of hormesis for epidemiology and medical statistics.

K e y w o r d s: hormesis, statistics, epidemiology, dose-response relationship, dose-response modelling, risk assessment, risk management.

1. Introduction

Everybody know that small amount of a drug may have completely opposite effect than a large dose of the same drug (chemical). Alcohol, caffeine, nicotine, which are inhibitors (poisons) in large doses, in small doses act as stimulants. The same concerns influence of physical factors like radiation or non-ionizing electromagnetic fields. Biological effects of low level exposures are very important but relatively not well-known. A special scientific journal devoted to these problems, BELLE Newsletter, has been established [1] but not many non-specialists knows about its very existence.

Small doses of toxic agents may be beneficial. The problem arises when one wants to define what is „small” - what is a small dose for one person is really a large one for another, and alcohol is the best example. There is a Russian joke: „**Q.** What is "nothing"? **A.** Nothing is one bottle of vodka for two men. If one of them does not drink...” But in other countries one bottle of vodka is considered to be „something” even for a dozen or so of men. The differences between individual sensitivity to any drug may really be tremendous even in one population and in the same age group. And when experiments on animal models are carried on one needs to remember that no observed effect level (NOEL) for animals may be several times greater than no effect level (NEL) for an average human, which in turn may be an order of magnitude greater than that for a sensitive human and an order of magnitude lower than that for a non-sensitive human (cf. [2]) (Fig. 1). It is really weird that in medical applications of statistics, such as drug testing or risk assessment, one often completely forgets such an everyday experience and says: „Let’s assume that all individuals in the sample are identical”. Humans are not molecules in a volume of an ideal gas, and not members of a normally distributed ”specimen” [3].

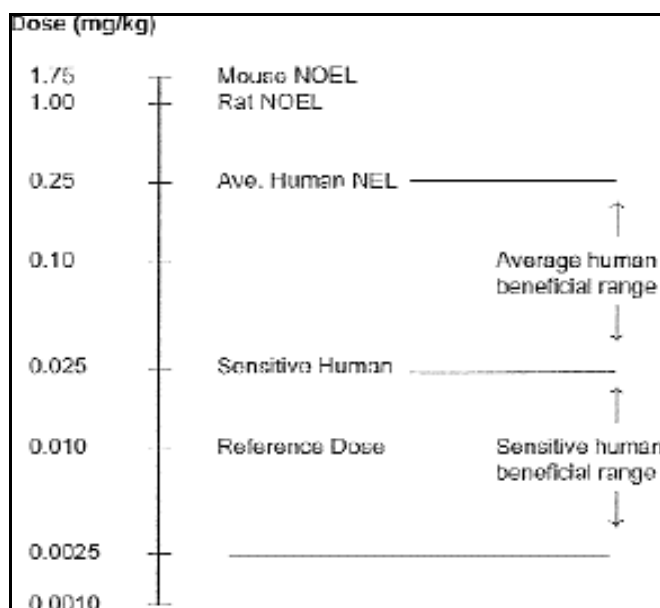


Fig. 1. Beneficial doses for average and sensitive human. Adverse health effects occur at high doses and beneficial effects from NEL to a factor of 10 below NEL (after [2]).

2. Non-linear dose-response curves - hormesis

One often expects linear dose-response pattern and is rather surprised finding that the effect on some individuals is even opposite than that expected from such an assumption of linearity. But already in XVI century German alchemist and physician Theophrastus Bombastus von Hohenheim (1493-1541), who coined for himself the name *Paracelsus*, had recognized with respect to the medical use of small amounts of toxic chemicals that their efficacy depended principally on the dose. The dose-response curves for quite a wide range of toxic agents follow a typical pattern, termed the β -curve; in other cases, especially in carcinogenicity studies, the dose-response curves follow U-shaped pattern, which is inversely comparable to the β -curve, but with toxicity inferred as an increase rather than a decrease in the dose [4,5] (Fig. 2).

