Biological Effects of Low Level Exposures

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THE ROLE OF HORMESIS IN INDUSTRIAL HYGIENE/OCCUPATIONAL HEALTH

INTRODUCTION

Over the past decade there has been an increasing recognition of the occurrence of hormetic-like biphasic dose responses within the biological, toxicological and biomedical sciences. Hormetic dose responses have been shown to be highly generalizable and are observed across a broad range of biological models affecting a wide range of endpoints as well as being independent of chemical class and/or physical agent. This broad generalizability of hormesis has led some risk assessment oriented scientists to explore the implications of hormesis in the standard setting process. The predominant focus of these activities has been directed to assessing the implications of hormesis for community exposures to non-carcinogens and carcinogens. The present issue of the BELLE Newsletter extends the evaluation of the potential risk assessment implications of hormesis into the realm of industrial hygiene/occupational health. This issue features a white paper by Drs. Michael Jayjock and Philip G. Lewis, who argue for a role of hormesis in the derivation of occupational health standards. Upon the completion of the manuscript by Drs. Jayjock and Lewis it was sent to six scientists for expert commentary. Their comments follow the manuscript of Drs. Jayjock and Lewis. It is our hope that this issue of the BELLE Newsletter will both challenge and encourage those in the field of industrial hygiene to explore the scientific foundations of hormesis and its potential applications to their field.

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This paper considers hormesis as a valid and potentially valuable alternative hypothesis for low-dose response in the context of occupational health risk assessment. It outlines the current occupational risk assessment paradigm and its use of high-dose toxicological data in setting occupational exposure limits (OELs). This present effort is a call to science to investigate the potential promise of hormesis in providing a prima fascia experimental evidence for a low-dose threshold of toxic effect to chemical agents. The scientific effort and advancement advised in this piece could also lead to experimentally validated quantitative estimates of the toxic effect extant at occupational exposures in the region of the OEL.

Keywords: hormesis, low dose, threshold, risk assessment, occupational, exposure limit

INTRODUCTION

The industrial hygiene risk assessment paradigm relies primarily on occupational exposure limits (OELs) to estimate and ascribe a level of exposure that is safe for workers. That is, the industrial hygienist (IH) typically compares measured or estimated airborne levels in the workplace with these exposure limits and if the exposure levels are significantly below the limits they declare the situation to be essentially "safe" and without unacceptable risk. If exposure exceeds the exposure limit then controls are implemented.

When an IH compares measured or estimated exposure (EXP) to the exposure limit (OEL) he or she almost invariably does so with the classic hazard index ratio of EXP/OEL. For them, the OEL in this world embodies the toxicity half of the equation. In this prevailing scheme the industrial hygienist views the OEL as a graded indicator which is inversely related to the toxicity of the substance. Thus, a low OEL signifies a relatively high quantitative measure of toxic potential for the controlling adverse health effect and a high OEL a relatively low level of toxic effect per unit dose. Thus, if the OELs are reasonably well established and well explained, we believe this time-honored approach allows exposure experts and other non-toxicology experts and stakeholders to put the estimated exposures into context.

Indeed, if we assume that the agent's health effect or toxicology represents half the knowledge needed to do a risk assessment (with exposure representing the other half) then essentially all of the judgment related to the toxicology of the compound in the context of workplace exposures can be considered to reside within this limit (i.e., the OEL).

Our experience is that many if not most practitioners of human health risk assessment and almost certainly a majority of those involved in the practice of industrial hygiene believe in thresholds of toxic effect. That is, the typical industrial hygienist (IH) trusts that at some relatively low level of exposure of any agent that no one (no experimental animal or person) will die or suffer any ill-effect as a result of that exposure. Further, as industrial hygienists we have faith that this zero response level or zero risk threshold will be irrespective of how large the exposed population might be at that critical threshold dose.

What we **believe** and what we have reasonable power to assert or prove with the data and scientific certainty are quite different matters, however. Our view is that this disparity between belief and supported scientific evidence engenders a reasonably high level of controversy and conflict within the stakeholder community for occupational health and safety. Also, controversy born of opinion or belief versus scientific substantiation is not limited to the occupational arena since the same basic approach to overall risk assessment as described below is used with regard to community and other venues of non-occupational exposure.

Without going into the detailed mathematical discussion, it suffices to say that the statistical power of our classical quantal test of toxicology (numbers responding/numbers tested in groups) are quite limited. Indeed, it can be shown rather convincingly that the dose that produces zero response in a tested group (i.e., the **No Observed Effect Level** or NOEL) could represent a response level as high as 20% in a real world population of reasonable size. Based on a computer simulation study, Leisenring and Ryan[1] show that the average NOEL for quantal data could actually represent 3 to 21% response level in a population depending upon the experimental design and shape of the dose-response

curve. This is obviously a significant level of risk for animals and humans if they have the same response potential and is usually only a moderate extrapolation from the lowest observed effect level in many tests of toxicity.

The binomial theorem specifically and precisely quantifies this relatively low level of statistical power. Using the theorem one can calculate the probability of having zero response (i.e., a NOEL) in a test of 20 animals in which the true level of adverse toxicology response to the agent is 5%. It is simply:

$$\text{Probability} = q^n$$

In this equation q is the proportion of the population that is truly negative or unaffected by the exposure. In this case q = 0.95 and the number tested or "n" is 20. The probability of having a NOEL in this case is 0.37 or 37%. That is, there is a greater than 1 in 3 chance that any test of 20 animals will show no adverse health effects at the NOEL dose. This occurs despite the fact that exposure at this level (the NOEL) would have adversely effected 5% (50,000 in every 1,000,000) if we tested the full population.

We could increase our scientific knowledge and confidence in any apparent threshold of toxic effect by looking at multiple indicators. Looking at the apparent thresholds of effects from a toxic agent in multiple biomolecular systems within the same animal would enhance our confidence that a true threshold may exist; however, these types of data are so rare as to not be a factor in the vast majority of analyses.

Thus, our opinion is that we are currently in a situation in which our beliefs and expert judgement as risk assessors (those estimating the dose-response) and risk managers (those choosing the point on the dose-response curve that is acceptable as an OEL) do not have a strong basis and proof in science. As mentioned above, we believe that this situation has set the stage for controversy and conflict among the various stakeholders in the process.

We have followed the efforts of the BELLE organization for a number of years and frankly view hormesis as having the potential of showing the way for more effective toxicological testing while providing a significantly stronger scientific underpinning of our occupational and other exposure limits. In the remainder of this article we will further develop the details of the current state of affairs and our reasons for viewing hormesis with hope. Finally we will provide our ideas for going forward with a new toxicology testing approach designed to explicate, quantify and communicate the reality of risk to workers exposed at or below the OEL.

LIMITATIONS OF CURRENT APPROACH FOR SETTING OELS

For the purpose of clarity, let us briefly recount the manner of most toxicological testing done in the last century and the beginning of this one. In the standard repeat dose toxicology test 300-1000 ostensibly identical test animals are divided randomly into 3 to 5 equally sized groups. The control group receives no treatment with the chemical. The low-dose group receives a dose of the test substance designed to render either no response or a minimal toxic response. The high-dose group is given a dose that is intended to produce a strong toxicological response without lethality to the test substance. The intermediate dose groups are anticipated to provide transitional levels of response.

In this example, the metric or measure of response is a simple proportion within each group, i.e., the number of animals responding with a toxic outcome (frank disease, tumors, morphological defects, etc) is divided by the number tested in that group to render a percentage effected. This is an "all or nothing" or quantal measure of toxic effect. That is, any particular animal in a test group at a specific dose was either considered to have had a toxic response or it did not.

