BELLE NEWSLETTER

Biological Effects of Low Level Exposures

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SHOULD HORMESIS BE THE DEFAULT MODEL IN RISK ASSESSMENT?

LETTER TO THE BELLE READERSHIP

Several important developments are taking place that relate to BELLE and its impact on the field of toxicology and related disciplines. BELLE will be expanding its range of activities within the University of Massachusetts School of Public Health and Health Sciences at Amherst, MA. This will also include the development of a University administrative initiative to explore an expanded integrative range of BELLE activities within the teaching and research mission of Schools and Colleges outside of Public Health, especially within the biomedical areas. The University will also assume ownership and publish the journal ***Nonlinearity in Biology, Toxicology and Medicine*** *which has been published for the last two years by Taylor & Francis (see page 2). The journal will be published starting in the first quarter of 2005 under the auspices of the BELLE initiative, further enhancing the credibility, visibility, and reach of BELLE. The new University ownership and organization will represent a marked improvement with respect to control of activities and directing of resources in a more focused manner. It will complement the continuing publication of the BELLE Newsletter where no changes in current activities are planned.*

The ***International Hormesis Society (IHS)*** *will be created to promote the scientific study and evaluation of hormesis within the BELLE initiative (see page 2). The members will receive the journal, have an annual scientific meeting and participate in the overall direction and governance of this Society. As with other scientific societies, IHS would require application, meeting Society membership criteria, annual dues, and active participation in advisory and governance committees, etc. Furthermore, the annual BELLE symposium, now called the Hormesis Conference, would become the International Hormesis Society's annual meeting (see page 4).*

The developing hormesis activity is an expansion of the overall BELLE initiative. These expanded activities, with a clear but nonexclusive focus toward the concept of hormesis, represents a logical, positive, and expected outgrowth of the directions that BELLE activities have been directed toward over the past several years. Therefore, the readership is being invited to become more actively involved in the BELLE activities as members and leaders of the new ***International Hormesis Society****, attendees of the Hormesis Annual Conference and scientific contributors/subscribers to the* ***Nonlinearity in Biology, Toxicology and Medicine*** *journal.*

The BELLE Advisory Committee and I look forward to this expansion in activities and invite your participation to improve understandings of the dose response in the low dose zone for chemicals, pharmaceuticals, and radioactive agents and their implications for risk assessment, public policy and society.

— Edward J. Calabrese, Ph.D.

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NONLINEARITY IN BIOLOGY, TOXICOLOGY AND MEDICINE JOURNAL

Starting January 2005 the journal **NON-LINEARITY: Biology, Toxicology and Medicine (www.nonlinearity.net)**, now entering its third year, will be editorially directed by BELLE, published and owned by the University of Massachusetts/Amherst. The consolidation of all journal activities under the auspices of BELLE is designed to enhance both the visibility and leadership role of BELLE in the area of low dose biological effects as well as to facilitate an improved promotion of the journal and a more direct interaction amongst contributing authors, BELLE and the scientific community.
NONLINEARITY in Biology, Toxicology and Medicine has an internationally recognized editorial board, a strong peer-review process, with all final manuscript decisions on publication made by Associate Editors with recognized excellence in their respective areas. A listing of the papers published in NONLINEARITY: Biology, Toxicology and Medicine over the past two years can be found on the journal website. We invite you to subscribe to the journal as well as becoming a contributor via the submission of relevance manuscripts. To subscribe to the journal please visit the journal website (www.nonlinearity.net) and follow the directions for subscription.

INTERNATIONAL HORMESIS SOCIETY

GOAL

A growing number of scientists, including toxicologists, pharmacologists, biostatisticians, epidemiologists, occupational and environmental medical researchers and others have begun to display considerable interest in the topic of hormesis, a dose response phenomenon characterized by a low dose stimulation and a high dose inhibition. While there are many professional societies that have a general interest in dose response relationships, none explicitly is devoted to the topic of understanding the nature of the dose response in general and hormesis in particular. The diversity of professional societies that may consider dose response issues, including hormesis, is nonetheless quite broad ranging from the agricultural to the biomedical and clinical sciences. However, nearly without exception, these societies tend to be strongly organized around professional advancement and not focused on specific scientific concepts. This makes the issue of hormesis one of diffuse interest across a broad range of professions. The present situation represents a major obstacle for the integrated assessment of the dose response in general and hormesis in particular. In order to provide intellectual and research leadership on the topic of hormesis, a new professional association has been created called the International Hormesis Society (IHS).

The Society will be dedicated to the enhancement, exchange and dissemination of ongoing global research efforts in the field of hormesis. In addition, the Society will also strongly encourage the assessment of the implications of hormesis for such diverse fields as toxicology, risk assessment, risk communication, medicine, numerous areas of biomedical research, and all other biological disciplines including relevant engineering domains dealing with the dose response.

LOCATION

The International Hormesis Society will by administered by BELLE, School of Public Health & Health Sciences at the University of Massachusetts at Amherst.

MEMBERSHIP

The IHS is a professional society designed to enhance understanding of the nature of the dose response and its implications for science and society. Those individuals with a professional interest in these areas will be eligible for membership. Applicants for membership must complete the attached membership application form. Corporate memberships would be $1000.00 (U.S.) per year while Individual membership dues will be $125.00 (U.S.) per year. Student memberships are encouraged with an annual dues set at $10.00. Applications should be mailed to the **BELLE Office, Environmental Health Sciences Program, Morrill I, Room N344, University of Massachusetts, Amherst, MA, 01003.**

As part of IHS membership, each corporate and individual member will receive a subscription to the journal **Nonlinearity in Biology, Toxicology and Medicine**, which is a peer-reviewed quarterly journal. In addition, there will be a Society Newsletter developed for the membership. There will also be an annual conference to which all society members will receive a reduction in registration fees.

INTERNATIONAL HORMESIS SOCIETY

Application for Membership

Application for the following membership category (mark only one):

Corporate Membership	☐	$1,000.00/year
Individual Membership	☐	$125.00/year
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First Name: _____ **Date of Birth:** _____

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_____ _____
Account Number *Expiration Date*

Completed application forms should be mailed to:
BELLE Office
Environmental Health Sciences Program
Morrill I, Room N344
University of Massachusetts
Amherst, MA 01003

Telephone: 413-545-3164
Fax: 413-545-4692
E-mail: belle@schoolph.umass.edu

Signature of Applicant **Date**

BELLE Announces...

4th International Conference on

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- Industrial hygiene
- Legal implications
- Risk Communitcation

Conference Co-Directors:
Edward J. Calabrese, Ph.D. and Paul T. Kostecki, Ph.D.
Under the auspices of the BELLE Advisory Committee

For further information please contact:

Denise Leonard, M.S.
Environmental Health Sciences Morrill I, N344
University of Massachusetts
Amherst, MA 01003
Phone: 413-545-1239
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INTRODUCTION: SHOULD HORMESIS BE THE DEFAULT MODEL IN RISK ASSESSMENT?

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Hazard assessment toxicological studies, including the chronic NTP bioassay, are not designed to assess explicitly the concept of hormesis. The study design limitations include the number of doses, the dose spacing, the requirement for a certain number of doses below the NOAEL, the use of animals and endpoints with an appropriate background disease incidence, possible temporal evaluation, need for replication and possibly other considerations. Thus, in order to assess properly the possibility of hormetic dose responses considerably more time and resources are needed. Given the excessive burden these constraints are likely to impose, "proving" hormesis for each toxicological question is not only an unattractive option but a highly impractical one as well. Nonetheless, recent findings suggest that the data are convincing that hormesis is not only highly generalizable across biological model, endpoint measured and chemical class, with mechanistic understanding, but also more dominant than other dose-response models including the long revered threshold model (Calabrese and Baldwin, 2001, 2003). If this is the case, then how can the concept of hormesis be practically integrated into the risk assessment process to enhance the work of toxicologists and risk assessors rather than continuing its marginalization by the need for economically (not intellectually) burdensome proofs for each specific case? More specifically: "AT WHAT POINT, IF EVER, COULD/SHOULD HORMESIS BE EMPLOYED AS THE PRINCIPAL DOSE RESPONSE DEFAULT ASSUMPTION IN RISK ASSESSMENT?"