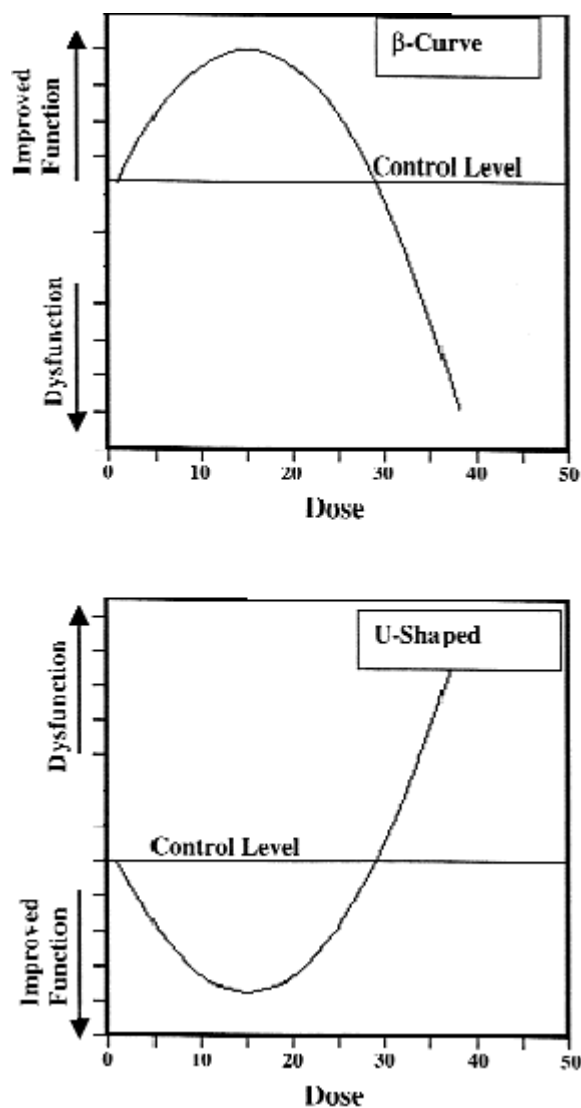


Fig. 2. Simple examples of hormesis - β -curve and U-shaped dose response curve. Low doses are beneficial while high doses are harmful (after [5]).

The word *hormesis*, derived from the Greek word $\acute{\omicron}D: VT$ [hormao], meaning "I put in motion" (infinitive: $\acute{\omicron}D: \bullet<$) which is modified word *hormon* ($\acute{\omicron}D: \acute{\alpha}<$), was coined to describe mild stimulation effects induced by low doses of agents which are detrimental or even lethal at high doses. Now hormesis in general denotes any effect induced by low doses of an agent that can not be predicted by the linear extrapolation of effects induced by high doses of the same agent.

3. Chemical hormesis

Hormesis may be found at biochemical, cellular, and organic levels, in all the major taxa as a consequence of exposure to every class of chemicals, from metals and pesticides to antibiotics, as well as to ionizing and non-ionizing radiation. Hormesis is not a specific effect of the agent that induces it, since it can be induced by such a wide variety of agents of different kinds and it follows a similar pattern. Hormesis is most probably a consequence of an adaptive response, common to biological systems.

The best known hormetic-type effects, in the experience of most, are the stimulatory effects of alcohol, caffeine or nicotine, all of which are toxic at high concentrations (Fig. 3, cf. [6]). Another example is nitrogen oxide (NO), a very simple chemical compound, that has been known as a serious air pollutant, produced in combustion of gasoline, causing acid rain and smog; the same nitrogen oxide is a metabolite of nitroglycerine and other nitrovasodilators which is responsible for their regulatory action on heart and on blood pressure. It was also demonstrated that a substance produced by endothelium cells which had been called EDRF (endothelium-derived relaxing factor) and thought to be rather complicated, is nothing else but the same simple NO. In small concentration NO acts like a hormone. Mechanism of action of NO is still unclear, but it seems to confirm hypothesis that functional complexity of living systems is probably due to a superposition of an immense number of a very few simple basic mechanisms on molecular or even sub-molecular level.

In many cases too much of a drug can be as bad for the organism as too little. This may concern so widespread nowadays vitamin supplements. Physicians in Los Angeles have reported cases of patients with osteoporosis who apparently made their bone problems worse by taking excessively high doses of vitamin D [7]; since then Institute of Medicine of the National Research

Council established a safe upper limit dose for vitamin D intake to 50 μ g i.e. 2000 IU per day for adults. Recently British clinical cancer prevention study demonstrated that male smokers receiving for more than five years beta-carotene supplement (20 mg/day) had significantly more deaths from coronary heart disease than those who did not receive beta-carotene [8]. Also anti-arrhythmic drugs (such as encainide, flecainide, or moricizine), which were supposed to help patients after myocardial infarction, were shown to be not only ineffective but even harmful - they actually increased patients mortality [9-11].