As mentioned above, this standard repeat-dose toxicology testing method administers a maximally tolerated or frank effect-level dose to the top group and a few fractions of that dose to other groups to estimate the dose-response. One or more of the lower doses typically results in no effect that is distinguishable from the unexposed control and this is designated as the no observed effect level or NOEL.

In the classic approach, the NOEL is divided by a safety factor to render an occupational exposure limit (OEL). The safety factor (SF) accounts for uncertainty of several types to include testing a relatively small number of animals for less than a lifetime to predict the lifetime risk to all humans and the difference in potential susceptibility between the test animals and humans.

$$OEL = \frac{NOEL}{SF}$$

In this scheme, there is almost never any testing at or around typical workplace concentrations (i.e., the subsequent OEL) nor (except in the case of OSHA's assessment of carcinogens) is there usually any mathematical modeling of the dose-response data from this testing that results in an OEL. The sizes of the safety factors applied to the NOEL are derived from a historical perspective borne of expert judgment and experience with the largest factors (SFs) used for the most dreaded toxicological effects.

A critical foundation of this classical approach is that the OEL rendered with the above method represents an exposure that is below some threshold of toxic effect for "nearly all" workers[2]. We find this framing and terminology to be somewhat inconsistent and dissonant in that the established threshold is indeed not a threshold for at least some acknowledged but finite portion of the exposed human population.

A logical question becomes how large is this hypersusceptible portion of the exposed worker population? Indeed, a scientifically rational answer would be invaluable in informing those setting the OEL and in advising other stakeholders as to the best expert estimation of the residual risk for persons exposed at some fraction of the limit. Unfortunately, the above-described methodology is incapable of and does not attempt to provide a scientifically reasoned and quantitative answer to this question.

The authors believe that the value and inherent meaning of any OEL should be reasonably open to those responsible for controlling the exposure and for those receiving exposure in accordance with these limits. We recently outlined an approach that provides an explicit attempt to gauge and present the uncertainty and subsequent quantitative level of residual risk present at any OEL[3].

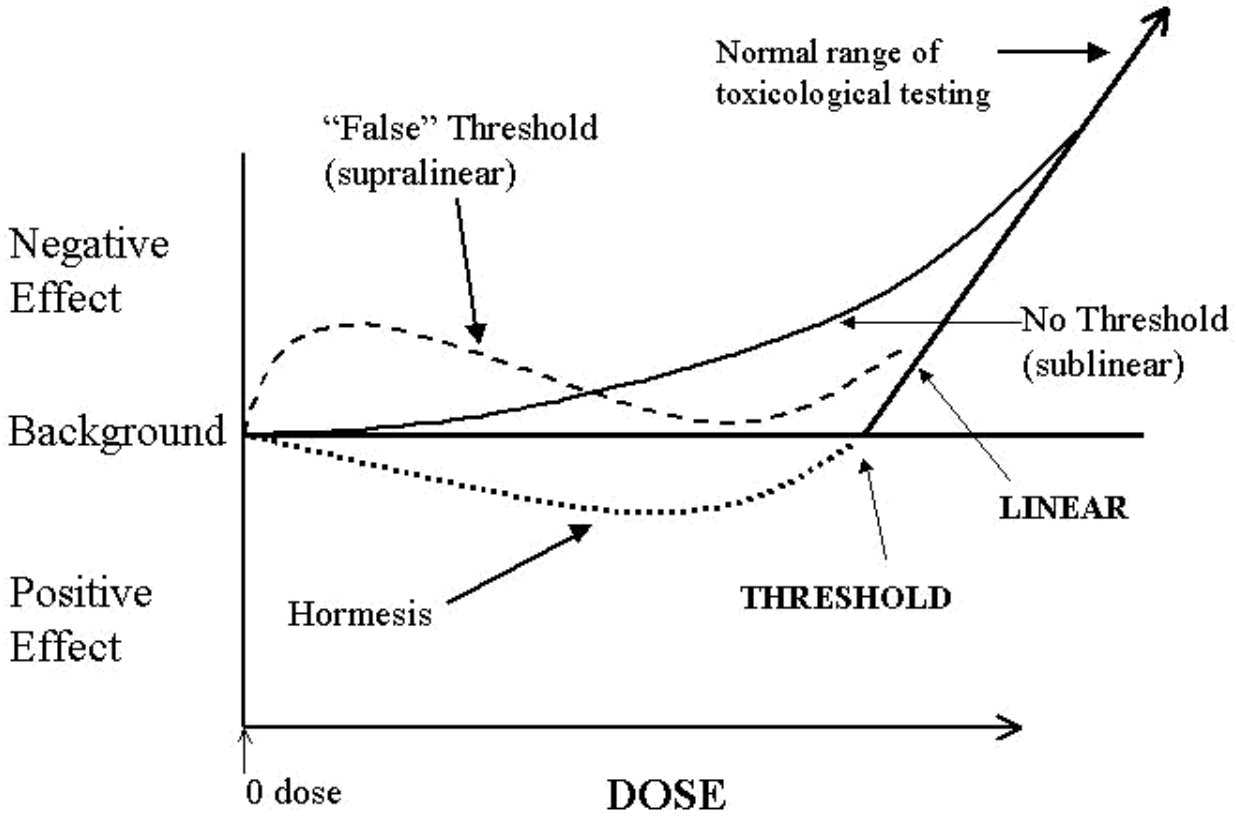
Briefly, our suggestion is that the risk at the OEL should be estimated based on available toxicology data and presented in the context of conceptual models with transparent and testable assumptions. Which model one uses for the worst, best or middle case estimates is a science policy issue that might best be decided by a consensus of the body politic and persons with standing in the process including all classes of stakeholders. The point is that this type and level of analysis arguably provides more contextual information to those using the exposure limit. Anyone examining and using it may chose to accept or reject the suppositions underlying it but the model estimates stand, not as a declaration of reality, but as an explicit and transparent quantitative portrayal or representation of reality. Like any piece of science it stands open and ready to be replaced by any superior model with a stronger database and more objective technical rationale. Its potential strength lies in the fact that it is an open declaration that provides a cogent and quantitative measure for testing and refining the model to better approximate reality.

ABSENT DATA - DECLARATIONS ABOUT LOW-DOSE RESPONSE ABOUND

Clearly, any modeling approach such as we are advocating could lead to further controversy and contention among the various stakeholders regarding which models were specifically chosen to estimate the low-dose response. Indeed, this becomes an argument without data since we almost always only have experimental information about the toxic effects at high dose and not in the region of low-dose comprising actual exposure (i.e. around the OEL).

In figure 1 below we have attempted to depict the relationship between dramatically different assumptions inherent on the shape of the dose response curve at

FIGURE 1



extremely low doses for the following situations:

No Threshold (sub-linear from zero dose)
"False" Threshold (supra-linear from zero dose)
Threshold with Hormesis

The best case (i.e., least risky) as described above is a threshold with hormesis. The next-best is a threshold without hormesis in which the risk goes to background or zero level at some finite dose and remains there until zero dose.

The worst case is the supra-linear model in which the risk rises rapidly from zero dose and then appears as a threshold or near-threshold at higher doses. Such an implausible worst-case scenario would appear to describe the situation thought to exist in the cases of endocrine disruption and multiple chemical sensitivity and could potentially describe the responses at low doses first for wildlife and then humans. In this hypothetical setting there may be a threshold or point at which there is no apparent adverse effect. However, to such doses below this apparent background risk area either for one material or for several materials in combination there would be a significant adverse effect similar to, or in some cases different than, effects seen at higher tested doses. We personally find this to be an unlikely model of reality.