REFERENCE

Calabrese, E.J. (Editor). (2003). Special issue: Hormesis: Environmental and biomedical perspectives. Crit. Rev. Toxicol., 33(3-4):213-424.

Calabrese, E.J., and Baldwin, L.A. (Editors). (2001). Introduction: Scientific foundations of hormesis. Crit. Rev. Toxicol., 31:354-352.

HOW MUCH IS ENOUGH TO ACCEPT HORMESIS AS THE DEFAULT? OR "AT WHAT POINT, IF EVER, COULD/ SHOULD HORMESIS BE EMPLOYED AS THE PRINCIPAL DOSE RESPONSE DEFAULT ASSUMPTION IN RISK ASSESSMENT?"

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To consider where we want to be tomorrow my sense is that we first need to consider where we are today. In this treatment I will attempt to do this with the more general example of non-carcinogenic chemicals. The primary method of conducting toxicology today remains the testing of a relatively few animals at high dose for morphological or behavior changes. I have always found this to be a somewhat unrefined system fraught with uncertainty.

An important question becomes: How do we handle the intellectual insecurity of such issues as:

- animals as surrogates for humans,
- the testing of a relative few as representative for all and
- tested exposures that are typically orders of magnitude above those realistically anticipated in the real world ?

The short answer for me is that we manage this cloud of uncertainty by attempting to purposely overestimate the risk. I have heard a number of colleagues say "The purpose of a toxicity study is to find toxicity". Thus, the toxicological doses are chosen to provide a ranges of adverse responses. Starting at the top with a frank untoward health effect in the test animal that then monotonically decreases with decreasing dose and finally results in a low-dose response that is indistinguishable from the untreated controls (this is the much sought after and somewhat variable No Observed Adverse Effect or NOAEL). Given the lack of confidence that results from the above uncertainty inducing elements of species, statistics and exposure level, the standard procedure with non-carcinogens is to divide the NOAEL by an expert-generated but somewhat subjective safety (SF) or uncertainty factor (UF) to arrive as an exposure level that is declared to be essentially "safe".

Depending on the size of the SF or UF and the population at risk this "safe" exposure may or may not be forwarded as being protective of all persons exposed at or below that level. For example, in the case of the work place exposure limit forwarded by the American Conference of Industrial Hygienist, these levels are explicitly represented as being protective of "nearly all" workers exposed at these levels for a working lifetime.

Even though it may not be stated openly, from my perspective, the above appears to be based in the working hypothesis that non-carcinogens conform to a threshold model of toxicity and that the exposure limit is hopefully at or below the threshold for "nearly all" or everyone.

Looking at this current reality objectively, I have asked myself, "Is this the best that we can do?" Indeed, a few years ago Phil Lewis, Jerry Lynch and I wrote an opinion piece outlining an approach that would use the available data and mathematical modeling to ascribe the level of residual risk that might be extant at any exposure limit or other assigned "safe" level of exposure (Jayjock, Lynch and Lewis, 2001) . It was basically an attempt to deal with the same types of uncertainties as outlined above but to do so in a more quantitative, transparent and ostensibly less subjective manner. In the end, however, the same problem prevails regardless of the approach, ***the inherent quality of typical toxicological data are simply too poor to allow for an understanding of what really occurs in human tissues at the relatively low-doses generally extant in the environment.***

This is not to criticize the current system merely to explain its limitations. My sense is that it has served us well especially in the context of a quote I once heard from a famous leader whose name escapes me:

"Some questions can not be answered but they must be decided."

I believe that for the most part the folks setting exposure limits using this methodology have done the best they could within the confines of the information and science. I believe it is, however, exactly this lack of available knowledge provided by the current paradigm that will keep hormesis from ever being used within it.

In short, I do not believe that we will ever be able to move off of the threshold hypothesis if we continue with the current toxicological testing paradigm and its concomitant lack of elucidation. I believe that a basic change in how we do toxicology is needed.

I agree that those who study hormesis are making an increasingly stronger case for it as a viable and perhaps preferable hypothesis. Recent findings do indeed suggest that the data underlying the theory are convincing and that hormesis is not only highly generalizable across biological systems, toxicological end-points and chemical class, with mechanistic understanding, but also more dominant in nature than other dose-response models including the threshold model.

I agree with the mounting evidence; and I believe that hormesis should be the hypothesis of choice in risk assessment. But what might this mean in practical terms? One obvious and expensive possibility would be to conduct toxicology testing in a manner similar to the current practice but to shift the emphasis to low-dose response. That is, establish the toxic end-point with a few animals at high dose and dedicate the remaining resources to elucidating a NOAEL and looking for signs of stimulation at a reasonable fraction of the NOAEL. I believe that this would clearly be more expensive but it is at least potentially doable and could provide direct evidence of hormesis for that class of compounds.

The truth is that I honestly do not think that the "more of the same" approach described in the above paragraph would be a cost-effective line of attack. Nor do I think it will happen. My sense is that we simply need to be able to look much more deeply into the "black box" of human tissue response to chemical exposure and to do this we need to develop or otherwise exploit the new tools of molecular biology.

So my answer to the question posed for this piece is that ***we will only be able to move forward with hormesis as a default hypothesis after the development and use of tools from the realm of molecular biology.*** I offer this as someone with a professional background long in engineering and short in biology. Hopefully, my lack of specific knowledge in this area will not be too damaging to the credibility of the message or to the potential utility of what I am suggesting.

My sense is that we need to use the emerging and "hot" technical areas of genomics and protein-omics to determine what systems and biochemical substances are being turned on and turned-off during environmental exposures to toxicants. Combining the knowledge of these changes with information on the concurrent adverse and adaptive physiological effects in humans and animals models should start to reveal what this all means relative to the health and well-being of the exposed individual. I believe it will also clearly reveal the reality of hormesis. Indeed, it would make little sense to do any of these experiments without looking for (*i.e.*, hypothesizing) and quantifying a hormetic effect at low dose.

My sense is that all this it will also raise the level of complexity in risk assessment significantly. I believe it is going to take quite a bit of work to sort out the negative health effects that result from the induction or inhibition of multiple sites within humans and the animal models. Also, we already know that some negative health outcomes can be profoundly influenced by the characteristics of a person's specific genome. Clearly, we are going to have to deal with the hyper- and hypo- susceptible individuals. Indeed, it may be entirely possible that any reasonable and politically and economically practical exposure limit will only protect "nearly all" persons because of this reality. At least we may have some idea as to who the hyper-susceptible individuals might be, assuming that individual genetic testing will almost certainly happen in the future. Given that knowledge we should be able to protect or at least inform and thus potentially safeguard everyone.

We would, of course, not test every chemical of interest unless the tests were exceedingly cheap. We should, however, test and fill out a matrix of chemical classes. Doing this, we will eventually have enough data and knowledge to start to interpolate or otherwise bridge within the emerging pattern of information, which I have no doubt will include hormesis.

So as a final comment, I believe that the use of hormesis as a default hypotheses is ultimately coming we simply have to first change the entire toxicological testing paradigm. I believe that change is also approaching.

REFERENCE:

M.A. Jayjock, P.G. Lewis and J.R. Lynch: Quantitative Level of Protection Offered to Workers by ACGIH Threshold Limit Values (TLV^{R}) Occupational Exposure Limits, *Am. Ind. Hyg. Assoc. J.* 62 : 4-11 (2001).