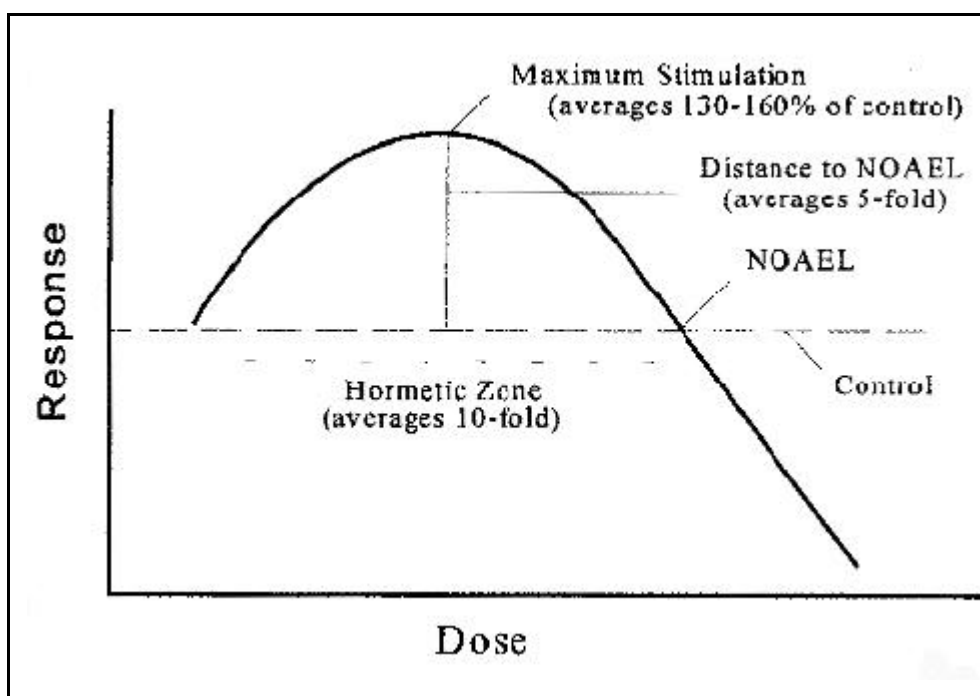


Fig. 3. Dose-response curve depicting characteristics of the chemical hormesis zone. Note that the magnitude of stimulation is typically 30-60% greater than control values while the zone of stimulation extends on average approximately over a 10-fold range (after [6]).

More and more „strange” non-linear effects in drug action and in radiation studies are reported in scientific literature. A database of studies demonstrating objective evidence of hormesis is being created [12].

4. Radiation hormesis

Non-linear dose-response effects concern not only chemical but physical exposure as well. U-shaped relation of relative risk of lung cancer mortality to radon exposure [13] is a good example. Mifune and his co-workers [14] indicated that with an average indoor radon level of 35 Bq/m³ the lung cancer incidence was about 50% and the mortality rate caused by all types of cancer was 37% lower of that in a low-level radon region. In the United States, a study that covered 89% of the population found that the people living in houses with higher than average radon air concentrations, had a lower mortality from lung cancer [15]. Similar results showing a lack of positive correlation between lung cancer and indoor radon levels, were reported from China [16] and other countries [17].

Recently many epidemiological studies have indicated that ionizing radiation, like many physical or chemical agents (UV, vitamins, hormones and trace elements), can be beneficial at low doses, leading to such effects as increase in growth and development rates, increase in mean life span, improving of fertility, stimulation of immune reactions. Mice treated with low-level radiation were more resistant against bacterial disease. Luckey published a large collection of references supporting immunostimulatory effects of low doses of ionizing radiation [18]. In several experiments, small initial radiation doses have been shown to improve the survival rate of animals subsequently irradiated with large, near lethal doses; in other experiments, an increased life span was found in animals irradiated with doses between 250 and 3000 mSv (cf. [19])

The obvious hormetic effects were sometimes not noticed even by the authors themselves (Table 1).

Table 1.

Death from breast cancer among 31,710 Canadian women, exposed to radiation at fluoroscopic examinations. Authors concluded that „The data were most consistent with linear dose response relation” and did not comment on the hormetic effect evident at 100 - 190 dose range (after [19]).