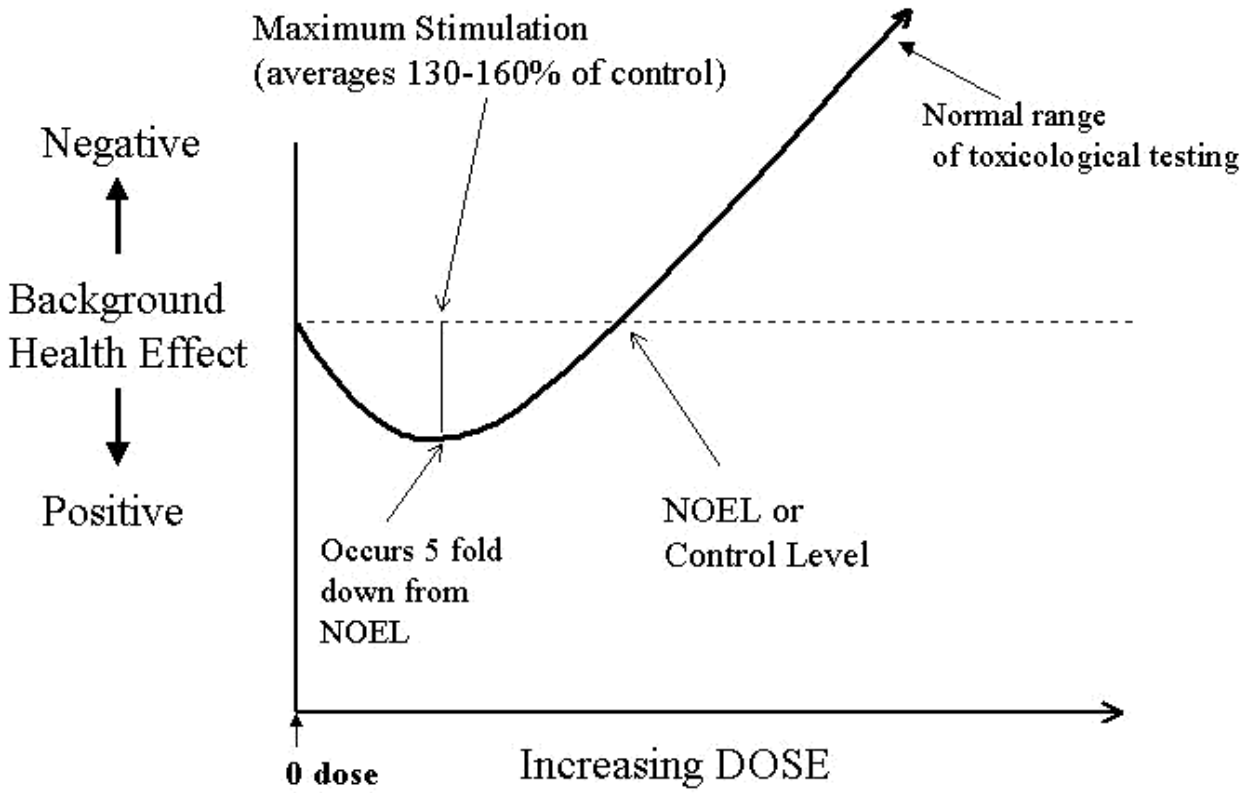
Without good scientific data there is undoubtedly a great deal of controversy around the existence of low-dose responses postulated by theories of hormesis, no-threshold and false-threshold dose-response as we have outlined them. That said, these competing theories make testing and elucidation of the situation at lower doses even more important. We simply and clearly need to apply our scientific attention and testing to what actually is happening at doses much lower than those typically used in most toxicological testing protocols.

HORMESIS AS THE LOW-DOSE RESPONSE HYPOTHESIS OF CHOICE

As mentioned above, there is often a distinct difference between belief or prevailing opinion and a scientifically supported premise. Given the above explanations of low-dose response the authors prefer hormesis as a working hypothesis of low-dose response. We believe it to be true because it makes sense to us on an intuitive level. Indeed, we can all think of situations where it is operational especially in the area of vitamins, essential minerals and pharmaceutical chemicals and ethanol. However, a recent study of the literature provides substantial evidence that this effect may be operational across a broad range of species and compounds [4]. The general outline of the theory and the finding of this literature search are in Figure 2 below:

In the realm of occupational health and safety, reported medical research on the controlling occupational health hazards of some pesticides (i.e., neurotoxic-

FIGURE 2



ity from cholinesterase inhibition) shows that biomarkers of this effect are indeed well described by a hormetic or J-shaped low-dose response curve[5,6]. Although we could not locate tests of any specific pesticide active ingredient, we did find studies in which low doses of some cholinesterase inhibitors are showing marked improvement in memory and are being considered for the treatment of patients with Alzheimer's disease[7,8].

We view all of the above as intriguing facts that plainly point to hormesis as an appropriate alternative hypothesis for low-dose response. Indeed, we are admittedly biased in suggesting it to be true. Allow us for the moment to assume that the essential universal existence of hormesis in describing low-dose response to chemical exposure is true. This means that we should be able to provide *prima fascia* evidence of a threshold of effect and the location of the low-dose threshold. This in turn will supply significantly more certain knowledge of the dose-response at or around the occupational exposure limit (OEL). It would also explicitly support the quantitative estimate of risk extant at our OELs.

Unfortunately, the current toxicological database and testing paradigm designed to feed the process of setting OELs does essentially nothing to explain the realities of low-dose response or prove-disprove the hypothesis of hormesis. We believe that a new approach to toxicology testing is required to reveal the scientific facts, help settle the issue of hormesis and inform all of the stakeholders in the process.

A NEW APPROACH TO TOXICOLOGY TESTING

We believe that one of the reasons that the scientific community has generally not looked at responses in the low-dose region of toxicity is, beyond the question of expense, the assumption that an adverse toxic response monotonically decreases to zero at some low-dose or at the ultimate low-dose of zero. It can be plainly demonstrated with statistics that detecting small differences from zero (i.e., a very low or zero dose response) is extremely problematic and perhaps impossible. Thus, if this belief in a monotonically decreasing risk to low or zero dose is the working hypothesis then it makes little sense to examine responses at low levels because they will be indistinguishable from zero. Indeed, if true it would require an impracticably large number of test animals to discern any small (1% or less) reaction to low dose. Hormesis suggests that a much different reality is operating at low-dose. If hormesis is the current hypothesis to be tested then the experimental examination of the low-dose region can pay big dividends in our understanding and estimations of real risk.

Consider the profound information provided by figure 2 and its potential impact on experimental toxicology. Note specifically the prediction of this theory that at some specific low dose there is zero reaction and that below that dose is a positive physiological response (i.e. a reduction in the background of a negative marker) as a result of the exposure. The task for the toxicologist is to determine the appropriate and useful markers of the toxic effect that typically have a non-zero background level within the body and are thus subject to reduction via hormesis.

The general theory of hormesis as shown in figure 2 indicates that the point of maximum reduction below the threshold dose for such a marker results in a "signal" of about 30-60% below background. Detecting and documenting such an effect should be well within the realm of good laboratory practices. Indeed, relatively simple calculations of statistical power show that a 25% effect will be detected at the 5% level of significance with 11 observations given that the coefficient of variation for the dependent variables is 10% or less.[9] What remains is for the toxicologists to identify the relevant biomarkers for the adverse toxicological effects in order to elucidate the hormetic dose-responses for compounds of interest.