A CRITIQUE OF THE USE OF HORMESIS IN RISK ASSESSMENT

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SUMMARY

There are severe problems and limitations with the use of hormesis as the principal dose-response default assumption in risk assessment. These problems and limitations include: (a) unknown prevalence of hormetic dose-response curves, (b) random chance occurrence of hormesis and the shortage of data on the repeatability of hormesis, (c) unknown degree of generalizability of hormesis, (d) there are dose-response curves that are not hormetic, therefore hormesis cannot be universally generalized, (e) problems of post hoc rather than a priori hypothesis testing, (f) a possible large problem of 'false positive' hormetic data sets which have not been extensively replicated, (g) the 'mechanism of hormesis' is not understood at a rigorous scientific level, (h) in some cases hormesis may merely be the overall sum of many different mechanisms and many different dose-response curves - some beneficial and some toxic. For all of these reasons, hormesis should not now be used as the principal dose-response default assumption in risk assessment. At this point, it appears that hormesis is a long way away from common scientific acceptance and wide utility in biomedicine and use as the principal default assumption in a risk assessment process charged with ensuring public health protection.

Key Words: hormesis, dose-response, risk assessment, default assumption

A special 2001 issue of Critical Reviews in Toxicology (1) was guest edited by Drs. Edward Calabrese and Linda Baldwin. This issue contained about 340 pages of articles on hormesis, most written by Calbrese and included constructive criticism and commentaries by other individuals including Drs. Wayne B. Jonas (2), Kenny Crump (3) and Arthur Upton (4). In this article quotations from these three people together with those of Lave (5), Kitchin (6) and Christiani and Zhou (7) will be used in our critique of the use of hormesis in risk assessment. In this article, our intent is to attempt to answer the question 'At what point, if any, could or should hormesis be employed as the principal dose-response default assumption in risk assessment?'

A short answer would be Hormesis should not now be used as the principal dose-response default assumption in risk assessment. As noted by Lave (5), 'Thus, the task of demonstrating that hormesis is true is challenging, difficult and time consuming. We are therefore unlikely to see hormesis play an important role in regulation for many years.' We agree with Lave (5) and think that at this point, hormesis is a long way away from common scientific acceptance, utility in biomedicine and use in risk assessment to ensure public health protection.

Statements about the future possible use of hormesis in risk assessment are very speculative, as are predictions of political elections. Some of the weakness of hormesis as a dose-response theory and/or basis for risk assessment are given below. Many of these weaknesses are well illustrated by quotations from prior articles on hormesis which are numbered in presentation order and grouped by the contributing author. These quotations have been annotated in indented format by us (Kitchin and Drane):

Items 1 to 5 are from Wayne B. Jonas (2)

1. 'Most crows are black. If you see a white crow it is surprising and proves that all crows are not black. It tells you little else however.'

Thus dose-response curves that appear to be, or actually are, hormetic do exist. This 'fact' does nothing to establish the prevalence, generalizability, utility or mechanism of hormetic dose-response curves.

2. 'Literature reviews no matter how well done cannot be better that the data contained in the original studies themselves.'

The original dose-response studies cited as

evidence of hormesis were not designed to prove, or disprove, the existence of hormetic dose-response curves. This makes literature reviews and interpretations based on such a literature review a post hoc matter and not an a priori test of a scientific hypothesis.

3. 'Publication is no guarantee of quality.'

The scientific standards of repeatability by other laboratories, understanding at a rigorous scientific level and generalizability to the status of a scientific theory or law are not met by mere publication in one or more journal articles.

4. 'In the former one would want to assure proper dose verification, randomization of samples, blindness of outcome measures, proper statistical analysis, and full reporting of all data.'

All five of these factors contribute to a quality dose-response study. Too often one or more of them are lacking in studies interpreted to be hormetic. For example, trying to do a current modern day statistical analysis of the 1951 Moskwa and Ber seedling growth study (8) without the original data and using the results in a post hoc manner to argue for hormesis or for the use of hormesis in risk assessment is extremely problematic. Obtaining the needed future research funding to pay for such high quality a priori dose-response studies would be a difficult task.

5. 'Investigate models where hormesis does not occur to find out why.'

If hormesis is a generalizable and unifying hypothesis, then it should occur either nearly 100% or 100% of the time. Thus we should ask the questions 'Why is hormesis not observed in every single dose-response study?' Not all dose-response studies result in hormetic dose-response curves. Using the data compiled by Calabrese and Baldwin (1), 99.6% of the 20,285 journal articles examined did not show positive evidence of hormesis. Why do risk assessments based on a dose response theory (hormesis) which is not observed in many or all scientific experiments?

Items 6 to 10 are from Kenny Crump (3)

6. 'Although there are many convincing examples of hormesis, the overall prevalence of hormesis is an open question.'

Some of the more convincing examples of hormesis may occur in the areas of dose-response curves with essential nutrients and some pharmaceuticals which are toxic at greater than therapeutic concentrations. However convincing some hormetic examples are, the prevalence of hormesis among chemical exposures in general is not known.

7. 'No matter how the Calabrese et al. database is evaluated, it is difficult to see how it can be used to estimate the prevalence of hormetic responses in general. As noted earlier, even if the number of the 1000+ studies demonstrating hormesis was known with certainty, this would only provide the numerator for a percentage. It is by no means clear what number should be used for the denominator'

Prevalence is a ratio of the number of 'cases' in a population divided by the total number of subjects, items or events in the population under investigation. An estimate of the prevalence is obviously the number of cases in the sample divided by the total sample size. Thus, Calabrese et al. have tried to estimate the prevalence of hormesis and have given us their best estimate of 86 hormetic journal articles in 20,285 total journal articles examined (0.4% prevalence). Crump refers to 'the 1000+ studies demonstrating hormesis' as standing alone without adequate knowledge of the number of those studies reviewed that did not show evidence of hormesis. We know less about the number of dose response curves that did not show evidence of hormesis or how representative the three journals studied (Environmental Pollution, Bulletin of Environmental Contamination and Toxicology and Life Sciences) are of the total biomedical literature.

8. 'The attempts at estimating the prevalence of hormesis reviewed herein did not adequately control for false positives. . . . '

In a prevalence study, cases showing evidence of hormesis must be validated to be hormetic instead of proceeding on the interpretation and belief that hormesis is present. Without validation, some of those impressions of hormesis will certainly represent false positives. A curve that appears to show hormesis does not mean hormesis is present. That is, at a very fundamental level there needs to be a definition or test of hormesis that would allow investigators to validate the presence of suspected hormesis regardless of the investigators interpretive views. We do not have that definition which, from a mathematical and biophysical point of view, is a set of axioms representing an abstraction of the hormetic process. Those axioms could then be used to create conjectures, which when proved, become theorems. Those theorems when subjected repeatedly to experimental evidence, either validate our presumed knowledge of the hormetic process or refute our current working model of dose-response relationships. Another way of begging for a definition based on fundamental scientifically valid axioms is the question, "Will the experiment that showed 'hormesis' in the original study give the same results upon repetitions of the study?" This has been rarely demonstrated. If it is demonstrated even once, does that mean the mechanisms of hormesis are well understood? The answer currently is "No."

9. 'If the data set was the most hormetic looking out of 100 examined, then to conduct a statistical test for hormesis at the standard 0.05 level one should use p= 0.0005 (the solution to 1-(1-p)exp100 =0.05) rather than p=0.05.'