Dose (mGy)	Standardized rate per 10 ³ person-years
0 - 90	578.6
100 - 190	421.8
200 - 290	560.7
300 - 390	650.7
400 - 490	610.0
700 - 990	1362
1000 - 2900	1382
3000 - 5990	2334
6000 - 10,000	8000
>10,000	20,620

Increased longevity and decreased cancer death rates have been observed in populations of the U.S., China, India, Austria, and the United Kingdom exposed to high natural background radiation [19]. In a very large scale study in U.S.A, it was found that the mortality rate due to all malignancies was lower in states with higher annual radiation dose [20]. The Hiroshima and Nagasaki data indicate that a single irradiation with doses between 400 and 600 mSv did not cause detrimental effects in the next generation. Unexpectedly, rather positive effects appeared ([17], [19]). Among those who received doses lower than 200 mSv there was no increase in the number of total cancer death. In fact, mortality caused by leukemia was lower in this population at doses below 100 mSv than among the non-irradiated inhabitants. Similarly unexpected results were obtained in one of the best studies in human genetics carried out in Hungary before and after the

Chernobyl accident. Several serious congenital anomalies occurred after the Chernobyl accident with lower frequency than before the accident [19].

As far as people occupationally exposed to low radiation doses are concerned Gribbin et al. [21] studied 13,491 employees of Atomic Energy of Canada Limited. Mortality due to all causes in both irradiated groups was 28% lower than in non-irradiated group. This difference was statistically significant, and according to UNSCEAR, cannot be due to the "healthy worker effect" ([17], [19]).

Hypothesis on linear, no-threshold dose/effect relationship (LNT), on which the current regulations in radiation protection are based, led to the widely spread believe that even the smallest amounts of radiation are liable to cause deleterious genetic or somatic effects. Numerous results of experiments are in contradiction with LNT hypothesis. Radiation hormesis goes beyond the notion that radiation has no deleterious effects at small doses: at small doses new stimulatory effects beneficial to the organism occur that are not observed at high doses. The possibility that low doses of radiation may result in changes in cells and organisms, which reflect an ability to adapt to the effects of radiation, may inspire the authorities to begin a more realistic approach to problems of estimating and managing the risks of ionizing radiation. Until recently, reports by national and international organizations, including UNSCEAR, ICRP, BEIR, and USEPA consistently failed to acknowledge the hormetic effects ([17], [23]--[26]).

5. Hormesis and biological regulation

Hormesis may be an effect of the common feature of biological regulating mechanisms - over-correction is the best strategy on first exposure to low doses of practically any agent, since in effect it anticipates the possibility of higher doses.

Growth control has been perceived as *homeostasis*, or the regulation of state, rather than as a process controlled by its rate, which is correctly termed *homeorhesis* (Fig. 4, cf. [27]). Biological processes, for example biosynthesis, are rate-controlled processes showing different patterns reflecting the behavior of a control mechanism responding to various loads. The process must be deviated from its equilibrium rate in order to activate the mechanism that regulates it. Various factors in the feedback loop contribute to a delay between error detection and the response to counter it. Consequently processes regulated in this way tend to fluctuate characteristically when disturbed, typically oscillating with decreasing amplitude until equilibrium is restored.

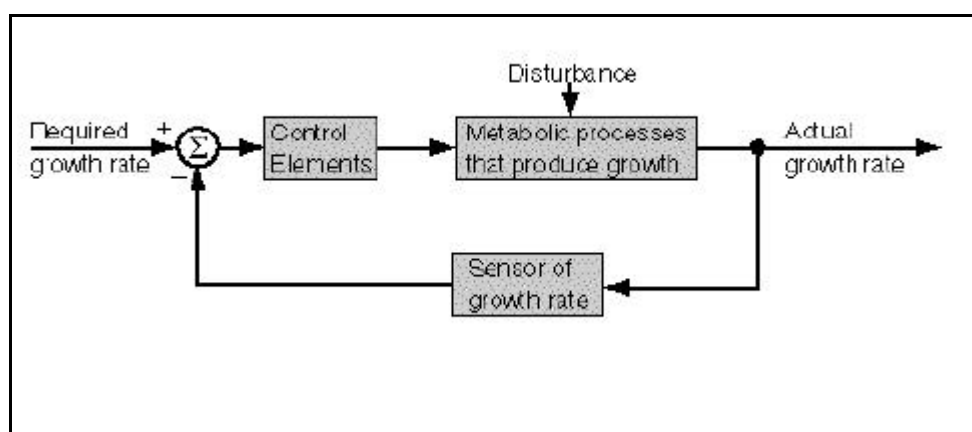


Fig.4. Cybernetic schema indicating the features of a simple feedback mechanism such as could be regulating growth (after [27]).