Consider the distinct possibility that an exposure to a single agent will cause different biological effects and end-points with different dose-response functions. To further develop this possibility consider that one effect starts at the lowest dose and increases monotonically with increasing exposure (i.e. non-threshold) while the second provides a benefit at low dose that is reversed at higher doses (i.e. hormetic). The sum of these two could easily result in a net positive effect at low dose up to a threshold. We believe that, if hormesis is indeed operational, many if not most biological responses to chemicals could be of this nature.

It is not difficult to imagine that the above information would have a dramatic effect on our knowledge and control of the risk posed by occupational exposure to chemicals. As mentioned above, identification and documentation of the point of maximum stimulation provides prima fascia evidence of a threshold of toxic effect and specific information about the location of that threshold. The current or proposed OEL can then be compared with this threshold and if it is above it the quantitative level of risk extant at the OEL could be estimated. Indeed, we believe that it is difficult to overestimate the potential impact and importance of this science to informing process of risk assessment and management.

Also as mentioned above, a critical challenge for the toxicologist will be to relate the biological markers of toxic effect to quantitative estimates of the level of risk. Almost certainly this will lead us into much more complicated and sophisticated mechanistic analyses than are typically conducted in most of today's toxicological laboratories. For example, it is entirely possible that lower doses stimulate detoxifying metabolism while higher doses overwhelm it. We will need to elucidate these mechanisms as we develop and implement the analytical tools that will allow us to see and measure these changes. We also face the challenge of using this new approach in determining the relationships between multiple chemical stressors in the context of aggregate and cumulative risk. The daunting challenges notwithstanding, we view hormesis is a valid hypothesis of dose-

response worthy of significant and serious experimental investigation in the realm of occupational health and safety.

ACKNOWLEDGEMENT

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COMMENTS: IMPLICATIONS OF HORMESIS FOR INDUSTRIAL HYGIENISTS

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The concept of hormesis has been around for a long time, certainly, at least for most of the 20th century. The early tissue culture scientists were aware of the necessity of adding vitamins and hormones to cell cultures as well as the adverse effect of these compounds if their concentration were too high. H.F. Smyth, Jr. (1967) described hormesis in his explanation of sufficient challenge. The difference between immunological tolerance and an allergic reaction depends on the amount of antigen presented to an individual, as well as on the route of exposure and the timing of exposure (Barrett, 1991). As an environmental toxicologist in the mid-eighties I reviewed hundreds of published and unpublished studies in which hormesis was apparent. Whether hormesis is an observable, measurable phenomenon is not the controversy. The concern, I believe, is twofold.

First, accepting hormesis as an important and valid part of the dose-response curve questions, or is perceived to question, the validity of using of the linear dose-response curve as the central tenet of quantitative health risk assessment. A tremendous amount of energy has been spent during the last two decades on extrapolating unknown points from experimentally derived points on that line and on devising methodologies to define confidence limits on either side of that line. Hormesis is particularly troublesome because it contradicts some of the assumptions that have been made about extrapolating from the high exposure levels of experiments to the low exposure levels more typical of environmental and occupational conditions.

Second, recognizing hormesis will change the regulatory process. Although the regulatory process ostensibly relies on science, it is outside the realm of science per se. The regulatory process attempts to define an exposure level that is "safe,"which is a value

judgement outside the realm of science (Ottoboni, 1984). The regulatory process first introduced the concept of safety factors with the Food and Drug Administration in the fifties. The regulatory process in not interested in how something works, but rather it is interested, almost exclusively, in whether or not it is safe. Accepting hormesis might lead to perceiving "small" amounts of chemicals as being "beneficial."

Dr. Jayjock's paper reviews the reliance of occupational exposure limits on identifying a no observed effect level (NOEL) and then dividing that exposure level by safety factors. Once a NOEL is identified safety factors to account for the unknown effect of extrapolating from one species to another and to account for intra-species variation are used. Often the lowest dose in the toxicological data base, however, results in an effect. If that effect is not judged to be adverse this level is called a no observed adverse effect level (NOAEL); if the effect is judged to be adverse, it is called a lowest observed adverse effect level (LOAEL). Then yet another safety factor is applied because of the uncertainty of knowing at what dose level the chemical produces no effect.

When regulators evaluate the toxicological database for any particular chemical there may be a variety of different species evaluated. Each species evaluated may have a dose-response curve with a different slope. Sometimes the different species exhibit changes in different endpoints, for example, the rabbit may exhibit kidney changes, but monkeys may exhibit liver changes. In addition, the difference between an observed effect and an observed adverse effect my not be entirely clear. For example, organophosphates depress acetylcholinesterase. The first signs of this depression occur in the blood. At higher doses the acetylcholinesterase in the red blood cells also decreases. At even higher doses, acetylcholinesterase in the brain is depressed. Most would agree that depressed brain acetylcholinesterase, even in the absence of neurological symptoms, is an adverse effect. But how about depressed acetylcholinesterase in the red blood cells or only in serum? The experimental dose on which to base an occupational exposure limit always involves a judgement and, therefore, it is always arguable.

The importance of Dr. Jayjock's paper for industrial hygienists is its suggestion that hormesis be used as an indicator of whether or not an occupational exposure limit is reasonably protective. To determine whether or not a chemical is safe is an unattainable goal within the framework of science. As shown by the works of Drs. Calabrese and Baldwin (2001), hormesis has already been demonstrated in many regulated chemicals. Various toxicological studies, many of them two year chronic tox studies performed by individual companies, were reviewed by the U.S.EPA in the mid-eighties under the classification of Confidential Business Information. The phenomenon of hormesis was evident in this data base. If all the chemicals for which there is evidence of hormesis were selected, the dose at which hormesis occurs in these chemicals were identified and compared with occupational exposure limits promulgated and/or recommended for these chemicals, these two areas or points on the dose response curve could be compared. If the occupational exposure limit were equal or less than the hormetic dose, it would indicate that the occupational exposure limit is reasonably protective. This would validate the use of some exposure limits, perhaps even many of the limits for the more common chemicals used industrially, on the basis of hormesis.

Despite the promising effectiveness of using hormesis to validate the use of occupational exposure limits in cases where the data is available, integrating the concept of hormesis into the current health risk assessment methodology would still present problematic concerns. Some of these concerns include: (1) is the effect observed at the hormetic level produced by the test chemical on the same endpoint that is affected at the toxic dose? (Roberts, 2001; Jonas, 2001) (2) in multiple exposures to chemicals which all exhibit hormesis is the hormetic effect additive? synergistic? antagonistic? (3) if data on hormesis is not extractable from current experimental results should more research be conducted? And (4) once a hormetic dose has been established, is there a way to prove that exposures to a lower dose would not result in adverse effects?

Use of the dose response curve as the central tenet of quantitative health risk assessment will be replaced, not because of hormesis, but because of advances made in molecular genetics, proteomics and the mapping of the human genome. As these fields become more sophisticated, the ability to manipulate genetic susceptibility and the interaction of environmental chemicals with the human genome will develop. No longer will individual variation within the human population need to be treated statistically, nor will safety factors need to be applied in determining a "safe" dose. This new ability to identify and manipulate specific genes will shift the emphasis from statistical methods to individual evaluation. The application of molecular genetics and proteomics to toxicology will not, however, be without the introduction of new and more difficult problems.