If one wishes an experiment-wide alpha=0.05 when testing 100 data sets for positive evidence of hormesis, the probability that one or more data sets will be truly positive is 0.05 only if alpha for each of the 100 independent data sets is tested at the 0.0005128 level of probability. Conversely, if alpha is set equal to 0.05, as is often done in post hoc analysis, then testing 100 data sets for hormetic evidence will show positive results 5+/- 2.1794 times out of the hundred trials (mean +/- standard deviation). Thus, finding a single statistically significant positive hormetic dose-response curve in such a situation is hardly substantial positive evidence for hormesis.

10. 'Calabrese and Baldwin (1) selected only data sets that a priori appeared to be hormetic, so that there is no way to control for the false positive rate, or to generalize the conclusions from their database. Also, they analyzed their database using an ad hoc scoring system that is difficult to interpret and does not control the false positive rate.'

Remarks on false positives are under quotation #8 above. The absence of non-cases (in which hormesis is not observed) reduces their investigations to purely descriptive or observational studies, as there is no referent or control group (in the normal epidemiological sense). Even if the scoring system appears to be a good one, there is no way of determining how investigations with non-hormetic outcomes would score. Relative to normal models of the scientific method, investigations of hormesis are largely missing three very important components of the scientific method (steps 2, 3 and 4), which looks somewhat like:

1 Observation –>2 Induction –>3 Abstraction –> 4 Deduction–>
1 Observation –>2 Induction –> (etc.)
(and the cycle continues as long as the working scientific models can be improved and refined)

So far evidence for hormesis has largely been advanced in respect to step #1 (observation), but evidence for hormesis is inadequate in steps # 2, 3 and 4 (induction, abstraction and deduction).

Items 11 and 12 are from Kirk Kitchin (6)

11. 'There is no basis in a 'superior' science such as physics, chemistry, biochemistry, endocrinology or pharmacology that explains what hormesis is at the level of atoms, molecules and/or cellular macromolecules.'

The present theory of hormesis lacks the details required to build a sophisticated multi-component dose-response model. Words and biological concepts like evolutionary pressure, modest overcompensatory reaction, stimulated immune system, antimutagenic biosystem and adaptive response do not provide the needed level of scientific sophistication for quantitative risk assessment. Greater scientific detail is required to build a strong mathematical and scientific theory useful to extrapolate beyond available experimental data. Experimental data needed to justify particular hormetic mechanisms often does not exist. Other opposing dose-response theories (receptor-ligand, threshold, one hit, multihit etc.) do much better at meeting this high standard.

12. 'A problem that hormesis has in being more scientifically accepted is (a) proving that only one mechanism accounts for both the 'beneficial' and 'toxic' parts of the biphasic dose-response curve and (b) giving substantial evidence against the interpretation that 'hormesis' is the sum of many different mechanisms which add up to either 'beneficial' or 'toxic' in two different parts of the dose-response curve. Some examples of hormesis may consist of an initial beneficial dose region where several mechanisms are operating (just for the sake of argument let us say 3 mechanisms) and the overall sum of these 3 mechanisms is 'beneficial' to the organism. At higher, toxic, doses, many more mechanisms are operating (just for the sake of argument let us say 8 mechanisms) and the sum of all these 8 mechanisms puts the organism in the 'toxic' part of the biphasic dose-response curve. '

There are many examples of hormetic dose-response curves that may be multi-component in nature. Also there are several good compilations of important biological defense mechanisms which may contribute to experimentally observed hormesis. Several examples are given below:

(a) In the 1999 article by Pollycove and Feinendegen (9), at least nine major defense mechanisms are mentioned - reduced glutathione, superoxide dismutatse, catalase, peroxidase (antioxidant prevention), the many different enzymes of the repair of DNA damage and removal of persistent DNA alterations by apoptosis, differentiation, necrosis and the immune system. Considering the known biological complexity of DNA repair enzymes, apoptosis, differentiation, necrosis and immune surveillance, it is likely there are at least 100 biological defense mechanisms. Why then should we view an observed hormetic dose-response relationship as anything more than a sum of many different effects and processes?

(b) Teeguarden et al., (10) list nine defense mechanisms that can lead to apparent hormesis (attenuation of uptake processes, increased excretion, reduced bioactivation, increased detoxification, altered disposition, competition for receptor, cell cycle kinetics (DNA repair, cell proliferation, apoptosis), receptor up-regulation and/or down regulation and immune response).

(c) Recently, a mechanism and modeling based argument for multiple, rather than single, component processes contributing to hormesis has been developed by Conolly and Lutz (11). Their examples include (i) antagonistic action of two adenosine receptor subtypes, (ii) homo- and hetero- ligand dimers of androgen receptor complexes, (iii) induced DNA repair by a

treatment chemical and (iv) cell division delay caused by a treatment chemical.

I*tem 13 is from Christiani and Zhou (7)*

13. '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.'

First of all being true (in the sense of one or more positive examples) does not mean being universally true. Being universal does not mean being measurable. But let us suppose for the sake of argument that hormesis is biologically valid, universal and measurable. These three properties simply set the stage for well-defined a priori experiments to measure the presence or absence of hormesis and test the hormetic hypothesis over different regions of the experimental dose range (the x axis). Without a mathematical or statistical model, however, the experiment will want for statistical power to reject the hypothesis of non-hormetic responses in favor of the interpretation of a positive hormetic response.

In the papers reviewed by the Calabrese group (1), there are many examples of measurable responses that appear to be hormetic. There are sufficient numbers of defense mechanisms that ought to be able to lead to hormetic dose response functions under some circumstances. But at present, there is no experimental evidence that hormesis is universal. Furthermore, mathematical abstraction from experimental observations (such as exists in the area of receptor-ligand theory, for example) is not present. It is possible that in the future, several plausible theories of hormesis might be developed. Usually, that is the case before a scientific theory can be more fully developed and accepted. Finally, Calabrese and Baldwin (1) do not provide a statement as to why the positive evidence for hormesis is absent. For those experiments where there appears to be evidence of hormesis, there is no valid way of ascertaining the validity of the assertion of the presence of hormesis.

Item 14 is from Arthur Upton (4)

14. 'In light of the foregoing findings, national and international study groups generally have concluded that given appropriate adjustments for the dose, dose rate, and quality of radiation, the weight of evidence supports the use of the linear-nonthreshold dose-response model for radiation protection purposes in assessing the risks of mutations, chromosome aberrations and certain types of cancer in populations exposed to low-level ionizing radiation.'

Study groups concerned with the protection of populations from the risks of chemical exposures have generally used linear or threshold types (with safety or uncertainty factors) of risk assessment procedures. To date, hormetic approaches to radiation or chemical risk assessment have not been widely accepted in scientific circles or employed by government regulatory agencies which are charged with protecting public health.

CONCLUSION

There are severe problems and limitations with the use of hormesis as the principal dose-response default assumption in risk assessment. These problems and limitations include:

(a) unknown prevalence of hormetic dose-response curves,

(items # 6-10, 13), (1,3)

(b) random chance occurrence of hormesis and the shortage of data on the repeatability of hormesis,

(items # 2, 3, 8, 10)

(c) unknown generalizability of hormesis (in part because the prevalence of hormetic dose-response curves is unknown),

(items # 1-10, 12, 13) (1-3)

(d) severely limited generalizability of hormesis because numerous examples of non-hormetic dose-response are known,

(items # 1 and 5) (12)

(e) the argument for using hormesis as the principal default assumption in risk assessment is based on post hoc rather than a priori testing of the hypothesis of hormesis,

(items # 2, 3 and 7) (3)

(f) with retrospective post hoc searching of the scientific literature for hormetic dose-response curves, 'false positive' data sets may be a very significant problem,

(items # 6-8, 10), (1, 3, 7)

(g) the mechanism of hormesis is not understood at levels of scientific detail similar to the detailed alternative theories of dose-response such as Michaelis-Menton, receptor-ligand binding, single and multiple hit models or the Moolgavkar-Knudson carcinogenesis model,

(item # 11), (6, 7, 12)

(h) some observed cases of hormesis may merely be the overall sum of many different dose-response curves - some beneficial and some toxic.