The hypothesis that hormesis is the consequence of over corrections by rate-regulating control mechanisms to low levels of inhibitory challenge means that hormesis is a by-product of normal responses of biological systems that counteract the effects of inhibitors. The control mechanism that counteracts inhibition provides a ready explanation that at concentrations lower than the threshold of inhibition the control mechanism operates effectively to counteract fully the inhibitory load imposed by the toxic agent; at higher concentrations (corresponding to the lower part of the

downward arm of the concentration-response β -curve) the control mechanism becomes saturated by the overwhelming inhibitory load (Fig. 3). Even osteoporosis may be a result of over-adaptation [28].

6. Hormesis and chaos

While adaptation across generation (natural selection) is based on genetics, adaptation within generations is based on self-organization. Ability of easy adaptation is much more important for surviving of a living system than stiff adjustment to some strictly defined environmental conditions. Since chaotic systems adapt extremely easily they must be very important for life - thermodynamic equilibrium means stasis (death) [29].

The dynamics of a complex system, such as a living organism, can be viewed as a trajectory in a phase space, in which axes define e.g. the organism's concentrations of different enzymes, its blood flow rate, its frequency of encounters with various species, its intensity of participation in various behavioral activities etc [30]. The whole system may be considered as consisted of some minimal subsystems, represented by subsets of the whole system's phase space, which are only loosely coupled to one another, each one no longer being reasonably subdivisible. The dynamics of any such subsystem can be described as a trajectory in its corresponding phase subspace. Such a trajectory moves about until it encounters a region of that space called a basin of attraction, where feedback processes capture it, and then it remains there following a path referred to as an *attractor*, until eventually being shaken out by external forces. Self-organization may be considered as movement of the system into attractors in response to environmental changes. All living organisms, given time for transient behavior, inevitably fall into one of a great many attractors. Time lags in the

adjustment may produce oscillatory responses. For a living organism its dynamics must reach one of those many nonstatic attractors, each one realizing an alternate self-sustaining homeostatic mode. Chaotic systems and chaotic attractors (called „strange attractors”) are extremely sensitive to external conditions.

A stress is an environmental change that brings about a strain, i.e. a loss in energetic efficiency. Intermediate levels of stress, enough to jolt some system trajectories from their basins of attraction, may enhance the self-organizing kinetic „search” of the phase space for another attractor corresponding to a still more favorable homeostatic mode. Adaptation by attractor search is related to energy efficiency. Hormesis may be considered as a more rapid and a more complete adaptation brought about by a little environmental stress which jolts an organism from one attractor into a more energetically effective attractor [30]. On the other hand, too much stress can prevent biochemical and behavioral trajectories from settling in on any attractor, or at least into any but a very few of the deepest basins of attraction, severely limiting adaptation possibilities. This explains nonlinearity in dose-response behaviour.

Attractor hypothesis helps to explain negative influence of anti-arrhythmic drugs (cf. Chapter 3 above). Arrhythmia may be considered a transient state of heart adaptation - movement into a new more effective attractor. Stopping this adaptation process by the drugs may be harmful, leading to increased patient mortality.

6. Importance of hormesis for epidemiology and statistics

Ignoring hormetic responses in the analysis of data, in particular using models that explicitly cannot accommodate potential effects of hormesis, may lead to biased statistical estimates. There is the need to use models which allow for the presence of hormesis in drug testing and in

analysis of hazards [31]. Physiologically based pharmacokinetic (PBPK) models to include well-supported, biologically based models of carcinogen action are required to support a nonlinear approach to low-dose effects. The same concerns biologically based or case-specific dose-response models.