The regulatory process is under tremendous pressure to restructure its approach to risk assessment, not because of hormesis (Chapman, 2001), but because much of quantitative health risk assessment has been, or is perceived to have been, in a vacuum. Quantitative health risk assessment promulgated by the EPA in the eighties has become codified. Unfortunately, the current codified risk assessment evolved from methodologies based on mid-1900s science and, in some cases, no science at all. It is interesting that the use of safety factors started with the Food and Drug Administration and was not based on science. In the first half of the 20th century the "dread" disease was lung disease, not cancer, as it is today. Furthermore, studies in the nineties have indicated that economic factors correlate very well with the quality of health care that an individual receives, i.e., the higher individual income, the better the health care. Obesity is also another risk factor that has become, unfortunately, quite common. Pointing out

how risk needs to be evaluated as part of a holistic approach to creating societies, does not, in my view, minimize the importance of carefully controlling the waste and by-products that are put into the environment. It is very important, however, to integrate health risk assessment into the bigger, much more complex, view of what we value as a society.

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REVIEW OF IMPLICATIONS OF HORMESIS FOR INDUSTRIAL HYGIENE

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Disclaimer: These comments represent my personal review of this article. They should not be construed as implying an opinion on behalf of either ACGIH or the Threshold Limit Values for Chemical Substances Committee of ACGIH.

I am drawn to the concept of hormesis as a working model of biological organisms' responses to low doses, for reasons similar to those of Jayjock and Lewis. The concept does make intuitive sense, from an evolutionary point-of-view. Organisms that develop overcompensation responses to toxic insults at low levels are reacting in a protective manner that may give them an advantage over other population members.

Hormesis may, indeed, represent a better model for deriving the "no observed adverse effect level" (NOAEL) for occupational exposures to some chemical substances. Literature reviews by Calabrese and Baldwin (1998) suggest that hormesis usually occurs at a level 30-60% greater than controls. More importantly, they find that the maximum response usually occurs at a five-fold distance below the NOAEL. Armed with these two facts, and the appropriate experimental design, it could be relatively easy to arrive at a NOAEL from the "bottom up" rather than the currently-employed "top down" approach.

It was clear to those who first developed the OEL paradigm that exposure limits were "fuzzy" numbers—made of a mixture of uncertain scientific data and professional judgment. Early discussants of the OEL concept warned against their use as regulatory "speed limits" –and suggested they should always be expressed as a range. These warnings were ignored in the rush to

create regulatory levels with the advent of OSHA and EPA in the 1970s. Much time and effort has been expended on developing better "models" for exposure limits of all types, which did not serve to make the numbers any less fuzzy. No or little money has been spent in the arenas where the variability lies—e.g. measurement of exposures and health outcomes in animal and human populations, elucidation of the disease process, and selection of appropriate health end-points. Perhaps the application of hormesis to the design of toxicology studies could spark a much-needed revolution in thinking about OELs, moving us away from mathematical modeling to a better understanding of the underlying biologic processes.

There is one caveat I would offer to this discussion, however. It is important to keep in mind that hormetic responses may not be associated with every biological process. Overcompensation may yield evolutionary success in some instances, but it is just as likely to lead to unhealthy consequences in others. Since the biological end-point is of primary importance in the development of an occupational exposure limit (OEL), some thought should be given to those biological processes and outcomes most likely to exhibit a hormetic response, prior to the implementation of new experimental designs.

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COMMENTS ON IMPLICATIONS OF HORMESIS FOR INDUSTRIAL HYGIENE

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Although demonstrated evidence for hormesis of an agent could be important in setting occupational exposure limits (OELs) for industrial hygiene, several practical problems may limit the utility of toxicologic testing for hormesis. This commentary responds to the lead article of this section, in which Jayjock and Lewis propose using the results of tests for hormesis to guide the establishment of OELs. The principal difficulties may include: a different mechanism or even a different effect leading to the conclusion of hormesis; distinction between a threshold for a health effect and a crossover point in the dose-response relationship; estimation of threshold or crossover point from limited test data and estimation of slope at this point; sensitivity of tests for hormesis; and cost of testing. Nevertheless, the proposals of Jayjock and Lewis have considerable merit, and exploratory testing could be useful.

INTRODUCTION

In their lead article, Jayjock and Lewis call for toxicologic testing of occupational hazards at low levels of exposure as an aid to establishing meaningful occupational exposure limits (OELs). My understanding of their line of reasoning is as follows:

1. Many if not most hazards (principally, but not necessarily exclusively, chemicals) will exhibit hormesis at low levels of exposure.

2. Hormesis implies that some non-zero level of exposure poses zero risk of the health effect of concern for occupational exposures. That level can be described as a threshold.

3. Toxicologic testing of hazards at very low levels of exposure can provide information on:

a. Whether hormesis occurs, implying a non-zero threshold

b. The threshold exposure level

c. The shape of the dose-response relationship in the vicinity of the threshold

4. Armed with this information, industrial hygienists can make better decisions about setting an OEL for the hazard and understand how much residual risk might exist if exposure occurs near the OEL.

I will discuss each of these elements below.

DISCUSSION

1. Prevalence of hormesis

The simplest concept of hormesis is that the incidence of an adverse health effect is LOWER for low levels of exposure than at zero exposure. For example, if chemical x causes excess cancer at high doses, low doses will result in fewer cancers than the baseline rate for zero exposure. The data for liver cancer in rats from exposure to TCDD can be argued to show this pattern. Or if chemical y inhibits cholinesterase relative to baseline at high doses, low doses will result in enhanced cholinesterase production.

I think this concept is simplistic. Although vitamins and minerals clearly are beneficial at low doses and harmful at high ones, scurvy is not the toxic effect of concern for megadoses of vitamin C. Similarly, the adverse side effects of pharmaceuticals are rarely the same as the effect for which the drug was prescribed. Even in the case of cancer, I suspect that the mechanism of cancer prevention at low doses (e.g., stimulation of the immune system) is different from the mechanism of carcinogenesis at high doses (e.g., DNA damage). Therefore, a better concept of hormesis, in my view, is the recognition of a tradeoff between the beneficial and harmful effects of an agent. If I am correct, the hormetic behavior shown in Figure 1 of Jayjock and Lewis might well be the net result of a linear, no-threshold adverse effect and a plateauing beneficial effect with completely different mechanisms. Jayjock and Lewis acknowledge this possibility near the end of their article.

Although I am open to the idea that tradeoffs between beneficial and harmful effects of occupational hazards may be common, and that they should be considered in setting OELs, I am much less receptive to the idea that the simple model of hormesis (protection from the exact effect of concern at low levels of exposure) is very prevalent.

2. Existence of thresholds

If the simple concept of hormesis holds, then a non-zero level of exposure that produces zero excess risk must indeed occur. That conclusion also holds for the next most simple concept, in which the agent both causes a specific effect at high doses and protects against that effect at low doses, even though by different mechanisms. If the beneficial effect and the harmful effect are different, however, then the crossover point is not really a zero-risk level. Instead, it is an exposure level at which the VALUES of the beneficial and harmful effects are considered equivalent.

I therefore believe that it may be misleading to call the crossover point a threshold. Many if not most toxicologists and risk analysts think of a threshold as a value below which no effect, beneficial or adverse, is occurring.