(item # 11), (6)

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EXAMINING THE RISKS AND BENEFITS OF REPLACING TRADITIONAL DOSE-RESPONSE WITH HORMESIS

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ABSTRACT

In responding to Drs. Calabrese and Baldwin's question, "At what point, if ever, should hormesis be employed as the principal dose response default assumption in risk assessment? ", we examined the benefits of replacing traditional dose response with hormesis. In general, hormesis provides more complete useful information for risk assessment than does traditional dose-response. A major limitation of using hormesis as a default assumption in risk estimation is the difficulty of differentiating complex low-level hormetic responses from the placebo effect. A second limitation is that hormesis merely further defines one response. Most toxicoses have many responses. The most complete information takes all responses and their connections into account.

DEFINITIONS

Hormesis is the stimulation of a biological process at low concentrations of a toxin, followed by inhibition as doses progress to and then above the no adverse effects level (NOAEL) to higher dose levels considered toxic. This response may become our default dose-response in the 21st century. Drs Calabrese and Baldwin have asked to seriously consider the conditions under which hormesis could become this default response.

The answer lies in their recent review [1] where they state that hormesis will be adopted only if it offers improved explanations or means to solve problems [1-3]. In the review 1 and parallel manuscripts [2-5] they follow hormesis from its inception, through association with homeopathy to being an assertion that seems to make sense. The assertion fits many sets of data. The data were chosen with increasing rigor to eliminate the possibility of simply confirming a desired hypothesis. Both the data and the reviews of that data were peer reviewed. The data are widespread, ranging with few exceptions across all of biology [1-5]. Calabrese and Baldwin seem more interested in proving than disproving the hypothesis of hormesis [6, 7]; however, they correctly believe that hormesis provides more and improved information for problem solving [1-5].

If hormesis would replace dose-response, the underlying mechanisms of hormesis are important to understand. Qualitative dose response indicates that an increasing dose to target tissue leads to increasing toxicity [8]. To this assertion, hormesis adds that at concentrations ~20% of the NOAEL, toxins produce beneficial homeostatic responses. This beneficial response is related to an enhanced host immune (defense) effect and an enhanced ability of the host to repair damaged cells [1-5]. In this uncomplicated form, this information is exciting, and will add useful information for problem solving. These data summarize the benefits of hormetic responses [1-5]. If one considers the benefits holistically, the effects may be even more far reaching [9]. Hormesis' description of low level beneficial effects adds a positive aspect to the dose-response which will help in solving problems. For example, it has helped identify nutritional essentiality [10], vitamins, and has the possibility of identifying still more. Secondly, it helps us understand the connections of stress and readiness to the zealousness of general defense reactions [11]. However, on the surface, it seems unlikely that a little bit of brown field pollution is good for us [1-5].

To more fully understand the benefits and implications of hormesis, toxicologists or risk estimators must take into account the added risks, the downsides of low-level toxicologic stimulation and the increased healing capability. Restated, we must consider the price of being always alert, focused, turned on, forever vigilant. Most of us might react by saying that we're not forever focused, yet the hormesis description of the dose response may say that to a degree we may be [1]. Certainly, we must sleep, but our biological responses need not. Let's consider the possible effects of continuous low level toxicologic stimulation of hormesis.

Initially, we would expect a focused but heightened attempt or sense of sensory and physical discrimination [12, 13]. Steady state exercise in healthy humans could mimic the continuous central sympathetic stimulation [11]. Steady state exercise in humans leads to increased circulating noradrenaline and reduced variability of heart rate [14]. One might argue that steady state exercise, while fulfilling the criteria of NOAEL, can hardly be considered the low level stimulus of an odor below an odor threshold, where no odor can be detected. How-

ever, caffeine and nicotine present in humans can accentuate this response [15]. Continued stimulus causes partial desensitization of nicotinic receptors that will lead to habituation and promote dysfunction by continual occupation of desensitized receptors [16]. After sufficiently long stimulation, the possibility of degeneration or death of the receptors must be considered. Following olfactory injury, repair occurs, but it is less efficient in adult mice (6 months old) than in the young (1 month old) [17].

DISCUSSION

To decide the degree of complexity of the hormetic response, we review 6 case scenarios.

Case 1. Inhaled Carbon Black.

This dose-response is a product of the dose of carbon black to the target organ, the pulmonary parenchyma, and the response of the species to which it is delivered [18, 19]. Hamsters exposed to carbon black developed a mild transient hyperplasia of pulmonary alveolar type II cells after 1 day of exposure. This change was absent after 13 weeks of the same exposure. Fischer 344 rats responded more vigorously than F1B hamsters and developed lung tumors from chronic exposure to the same levels of carbon black aerosols. Hamsters have a vigorous pulmonary defensive response. Type II alveolar pneumocytes were stimulated by the carbon black exposure [18, 19].

Case 2. 3-Methyleneindolenine (3MEIN)

The toxic metabolite of 3-methyl indole, 3MEIN, is capable of stimulating pulmonary alveolar type II pneumocytes at lower concentrations, as indicated by type II alveolar pneumocyte hyperplasia in cattle affected at the lowest dose. Such cattle die when stressed, but most survive and recover uneventfully if monitored but not stressed [20, 21]. At higher doses of 3MEIN cattle die of acute respiratory disease within 6-24 hours [20, 21]. This description fits that of hormesis closely. It makes sense that type II alveolar pneumocytes making surfactant and repairing damage to the alveolar membrane by differentiating into type I alveolar pneumocytes would be stimulated by low concentrations of 3MEIN [20, 21].

Analysis of carbon black exposures and 3MEIN. In both the exposures to carbon black particles and 3MEIN, proliferation of type II alveolar pneumocytes occurs at low concentrations. Additional type II alveolar pneumocytes provide reserved epithelial cells to cover injured areas of gas exchange and to secrete pulmonary alveolar surfactant. Thus, the proliferation of these cells at low toxicant concentrations makes sense and provides information useful to problem solving for these 2 toxicants. These responses are typical of many reviewed by Calabrese and Baldwin [1-5].

Case 3. Lead

Lead's effect on erythrocytes (stimulation of erythrocyte production, preceeding toxic inhibition at higher concentrations) just might be beneficial and uncomplicated [22]. Lead is toxic to sulfhydryl functional groups of enzymes that are often in the mitochondrion. Therefore it makes sense that lead would stimulate erythrocyte production as a defense against inhibition of vital enzymes at higher concentrations [22]. It also makes sense that if even low concentrations of lead were toxic to vital neurons, additional erythrocytes would carry more oxygen to be available for such stressed cells.

When we examine the neurotoxicity of lead by using the functional indicator of intelligence quotient (IQ) in young children, a very different picture emerges. It appears that there is no "safe" blood lead concentration. Specifically, there is no concentration of blood lead below which IQ is not lost [23, 24] (no threshold of effect). Lead delays slightly the onset of mensuration in premenarchal human females. Again, in this case, no concentration of blood lead is sufficiently low to eliminate this effect. Even changing from 1-3 ug lead/dl shows the effect [24]. The reason(s) for this lack of threshold is unclear.

The hormesis portion of the erythrocyte response adds information that is useful in understanding lead toxicity. However, this information is incomplete because nerve and reproductive cells react differently to low concentrations of lead than do erythrocytes. Lead's lack of threshold for nerve and reproductive cells adds still more information, also useful to understanding lead toxicity. It makes sense that low levels of lead may stimulate erythrocytes to nurture nerve or reproductive cells exposed to these very low levels of lead and cushion the organism against their losses. With lead, examination of toxicities in erythrocytes, nerves and reproductive cells—as well as the connections between these toxicities—would appear to provide the greatest amount of information useful to understanding lead toxicity.