Statistical limitations made it impossible to describe empirically and accurately the shape of a dose-response curve in the low-dose region [20]. The existing guidelines for risk assessment by United States Environmental Protection Agency [25,26] and other agencies offer no guidance on calculating, interpreting, or communicating health benefits of low-level exposure to chemicals or radiation. Guidelines governing chemical and physical hazard and risk assessment will need to be updated to include guidance for analyzing hormetic dose-response curves and communicating the consequences of hormesis to the public.

General concentration-response models have been suggested for the analysis of hormetic concentration-response curves [32, 33]. Thus, the presence of sub-toxic stimulation does not pose any exceptionally difficult problems in the statistical analysis of dose-response data.

Any analysis method applied to data where hormetic patterns are possible should incorporate this possibility explicitly in the analysis. As we have shown, the removal of hormesis when it is present can lead to biased estimations. Models such as those suggested by Bailer and Oris [34, 35] allow for the possibility of hormesis, but are unaffected when hormesis is not observed. By not having data in the range where the curvature associated with the subtoxic stimulation would be observed, the correct statistical model for the observed data will not conform to the true model for the underlying hormetic concentration-response. There exists the necessity of good experimental design, both in the spacing of concentrations and in the range of concentrations tested, design which would directly incorporate hormesis in the routine testing.

The current support for the existence of a generalizable hormetic response [12, 36, 37] of toxic and in some cases carcinogenic compounds further legitimizes the notion that current linear low-dose default assumptions for carcinogens may be flawed. This has important implications for the implementation and interpretation of human drug safety testing and carcinogen hazard/risk assessment.

The LNT model assumes that harmful post-irradiation effects, e.g. neoplasms or genetic diseases, appear after both high and even the lowest, near zero, doses of radiation, and only the frequency of the effects is proportional to the dose. The model extrapolates information from a region of very high doses, absorbed over a short period of time (i.e. at high dose rate) - from where there are epidemiological data with a high degree of statistical confidence - to an unknown region of low, near zero, doses and extremely low dose rates. According to this hypothesis the dose-effect relationship is a straight line, so that even a dose close to zero has some detrimental effect. Thus, the linear hypothesis assumes that there is no dose threshold or limit below which the effects observed at high doses cease to appear. The hypothesis also justifies adding up the doses absorbed by a person at various times and in various parts of the body, without taking into account the duration of periods between particular doses.

To verify experimentally for very low doses radiation risk factors for carcinogenesis as predicted by LNT model one would need to use thousands and thousands of millions (!) of laboratory mice [19]. And as we mentioned before, the results obtained for mice may not be directly used for humans. It illustrates the fundamental limits to our knowledge in physics and biology. The term *trans-scientific* was proposed for such problems, trespassing beyond the limits of our knowledge [38]. Politicians often look to scientists to provide scientific answers when scientists can offer only trans-scientific answers.

LNT type of model has also been used by epidemiologists in other areas, e.g. when the relationship between blood cholesterol and coronary heart disease is concerned [39]. On the other hand, it has been also reported that not only does arteriosclerosis progression cease with cholesterol-lowering but that there is actual regression of atherosclerotic plaques [40].

Any analysis method applied to data analysis where hormetic patterns are possible should explicitly incorporate possibility of hormesis, because assumption of linearity may lead to classification of some experimental points as outliers, while these points may perfectly fit onto non-linear dose-response curve (cf. Table 1 and Fig. 5).