3a. Testing for hormesis

Jayjock and Lewis believe that toxicologic testing at low doses will reveal hormesis for at least some agents of interest to the industrial hygienist. They believe that the hormetic benefit will often be in the range of 30-60% below background at its peak. While I agree that such a decrease would be easily detectable for some endpoints, I am less optimistic about the frequency of such results. First, many of the health effects of concern to the industrial hygienist have relatively low baseline incidence. For example, the baseline incidence of liver cancer in the rats given TCDD was one or two per group. Even though the reduction in incidence was 100% at the lowest dose, the finding was not statistically significant and has not convinced anyone who believes in the linear no-threshold hypothesis that hormesis was involved. Second, I am simply not as optimistic as Jayjock and Lewis that 30%+ reductions in incidence (or in a graded response) will be common even in those cases where baseline rates are substantial. If toxicologists are uncertain about the location of a crossover point in the dose response, how likely is it that they will locate a test exposure that is close to the peak of the hormetic response?

3b. Threshold exposure level

For the same reason, I am concerned that even clear detection of a hormetic response will not necessarily help to locate the threshold or crossover exposure level. Unless toxicologists are willing to test several low levels of exposure, the shape of the dose-response relationship will remain uncertain, and the crossover point may not be much more precisely located than by the uncertainty (safety) factor approach.

3c. Shape of the dose-response relationship

Even if the testing were sufficient to locate the crossover point with reasonable certainty, the same limitations might prevent defining the shape of the dose-response relationship with any confidence. A policy-driven assumption about the shape might still be required.

4. Utility for OEL determinations

The comments above might suggest that I am very negative about the proposals of Jayjock and Lewis. That is not the case. If reliable, unambiguous information regarding hormesis could be generated for occupational hazards, their risk management could be much improved. Better determinations of appropriate OELs should be possible regardless of whether the observed beneficial effects are simple hormesis, as described above, or the more complicated case in which different beneficial and harmful effects must be traded off. One of the greatest limitations of current risk management is considering only risk of harm and cost of control in the tradeoff decision. For non-carcinogens, that limitation is compounded by having no measure of risk associated with the OELs; the potential benefit of lowering an OEL or the potential harm of raising it cannot be assessed. The simple fact that we are uncertain about the level of exposure for which a threshold or crossover dose occurs means that there is some risk of harmful effect for any level of exposure. Having an explicit dose-response relationship would enable such determinations. As with carcinogens, a policy-neutral risk assessment model would lead to better risk management, but even a model with policy-driven conservatism, like the linear no-threshold assumption, would permit tradeoffs to be made. The information that Jayjock and Lewis propose to be gathered would make better decisions possible.

I have one final caveat, however. For some agents, the cost of testing to demonstrate hormesis may outweigh the benefit of better determinations of the OEL. In the long run, such testing may well be advisable only for those agents for which current OELs are considered significantly burdensome. A pilot program to demonstrate whether the potential benefits of low-dose toxicologic testing are substantial seems desirable.

HORMESIS: THE NEW APPROACH IN RISK ASSESSMENT?

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Traditional approaches for setting the Occupational Exposure Limits (OELs) is dependent on the utilization of standard repeat-dose toxicology testing method to achieve the No Observed Effect Level (NOEL). In classical toxicological testing, the doses evaluated for toxicity have been significantly higher than workplace concentrations. Toxicity testing at workplace concentrations has not been feasible because of the large number of test animals required, and a lack of an established surrogate end-point. Modeling techniques for the levels of exposure between accept exposure and the NOEL have not been developed. Thus, there is felt to be a "safe" low level of exposure, followed by an increasing risk of negative health effects above a threshold. What subtle effects on health there are in this range of "safe" doses are unclear. Drs. Jayjock and Lewis discussed a new paradigm for the evaluation of occupational exposure levels of toxic compounds, through the concept of hormesis.

Hormesis is a dose-response phenomenon characterized by either a U-shaped or an inverted U-shaped dose response depending on the different end-point measured [1]. This U-shaped curve would suggest that there is some protective benefit to low levels of exposure until a threshold dose, where the negative effects of exposure become dominant. The concept of hormesis is still in development and is not accepted by all biological and medical scientists [2]. The search for hormetic responses in the toxicological literature reveals that 98-99% of studies cannot even address the hypothesis in an adequate manner[3]. Proponents of hormesis have argued that failure to observe hormesis may not be evidence of its absence, but rather due to the range and intervals between concentrations tested [4]. When studies are properly designed to evaluate biological activity below the traditional toxicological threshold, low-dose stimulatory responses may be observed with high frequency and display specific quantitative features [3]. A new database from the toxicological literature suggested that 245 (37%

of 668) dose-response relationships from 86 articles (0.4% of 20,285) satisfied requirements for evidence of hormesis [5]. In recent years, the development of the concepts and the applications of hormesis in human health risk and ecological risk assessment have been addressed in several workshops, and some journals have special issues to discuss the application of hormesis (*J. Appl. Toxicol.* 2000;20 (2); *Hum. Exp. Toxicol.* 2001;20 (3); *Hum. Exp. Toxicol.* 2001;20 (6); *Crit Rev Toxicol.* 2001;31(4-5).

Jayjock and Lewis advocate for the application of hormesis in the field of industrial hygiene. They compared three major dose-response relationship models: sub-linear no threshold model, supra-linear "false" threshold model, and threshold with hormesis model, and recommend hormesis as the low-dose threshold for the occupationally-exposed populations. They suggest the use of hormesis as a default assumption in the risk-assessment process [3], and propose that their ideas move forward a new toxicology testing approach (biological markers) designed to explicate, quantify and communicate the reality of risk to workers exposed at or below the OEL, based on hormesis. Yet to utilize a hormesis approach as a default assumption runs counter to the established approach of industrial health risk assessment where thousands of individual workers may be affected adversely.

The occurrence of hormesis has been suggested in various biological, toxicological, and pharmacological investigations [6]. Furthermore, hormesis has been described for various agents or mixtures such as pesticides, metals, petroleum products/constituents, solvents, and radiation. However, it is impossible even to test the hormesis hypothesis in many commonly employed experimental model systems for end-points of public health concern [3]. For this reason, it is difficult to convince scientists, policy makers, and the public to accept this theory as universal and to incorporate this phenomena into public policy [7]. The overall occurrence of hormesis remains very difficult to evaluate based on currently available data. Finally, the lack of a valid statistical test for hormesis is a major limitation when evaluating evidence for hormesis [8].

Another major limitation of using hormesis as a true biologic phenomenon is that the mechanism of the stimulation of hormesis is not clear. It is not known whether a toxic substance stimulates the immune system generally or the immune system response is toxicant-specific, as the enhanced responses at low doses do not necessarily mean the existence of hormesis [9]. Even if hormesis is biologically true, its assessment is limited due to the difficulties of study design, biological markers selection, statistical power considerations, model and end-point selection, and risk model approaches [3]. Toxicologists must find the "appropriate and useful markers" for compounds of interest to assess the risk of workers exposed at or below the OEL. Although the authors suggest such surrogate biologic models as end points, the problems associated with the practical evaluation and validation of such markers suggest that there is a long way to achieve the goal.

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HORMESIS AND INDUSTRIAL HYGIENE: A NEW HYPOTHESIS FOR LOW-DOSE RESPONSE IN OCCUPATIONAL RISK ASSESSMENT

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ABSTRACT

Jayjock and Lewis' study "Implication of Hormesis for Industrial Hygiene" represents a challenge for the scientific community to consider hormesis as a possible working hypothesis for redefining risk assessment strategy for low-dose exposures in the realm of Industrial Hygiene. This invited commentary aims at examining some aspects of the study for which no proven and conclusive scientific evidence has yet been found, such as the limited nature of some statistical tests, the calculation of the safety factor, the place occupied by hormesis in Industrial Hygiene and finally the impact that scarce knowledge of this phenomenon and rejection by part of the scientific community has on the possibility of using hormesis in the safeguarding of workers' health.