Case 4. Pulmonary Fibrosis

The pathogenesis of irreversible pulmonary fibrosis will be considered. Initially, one sees damage to pulmonary capillary endothelium and/or type I alveolar epithelium [11, 25-28]. The most desirable action following such injury is healing by primary intent, by proliferation of type II alveolar pneumocytes and their differentiation into type I alveolar pneumocytes. Intact capillary vessels are needed. Connective tissue content of lungs is increased, although no fibrosis is present histologically [21-25]. At higher doses and degrees of injury, pulmonary architecture is irreversibly changed and scarring develops [11, 25-28].

The lack of histologic fibrosis suggests an early stage of lung injury, before alteration of pulmonary architecture. The early stage of injury makes it possible for the lung to heal by primary intent. Increased proliferation to type II alveolar pneumocytes makes sense at doses which do not lead to fibrosis, as healing at higher doses will require such proliferation. Hormesis describes an immune (defense) response which will facilitate healing. The pathogenesis of early events describes a zealous defense response which leads to healing, parallel-

ing closely the hormesis paradigm. However the role of increased pulmonary collagen is not clear. Lung collagen's increase adds additional information to understanding the pathogenesis of pulmonary fibrosis.

It makes sense that increased collagen-connective tissue structure may be needed to support the increase of pulmonary alveolar pneumocytes. The collagen increase may reflect increased capacity to support healing, for endothelial regeneration or as a scaffold for regenerating epithelium. Alternatively, it is possible that reversible pre-fibrotic changes may add an as-yet-to-be-determined risk. We must define the process sufficiently to determine whether this pathogenesis conforms directly to hormesis, or is a little more complicated or even signals added risk.

Case 5. Diarrhea or Colorectal Cancer

In instances of colorectal cancer, ETEC shigatoxin-a binds to a receptor with guanylin or uroguanylin to alter a c-GMP gated channel and reduce the proliferation of colonic epithelium into colorectal cancer. This case exhibits molecular mimicry, exploiting the natural physiology of the colonic epithelium to promote the healing response [29, 30]. As the ETEC shigatoxicosis progresses, diarrhea may develop. This at least qualitatively fits the criteria of hormesis and provides information about low level collaborative responses useful to understanding the pathogenesis of colorectal cancer as well as the microecology of ETEC.

Case 6. Malodorant Gases

After binding to the odor receptor, malodorant gases cause an increasing central adaptation, progressing through detection of odor, specification of odor, annoyance, intolerance and finally somatic injury [31-37]. At or around the odor threshold, adaptation to odor is largely central [31-37]. Progression to more serious signs from the odor threshold is consistent with a dose-response relationship.

On surface examination it would appear that below the threshold there is simply no detectable odor. However, most of us know that the absence of a specifically bad odor heightens our perceived sensations of good odor, as exemplified by the good smell of wilderness relative to rural-urban interfaces. Secondly, we know that perception of an odor is a product of central integration where odor is first perceived as an odor and then a specific odor. Additionally, we know that mixtures of malodorant gases, some below their odor threshold, elicit higher stimulation of bad odors [31-37]. Finally, we know that stress shifts the perception of any odor to a lower concentration, and the perception of that odor as unfavorable [35].

The important question here is, does the sense of smell, complicated by central correction follow the rule of hormesis? Does concentration of malodorant below the odor threshold, when detection of malodor is possible, heighten our sensation of odor because the heightened sensation will be needed to detect the odor? Does the low level odor of a malodorant mixture confuse and reduce discriminatory ability? Is the absence of malodor the basis of heightened sensation of odors in remote location (where the air smells so good)? Since there is by definition no significant odor sensation at concentrations less than the odor threshold (where a bad odor can be detected but not specified), does this response resemble the placebo effect (an expectation of good odor), or alternatively, the hormesis effect? If so, how would one differentiate between a placebo effect or hormesis to specify the cause of this low response, which either allows sensations of better odors to be heightened in a stimulated cell, or contributes directly to such sensations from a placebo response where better smells are anticipated?

SUMMARY OF CASE EXAMPLES

We have described 6 situations. The effect of low level lead on erythrocyte function, the stimulation of alveolar type II cells by carbon black in hamsters and the stimulation of 3MEIN toward proliferation of alveolar type II cells fit the description of hormesis. In each pulmonary exposure case, using hormesis instead of the traditional dose-response provides added information about the stimulation of type II pulmonary alveolar pneumocytes below the NOAEL and that is useful for problem solving. The added risk of the low-level heightened response from lead or 3 MEIN stimulus is more clear in the case of 3MEIN where a type II alveolar hyperplasia is expected, but is not expected to cause functional impairment if the animals are not exercised [20, 21]. The question whether the type II alveolar pneumocyte hyperplasia meets the criteria of NOAEL must be considered [1-5]. If animals are not exercised they will recover, but they still will have faint remnants of this structural alteration [20, 21].

In early changes in pulmonary fibrosis, hormesis clearly gives more complete information about the early fibrotic events than the traditional dose-response does. Such information is useful for understanding the pathogenesis of pulmonary fibrosis and makes suggestions about its therapy. However, hormesis would not predict significantly increased collagen content in the lungs in the absence of histologic indications of fibrosis. Thus, hormesis provides more useful information, but alas potentially incomplete information.

The role of increased pulmonary collagen is not clear, but it may reflect increased capacity to heal or to support healing [11, 25-28]. If such information would be useful in problem solving, it is possible that increased collagen is needed as a support for endothelial regeneration or as a scaffold for regenerating epithelium. Alternatively, it is possible that reversible pre-fibrotic changes may add a yet-to-be-measured risk. Researchers have to define the process sufficiently to establish the degree to which this pathogenesis conforms directly to hormesis, is a little more complicated than a strict hormesis response, or hints at an added risk [11, 25-28]. Thus, the hormesis response in this case may only itself partially describe the

early changes of pulmonary fibrosis.

In colorectal cancer, ETEC shigatoxin-a binds to a receptor, alters a c-GMP gated channel and reduces proliferation of colonic epithelium. This process shows molecular mimicry, exploiting the natural physiology of the colonic epithelium to promote the healing response [29, 30]. This qualitatively fits hormesis and provides information about low level collaborating responses promoting an understanding of colorectal cancer as well as the microecology of ETEC.

With malodorant gases, hormesis predicts heightened sensations of good odors at concentrations below the odor threshold, which we take to be the no observable adverse effects level (NOAEL). Since the odor threshold is by definition the lowest significant perception of malodor, odor physiology would not predict heightened sensations of good odor [36, 37]. However, low bad odor could allow good odor to be unmasked. Alternatively, since adaptation is mostly central, heightened expectations of less bad odor produce a placebo effect which is difficult to differentiate from real defensive reactions. Low level perception of bad odor could lead to heightened defensive reactions and, if it persists, to desensitization. Thus, the perception of good odor in this instance could be a form of relief. The heightened perception of good odor would be additional information for problem solving if we could differentiate among the 3 causes: unmasking of good odor; expectation of good odor (the placebo effect); or a potentially undesirable response leading to desensitization. Thus, regrettably this is incomplete data, potentially as confusing as the low level odors that originate it. It may be difficult at present to differentiate among unmasking, the placebo effect, or the possibility of desensitization from heightened immunity (defense) and an ability to heal, the primary mechanisms of hormesis.

CONCLUSIONS

It would appear that in all the cases we discussed, hormesis provides more complete information than does traditional dose response. Secondly, it further appears that such information is both generally useful. Thirdly, in the case of Carbon Black and 3MEIN, the information is complete. These 2 instances suggest attempts at optimization38, satisfy the conditions of hormesis and are typical of many of those analyzed by Calabrese and Baldwin[1-5].