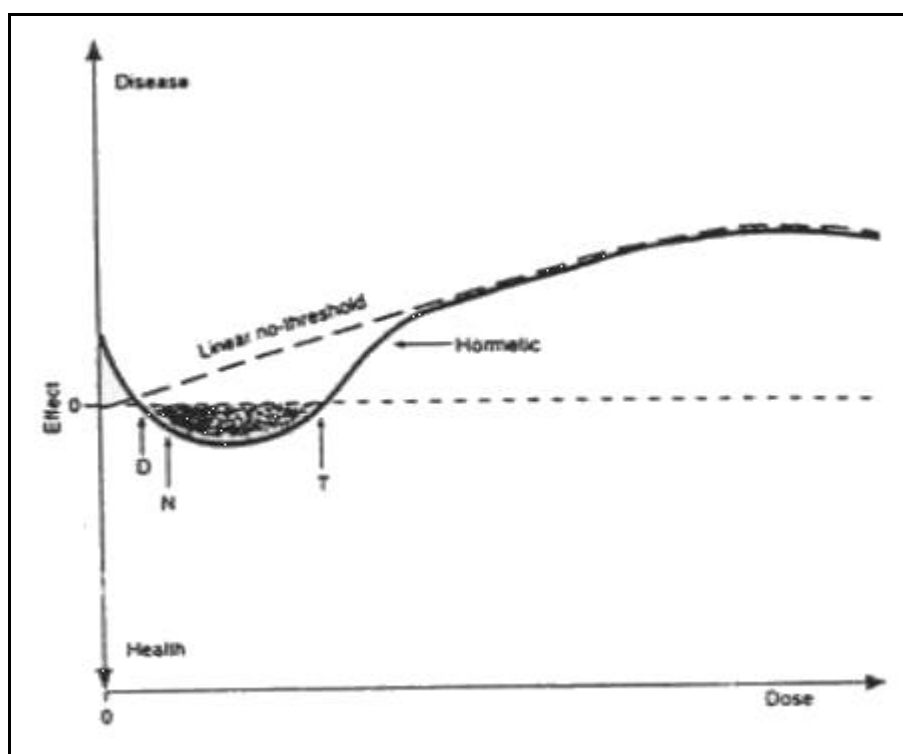


Fig. 5. Generalized biological response to chemical and physical agents. Deficiency symptoms are caused by deficit of an agent (dose less than D). Small doses (between D and T) are vital for good health (shaded area). Doses higher than T cause toxic or other harmful effects. N is the average global natural radiation dose. Dotted and solid lines represent linear no-threshold and hormetic dose-effect relationship, respectively.

7. Concluding remarks

Many analytic procedures simply ignore the possibility of hormesis or view subtoxic stimulation as a violation of a pattern of monotonic change - very often data are manipulated to fit monotonic pattern. Commonly utilized statistical tests are not optimized for use with nonlinear data. The assumption of monotonicity embedded in these tests results in a reduction of the power to identify changes in an unanticipated direction. This could lead to the prediction of adverse health effects from a dose that may cause no adverse effects or possibly have even health benefits under some conditions. Further development and improvement of methods for more accurate dose-response analysis and more realistic hazard and risk assessments is necessary.

There is the necessity of good experimental design - both in the spacing of concentrations and in the range of concentrations tested - that is, incorporating hormesis in the routine testing. Assessing risk for higher doses and then linearly extrapolating the dose-risk relation to low doses may cause serious overestimation or underestimation of the actual risk (Fig. 5).

One of the factors influencing interpretation of epidemiological data is a publication bias [41]. The linearity paradigm stands behind a selective treatment of epidemiological data in publications of respected scientific committees. Often the results are not published, since reviewers and editors claim that one would not expect an effect of risk decreasing at such a dose, sample size or length of observation; in the same situation, data showing a strong, although random, increase of risk are published [42]. Still rare are the textbooks like one edited by Bailar III and Mosteller [43] which discuss the strengths and weaknesses in research design in actual medical practice and show how methods and analysis affect published results.

The danger of extrapolation and the absurdity of the linear no-threshold paradigm is well illustrated by an anecdotic event I remember from my childhood. One very hot summer holidays on

the Baltic sea-shore I have got a friend who just loved coffee ice-creams. One day I found him sitting in the small local coffee bar over a cup of coffee. The 5 years old boy explained to me that he had not enough money to buy himself coffee ice-creams, but still enough for a small cup of coffee. He knew that when coffee is served it became colder and colder, and he decided that if he would wait long enough the cup of coffee became so cold it would turn out into coffee ice-creams. So he was sitting there, waiting and waiting... Despite of the whole due respect I have always had for scientists and for the distinguished scientific bodies, those who adhere to the LNT paradigm inevitably resemble me that small friend of mine. And the opinion on scientists expressed by James Watson in *The Double Helix* comes into mind....

The most likely reasons for failing to observe hormesis where it exists appear to be due to experimental design. Why hormesis was not observed more frequently? Just because we often don't see what we don't look for.

Abbreviations: NOAEL - No Observable Adverse Effect Level; NEL - No Effect Level; LNT - Linear-No-Threshold model; BELLE - Biological Effects of Low Level Exposures; UNSCEAR - United Nations Scientific Committee on the Effects of Atomic Radiation; ICRP - International Commission on Radiation Protection; BEIR - American National Research Council Committee on the Biological Effects of Ionizing Radiation; USEPA - United States Environmental Protection Agency.

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