Keywords: hormesis, risk assessment, low dose, occupational medicine, industrial hygiene

The aim of Jayjock and Lewis' study (2002) of the implications of hormesis in the field of Industrial Hygiene is intriguing since, with the exception of a few considerations published recently (1), there is no previous example of such a well-constructed work on this subject in the literature.

The Authors not only demonstrate their thorough knowledge of the basic concepts of Industrial Hygiene, but they also show they are aware of the limits risk managers and assessors face when attempting a correct evaluation of occupational risk in order to protect workers' health.

To ascertain whether hormesis could be a working hypothesis in the field of Industrial Hygiene, Jayjock and Lewis take up the scientific debate concerning the possibility that, at low-dose exposure to xenobiotics, there is a threshold level below which toxic effects may be excluded.

In the introduction, they point out that the existence of an effect threshold for toxic agents is "accepted" by most human health risk experts. The Authors then demonstrate the statistical weakness in the classical quantal tests used in toxicology. With the aid of a mathematical model, they show how in each experiment conducted at No Observed Effect Level (NOEL) in a group consisting of a limited number (n = 20) of animals, the probability that no effect will be observed is three times greater than the possibility of an observed effect. This apparently paradoxical result is obtained despite the fact that the model starts from 5% adverse responses to the toxic agent. The Authors indicate that this result has a dramatic impact when the real size of exposed groups is taken into consideration. In fact, in a large group of exposed subjects (e.g. 1.000.000), 50.000 would be affected. We agree with Jayjock and Lewis that the statistical power, and consequently the predictive capacity of tests of this type, which are commonly used in toxicology, may be inadequate.

The next paragraph in the study draws attention to a point that is widely shared by the scientific community: i.e. that of the interpretation of results obtained by means of current experimental models. Regarding this question, we fully share the Authors' belief that this aspect needs more thorough consideration. First of all, the observable toxic effects on groups of animals exposed to different doses are mostly documented using a quantal criterion. The dose administered (NOEL) to the group, at which no effect is observed, is then divided by a safety factor (SF) whose definition, is rather arbitrary.

We share the perplexity expressed by the Authors due to the fact that an Occupational Exposure Limit (OEL) defined in this way leaves uncertainty over the number of subjects who are not protected at this level. This emphasises the inadequacy of OEL as a predictive tool compared to the model published recently by the same authors (2). Furthermore, as the Authors clearly point out, the current OEL has the disadvantage of failing to provide information on dose-response relationships in the low- dose range, i.e. in the region of doses

where hormetic phenomena could occur.

In the paragraph "Absent data - Declarations about Low-Dose Response Abound" the Authors refer to three types of dose-response curves. The hormetic curve is taken into consideration first as being "the best case (i.e. least risky)" compared to the No-Threshold and "False" Threshold.

In our opinion, scientific proof is needed to substantiate the claim that hormetic curves are *a priori* less risky than linear ones. Jayjock and Lewis' interpretation of Fig. 1 in their study could be ambiguous as, once the experimental model (end point, type of animal, substance, administration route, doses, etc.) has been established, it must be assumed that there is one, and only one, dose-response curve. Therefore, in our view, it is inappropriate to compare the 'riskiness' of one-dose-response curve with another. Moreover, if an experiment resulted in a hormetic type dose-response curve rather than a linear one, or *viceversa*, evaluation would have to exclude any hypothetical advantage associated with the shape of the curve itself, and the comparison of two curves obtained by modifying only the end-point of the experimental model would be meaningless. Furthermore, on the basis of current knowledge, we deem any evaluation of "non harmful / harmful" effects to be premature, if not questionable since, as others have pointed out (3), if a phenomenon is considered non harmful for the organism under investigation, this may not be the case for the subjects related to it.

In our opinion, even if hormesis is recognised to be a generalizable phenomenon, evidence of its presence does not justify it being used as a "working hypothesis of low-dose response", given the possibility that, the dose-response relationship could be described by a different curve e.g. the No Threshold one. Careful examination of the text does however show that the Authors themselves claim only to "prefer" this working hypothesis, and even admit that they are "biased in suggesting it to be true".

Jayjock and Lewis recall that some biomarkers of neurotoxicity induced by cholinesterase inhibitors, are described by hormetic or J-shaped low-dose response curves (1, 4). In our opinion, an analysis of the two aforementioned studies should lead us to conclude that thorough investigation is needed before attributing hormesis (5), even if at first sight the relationship trend seems to indicate its presence.

With regard to a hormetic effect related to enhanced memory in laboratory animals (5), we must remember that the presence of a stimulatory effect at low-doses does not necessarily indicate hormesis since, according to Calabrese and Baldwin's definitions (5), hormesis also involves an inhibitory effect at high doses. Haroutunian et al.'s study (6) fails to report dose-response relationships for the test substances sufficient to substantiate the existence of any of the hormetic trends defined by Calabrese and Baldwin (6).

As far as Calabrese and Baldwin's study (1) is concerned, we agree with the Authors that the two dose-response relationships can be defined as hormetic curves since they satisfy the entry and evaluative criteria set in this study (1).

Likewise, it is difficult, on the basis of the only data available, to ascribe to hormesis evidence of improvements observed in patients affected by Alzheimer's disease following the administration of low doses of cholinesterase inhibitors (7) since, as stated previously, hormesis can only be verified in a dose range that also includes the inhibitory effect (5).

We disagree with the Authors' claim that , in the presence of the same substance characterised by two dose-response relationships (for example linear and hormetic) for two different effects, the latter can be added together. Moreover, it is not clear how this hypothetical sum can results in an overall beneficial effect at low doses.

We fully agree with Jayjock and Lewis' comments concerning the reasons underlying the lack of attention given to the study of low doses by the scientific community. Nevertheless, unlike the Authors, we prefer to adopt a more cautious stance regarding the potential dividends that laboratory study of low doses might provide in terms of improved risk assessment. Indeed, for substances where a hormetic effect can be detected experimentally, a threshold level should be established for humans. This is a highly complex task on account of intrinsic difficulties linked to the evaluation of external exposure to a single substance or combination of substances, to the intake route, to the choice of the control group and end-point as well as to time parameters.

In conclusion, Jayjock and Lewis' study "Implication of Hormesis for Industrial Hygiene" deserves credit for starting up a debate on a subject to which the scientific community has so far dedicated little attention for reasons that have already been fully illustrated (1). It is our belief that in the near future more interest will be shown in this topic and researchers will obtain and exchange more information on hormesis. In our invited commentary we have attempted to underline the positive aspects of Jayjock and Lewis' study and to add a few comments based on our experience in Industrial Hygiene. It is our opinion that a thorough and conclusive answer to the very serious questions posed by the Authors will only be available in a relatively near future when hormesis will have been definitively settled and its ethical implications will begin to be assessed with regard to occupational health safety.