In the remaining cases (lead, pulmonary fibrosis, colo-rectal cancer and malodorants) neither the traditional dose response nor hormesis provides sufficient (optimal) information for solving problems. Thus, while hormesis is an improvement over traditional dose response, the final form that evolves may be different from either the traditional dose response or hormesis. We project that this form will be holistic—look at all available indicators and connect information from each of the indicators into a concise picture of that toxicoses.

It is important to note that in all cases we discussed hormesis added information for solving problems about their toxicology. Thus, hormesis improved the information relative to that of conventional dose response. In lead toxicity and pulmonary fibrosis some critical information was missing, but in each of these cases hormesis added information to solve problems about the agent's toxicology.

It is with malodorant toxicoses that questions arise about the accuracy of the hormetic response and about our ability to distinguish it from a placebo response. In the special cases such provided, we must examine how assumptions of hormesis or alternatively traditional dose response limit the information available to solve the problems of malodorant gases. We believe that in examining such limiting cases we can take the next steps toward deciding that hormesis may be the 21st century's default assumption for the relationship of dose to response and how this association may still be improved further.

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HORMESIS AND RISK ASSESSMENT

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Calabrese and Baldwin (2001) provided compelling evidence for the widespread occurrance of hormetic effects after an exhaustive literature search. Two entire volumes of Crit. Rev. Toxicol. (2001 and 2003) have been devoted to various views and perspectives on hormesis including a conceptualization based on two nonmutational evolutionary principles, which are homeostasis and optimization. Similar to the long-accepted dictum (Paracelcus) that at high doses all chemicals, both man-made and naturally occurring, are toxic, the accumulated evidence has now reached a critical mass sufficient to postulate that at low doses all chemicals have hormetic(inhibitory signal triggering stimulatory overcompensation)/hormoligotic (stimulatory signal giving rise to inhibitory overcompensation) effects (biochemical, physiological, immunological exercises) (Rozman and Doull, 2003), although in many instances such effects may be immeasurably small. This makes currently used linear risk assessment models obsolete and scientifically indefensible although inertia is likely to prevent a move away from these models for some time. Thus, the question is not whether or not to incorporate hormesis/ hormoligosis into risk assessment, since this is a must, but how to do it and what type of experimental design is needed to generate suitable data.

Without regard to how many and what type of dose responses constitute hormetic/ hormoligotic and toxic effects (Rozman and Doull, 1999), they can be described by a β-curve or an inverted β-curve (Townsend and Luckey, 1960, Stebbing, 1982, Calabrese and Baldwin, 2001). If such a curve is sufficiently defined (which is the case for few chemicals other than vitamins and essential nutrients) the risk assessment is straightforward from the modeling point of view. The task from the mathematical point of view is to find a polynomial which best fits the data and then to determine the maximum of a β-curve or the minimum of an inverted β-curve for which there is a well-established mathematical procedure.

The maximum value of a β-curve or the minimum value of an inverted β-curve is defined by the first differential derivative (erste Ableitung), being $f'(x) = 0$ for both and for maximum the second differential derivative (zweite Ableitung) being $f''(x) \leq 0$ and for minimum $f''(x) \geq 0$.

This is not only a very simple risk assessment but also one which provides for risk managers an accurate point estimate which is based on data rather than assumptions.

The more difficult question is how to generate data to do the curve fitting or more pointedly how to design dose- and time-response studies for hormetic/ hormoligotic effects. Anticipation and identification of a hormetic effect is a most difficult task not unlike anticipation of toxic responses to a novel chemical. In addition to a profound knowledge of physiology, structure-activity relationship will be the only aid that science can offer in this endeavor in combination with educated guesses.

Hormetic/hormoligotic effects can exist from a time scale of seconds (Calabrese, 2001) to a life prolonging effect on a scale of years to decades (Rozman et al., 2005). Therefore, a cookbook type approach as currently used in toxicology will not help to identify homeostatic overcompensation responses. A logarithmic progression in time would identify such responses if the dose was known but even then it would be hopelessly expensive to be applied to a large number of chemicals. Therefore, the only logical and rational way to go about it is to accept the aforementioned dictum that all chemicals have hormetic or hormoligotic effects at low doses and then to look for them on a time scale of their presumed existence. If the overcompensation effect consists of sympathetic vasoconstriction, then such an effect must be studied on a time scale of seconds to minutes and not on a time scale of 14 days, 90 days, or 104 weeks. If the hormetic/ hormoligotic effect consists of prolongation of life then terminating animals at 104 weeks would clearly prevent the observation of such an effect. The time course of an overcompensation effect can only be approached intelligently if a profound knowledge of physiology is combined with an analysis like that of Rozman and Doull's (2000) scheme to determine if the rate-determining (-limiting) step(s) are of kinetic or dynamic origin. Establishing that the rate-determining (-limiting) step(s) are either being kinetic or dynamic, allows one to estimate the half-life of the hormetic/hormoligotic response, which then will permit the conduct of a time course study on the appropriate time scale. Knowledge of the kinetic or dynamic half-life will also allow one to identify the time point of maximum response and to choose the appropriate study design for carrying out dose response experiments. If conducted at the ideal time point hormetic/hormoligotic dose responses could be established with as little as three

doses, using a logarithmic progression with the lowest LOEL or the NOEL as the point of departure. It must be understood that the maximum of a hormetic/ hormoligotic effect depends on the half-life of the rate-determining step. If return to equilibrium is the slower step (which will be the case in most instances) rather than initiation of the homeostatic overcompensation itself, then this half-life will determine the maximum of the β-curve or the minimum of the inverted β-curve (Rozman, Doull, and Hayes 2001). A central role of time-responses at constant dose for hormetic/ hormoligotic effects is quite apparent. While other disciplines are eagerly incorporating time as a critical variable into their studies (Duboule, 2003), risk assessors and other modelers are deliberately avoiding time as an explicit variable even though it is impossible to conceive a toxicological experiment without thinking of time as a variable of toxicity.

Some people might argue that these ideas are not feasible because of the costs involved. This is not at all the case. A potent carcinogen such as 1,2,3,4,6,7,8-heptachlorodibenzo-p-dioxin (HpDCC) at a dose just 2.1 times lower than a higher dose which caused 16.6% lung cancer significantly prolonged the life of rats without causing any lung cancer (Rozman et al., 2005). This finding is compatible with the notion that all chemicals are toxic at high doses and since carcinogenicity is just one endpoint of toxicity, all chemicals are carcinogenic at high doses unless life span or another endpoint of toxicity interferes with the manifestation of cancer. Therefore, there is no need to conduct any additional carcinogenicity bioassays unless cancer is the most sensitive endpoint of toxicity for a particular chemical. This line of thinking obviates the need for large numbers of animals per dose group, which was driven solely by statistical considerations. As discussed earlier, other types of mathematics are needed to analyze the β-curve than those used currently by biologically invalid models. Thus, the number of animals could be significantly reduced per group and instead additional doses could be added to help define the time- and dose-responses of both hormetic/ hormoligotic and toxic effects.

Short of a radical rethinking of current study designs, there will be no progress in toxicology nor in the incorporation of hormesis/hormoligosis into risk assessment. The claim that understanding the mechanism of toxicity at the molecular level will improve risk assessment is an illusion invented by risk assessors in order to find justification to ignore toxicology and to continue number crunching which is nothing but mathematically formalized superstitution. Unfortunately, some toxicologists also commit this lapse in logical thinking. Toxicology is firmly rooted in the laws of thermodynamics (Rozman, 2003a, 2003b) and risk assessors are violating these laws with every linearized model. It is time to return to our roots and challenge risk assessors that by committing these pseudoscientific obfuscations they risk becoming laughingstocks like the people in search of a perpetuum mobile. Both toxicity and homeostatic overcompensation responses begin by molecular interactions between endogenous and exogenous chemicals. They propagate through a causality chain all the way to the manifestation of an effect at the organismic level. Modeling at any level, if correct and cause-effect related, cannot but yield the same prediction. Any model that does not live up to this criterion must be discarded. All current risk assessment models are in defiance of laws of toxicology/thermodynamics and therefore have no basis in science.