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COMMENTS ON THE JAYJOCK ET. AL. PAPER

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The paper by Jayjock and Lewis entitled "Implications of Hormesis for Industrial Hygiene"(1) and a similar previous paper by Jayjock, Lewis and Lynch entitled "Quantitative Level of Protection Offered to Workers by ACGIH Threshold Limit Values Occupational Exposure Limits" (2) critiques the precision of occupational exposure levels (OEL's) and similar standards. The authors point out that the stated objective of the ACGIH Threshold Limit Values (TLV's) to "protect nearly all workers from adverse effects following repeated exposure to the agent" fails to provide information as to the level and consistency of protection provided by the recommended value. It is true that some TLV's are more protective (have a greater margin of safety) than others but the documentation for such agents usually provides some justification (the nature and severity of the adverse effect or the inability to detect and/or quantitate the agent etc.). It is also true however, that part of the variability in the level of protection associated with each TLV recommendation results from the fact that the process used to establish TLV's is judgmental rather than being protocol/cookbook driven. The ACGIH TLV committee, like most groups that are involved in establishing OEL's uses the threshold value for the most sensitive adverse effect produced by an agent as the basis for setting the standard for that agent. A variety of factors are then considered in making the final recommendation including the variation in the sensitivity of individual workers to the adverse effect of the agent. Since this variability in sensitivity normally exhibits a gaussian distribution, in those cases where there is sufficient data, the standard error of the OEL

could be determined and listed together with the recommended value to provide a quantitative replacement for the "nearly all" estimate of worker protection. The industrial hygienist or other users of the OEL's could then simply use multiples of the standard error to calculate OEL values with associated risks of 1/100, 1/1000, 1/1,000,000 etc. A related approach which was evaluated by the Presidential/Congressional Commission on Risk Assessment and Risk Management (3) would be to replace the current single OEL value with a range of values that would encompass both sensitive and resistant individuals. In their original paper, Jayjock et al. (2) have suggested a somewhat similar approach to define the best, average and worst case estimates of OEL risks. They also suggested that the hormetic effect of an agent could be used to define the "best" case estimate and this suggestion has been extended and amplified in the current paper (1).

The recommendation that occupational exposure limits should include information on the level of protection provided by the established values could also apply to other single value standards or recommendations such as dietary requirements for vitamins and essential nutrients, drug dosages and to all such advisory and regulatory decisions in which intraspecies variability is a factor. Thus the development of methods or approaches which would improve our ability to quantitate and communicate this type of information would be of value both to the users and to those responsible for recommending such values. However the gaussian distribution and the standard error of an OEL value is directly dependent on the slope of the dose response curve and thus agents with a very steep dose response will have a narrow distribution and a low standard error. Conversely agents with a flat dose response curve have a broad distribution and a very large standard error which limits their utility for quantitating the margin of protection. This problem also limits the approach of using ranges of values since agents with a broad distribution and large standard error would have a range of values that would be impractical for regulating exposures. Most OEL's are based on an standardized exposure of 8 hours/day and 5 days/week and it is likely that the utility of the standard error in predicting the range of sensitivity within a population could be improved by defining exposure in terms of both dose and time since this would provide a more accurate response curve than one based on dose alone (4,5). The EPA program to establish Acute Exposure Guideline Levels for Hazardous Chemicals (AEGL's) uses both time and dose to define exposure and this has reduced the variability and uncertainty of the recommended values (6,7).

Since the concept of hormesis involves a U-shaped dose response curve with an inherent threshold, it is obvious that any agent exhibiting hormesis should be regulated on the basis of this threshold to preserve the beneficial effects and avoid toxicity. The recommendation by Jayjock et al. to use hormesis to improve the establishment of OEL's is a reasonable extension of this approach but there are practical limitations on implementing the suggestion. Hormesis may be a universal biologic phenomenon which occurs with all chemicals and agents but we do not have low dose studies that demonstrate hormesis for most of the agents for which we need OEL's and as the authors point out, obtaining this data would require a new approach to toxicologic testing. To support this kind of recommended change, the authors should provide examples from the existing hormesis data base to illustrate how their approach would be used in setting OEL's and the advantages of their approach in the same way that they have done in a previous paper (8) which also described a new approach for setting occupational exposure guidelines.

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We thank the commenters for taking the time to review and wrestle with the critical issues that we presented in this article.

We wrote about the implications of hormesis for industrial hygiene because of what we perceive is a critical need. Specifically, we believe that the current state-of-the-science represents an essential lack of information and accuracy relative to the effects of chemicals on humans at typical occupational and environmental exposures. The vast majority of toxicological testing done today observes or measures relatively simple end-points from doses that are at least one and sometimes several orders of magnitude higher than exposure levels experienced by people. We simply do not test at and therefore have no experimental knowledge of the effects at typical levels of exposure in the real world.

Some of the commenters disparage the use of mathematical models to estimate levels of residual risks at environmental concentrations, describing them as "protocol/cookbook driven" and needing to be replaced by a better understanding of the biological processes or the specific individual's genetic sensitivity. Our position is that the models represent the basic work product of the proper execution of the scientific method. They are the quantitative portrayal and description of reality disclosed and testable by experiments.

Choosing to become risk-based for decisions entails needs. Quantitative risk assessment requires a numeric estimate of the level of effect at the degree of exposure of interest and this invariably involves models. Any model, however, becomes dysfunctional when it is asked to predict in a realm for which there is no experimental data, *i.e.*, when asked to dramatically extrapolate to predict low-dose response. It is clearly not the fault of the model or the science if experiment data are not provided to build and validate its basic construct.

We wrote this piece to highlight the need to get these data to develop the science. This work would provide the vital, and today nonexistent experimental information, that will feed and validate the exposure-response models. We frankly and openly admit that we do not know what reality is at low dose. We clearly have opinions, we believe given currently available data that hormesis is operational. This would be a happy state of affairs if it is true because the theory predicts a "positive" detectable signal which in our view could provide experimental evidence of a practical threshold.

Some comments advise that if the beneficial effect from low exposure and adverse effect from high exposure are not the same then hormesis is somehow less legitimate. They argue that no net effect does not equal no effect or a true threshold. We agree, in its purest form we envision the experimental evidence as a measured biological marker of exposure and adverse effect which monotonically decreases with decreasing dose unit which reaches the same background level as that which exists at zero exposure. At exposures below this level the marker is less than background in the classic J-shaped curve. We would classify this type of experimental evidence as pure hormesis.

In a more complicated, probably more likely and ostensively less pure version, multiple negative health effects decrease monotonically with decreasing dose until they are balanced and then overcome by the beneficial effects of exposure. Given sufficient tools and data we would view this as a critical point of exposure. We could consider this point the threshold or frontier of net benefit to the organism. This might be classified as a practical hormesis and could be extremely valuable in gauging and managing the risk from chemicals.

We agree with comments that the science and data supporting hormesis is currently insufficient to change our regulations. Without good information about what is actually happening at low doses it would be extremely problematic to use low-dose extrapolation to predict residual risk at the OELs. This is especially true as pointed out for toxicants with relatively shallow dose-response curves. In these cases the model would predict relatively high levels of putative risk at the OEL. From our perspective we do not see this as a reason not to do the modeling and are frankly uncomfortable about the implications of the risk at low-dose for such compounds. We believe that high levels of putative risk at low-dose should be a call for investigation.

We see these comments as consistent with the main point of our article. In our opinion, the work of Calabrese and others has shown that hormesis is a valid

hypothesis worthy of testing and for developing the sciences of toxicology, industrial hygiene and occupational and environmental medicine. Given the development of tools to identify and measure the appropriate biological markers it should be easier to prove/disprove hormesis at low-dose than the current paradigm which assumes the monotonic decrease in response to zero at low or zero dose.

Our appeal is to the development of science and the generation of objective experimental evidence to prove or disprove the general existence of hormesis. The current toxicology testing paradigm of testing at high-dose and estimating/managing effects at low-dose appears to be incapable of providing the answer. We view the concept and promise of hormesis with a considerable level of hope. Indeed, this hypothesis may or may not be true but unless or until we turn our attention to actually determining what is occurring in living human tissue as a result of these realistic exposures we will continue to argue about our OELs without data.

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