Under conditions of kinetic steady-state (loading dose and maintenance doses) chronic toxicity of HpCDD obeyed strictly the dose (c) x time (t) = constant (k) = 1487 mg/kg•day paradigm, causing about 60% lung cancer. Substituting for time the average natural life span of the controls (720 $\pm$ 28 days) yields a carcinogenic threshold dose of about 2 mg/kg for HpCDD. A dose of 1 mg/kg significantly prolonged the life span of HpCDD-treated rats to 777 $\pm$ 29 days without the occurrence of a single lung cancer, a powerful hormetic response. Since HpCDD causes exactly the same spectrum of effects as 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) but is 125 times less potent as a toxicant (Stahl et al., 1992) the chronic c x t = k product for TCDD would be about 12 mg/kg•day. Substituting the average life span of controls yields a carcinogenic threshold dose of 0.016 mg/kg = 16 μg/kg for TCDD. This translates into a daily dose rate of 0.02 μg/kg or 20 ng/kg. EPA's reference dose for TCDD is 7 fg/kg which is about 3 million times lower than the NOEL calculated by the c x t paradigm. Rats would have to live 6.5 million years to get lung cancer from this dose of TCDD. This calculation illustrates the absurdity of the predictions of linearized models (Rozman et al., 2005).

The clear documentation of hormetic/ hormoligotic dose-responses at low doses of a multitude of chemicals provides a window of opportunity to make tabula rasa and start the era of toxicology as a science upon which reliable risk/safety assessments could be based.

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HORMESIS: HOW IT COULD AFFECT THE RISK ASSESSMENT PROCESS

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ABSTRACT

If the hormetic dose response were accepted as the default dose response model for risk assessment it could have important implications for environmental exposure standards for non-carcinogens and especially for carcinogens. Most notably it would lead to the recognition that carcinogens act via a threshold process rejecting the concept of linearity at low doses. The hormetic concept also provides agencies with a broader range of toxicologically-based exposure options, which permit a consideration for avoiding harm, as well as possibly enhancing benefits for both normal and high risk segments of the population. By dismissing hormesis, regulatory agencies such as EPA deny the public the opportunity for optimal health and avoidance of disease.

Key Words: hormesis, dose-response, U-shaped, J-shaped, biphasic, risk assessment

INTRODUCTION

In a recent paper eight criteria were proposed upon which to evaluate possible default dose-response models for risk assessment for non-carcinogens and carcinogens (Table 1) (Calabrese, 2004). It was then argued that the hormetic dose response model not only adequately addressed these criteria but did so more effectively than commonly accepted dose response models used in risk assessment such as the threshold and linear at low dose models. In an effort to extend that conceptual framework the present paper explores how the hormetic model could be used in the risk assessment process.

NON-CARCINOGENS

The current reference dose (RfD) scheme employed by the U.S. EPA for obtaining acceptable exposures to non-carcinogens is best characterized as a risk management plan that attempts to ensure that exposure to toxic substances is below any dosage that could cause even minor changes in a hypothetical generic high risk segment of the population. It is strongly influenced by risk assessment concepts and procedures but not governed by them. In fact, it has been governed by an overriding protectionist public health philosophy which purportedly ensures that RfD derived values err on the side of safety, the extent of which is generally unknown. Inherent in this scheme is the non-scientific but precautionary requirement to select the most sensitive endpoint in the most sensitive biological model of a well-conducted study.

Once the NOAEL for this most sensitive endpoint in the most sensitive model is obtained (e.g. highest dosage not statistically different from the control, or estimated dosage obtained via the use of a BMD approach) an interspecies uncertainty factor (UF) of 10 is typically applied to extrapolate from the average animal model response to the average human. This also assumes that the human would be 10-fold more sensitive than the most sensitive animal model. Then another factor of 10 is applied (10 x 10 = 100 UF) to account for interindividual variability in the human population. Other factors could be applied such as an additional UF for children based upon the Food Quality Protection Act. The RfD is then apportioned across the various media via a relative source contribution formula in order to derive a possible exposure standard for agents and media of interest. The question is how could acceptance of the hormetic model as the default alter this scheme.

Not Affected:

(1) **Hazard Assessment:** The principal goal of the hazard assessment process would remain the derivation of the NOAEL and LOAEL. That is, acceptance of the hormesis dose response model would not require changing current hazard assessment study requirements. The default model concept assumes that the hormetic model would be the most plausible dose-response model and to be used unless proven wrong with data. Since the hormetic zone is contiguous with the NOAEL and has its quantitative features (i.e., amplitude of stimulatory response, width of stimulatory response, and distance from the amplitude of the stimulatory response to the NOAEL) well defined there is no requirement to change the hazard assessment goal of defining the NOAEL. Thus, hormesis would not have to be proven/supported in any hazard assessment since it is assumed to be true as is the case with the current default models (i.e.,

threshold for non-carcinogens and linearity at low doses for carcinogens).

(2) **Use of Most Sensitive Model/Endpoint:** The use of the most sensitive animal model and endpoint would not be affected. This represents a judgment which reflects not only concern to protect the public health but also a sense of the general uncertainty in dealing with animal model data in the risk assessment process. Nonetheless, the continuing lack of knowledge of the capacity of the animal model to predict human susceptibility in a quantitative manner is a critical and overriding weakness in the existing human risk assessment process.

Affected:

(1) **NOAEL Derivation:** How the NOAEL is derived could be affected by acceptance of the hormetic dose response model (see Calabrese and Baldwin, 1998). However, any such modifications are likely to be modest and not of major quantitative significance.

(2) **Size of Interindividual UF:** Figure 1 presents a schematic of the RfD derivation process used by the EPA and how the hormetic model relates to it. The schematic provides two similar dose response representations with the only difference being the width of the hormetic zone (i.e., 10-fold or 100-fold immediately below the NOAEL for the rat, normal human and generic high risk human subgroup). The principal focus in this comparison is to discern whether and to what extent the EPA RfD would be placed into an hormetic (i.e., stimulatory) zone. In these cases, the RfD lies in the hormetic zone for the normal population for the 100-fold hormetic zone variation group. The high risk population subgroup would not achieve any hormetic response at the routinely-derived EPA RfD.

While the above comparisons provide a hypothetical framework for how the current EPA RfD scheme may be working, this schematic provides a way to visualize how the magnitude of the interindividual UF could be modified in order to achieve a regulatory objective that has as a goal to optimize a population-based hormetic response. In the case of the assumed 10-fold variation example, the hormetic response could be optimized for the normal population if the interindividual UF were reduced from 10- to approximately 5-fold, while it could be optimized for the high risk group if it were increased from 10- to approximately 50-fold. The hormetic dose response model can provide regulatory agencies with an array of public health options within the general context of a cost-benefit assessment. Consequently, the integration of the hormesis concept into the traditional risk management methodology provides an improved theoretical assessment of the current activity and a series of toxicologically-defensible options that could enhance public health goals that are absent in the current procedure.

Whether the theoretical estimate of benefit or harm to the human population would occur in most circumstances is generally unknown because it is highly dependent on the assumption used by the EPA that the average human is always more susceptible than the average animal model (i.e., typically a rodent) by a factor of ten. Nonetheless, this is the assumption that EPA uses in the risk management of non-carcinogen exposure.

CARCINOGEN REGULATION AND HORMESIS

The carcinogen risk assessment process has a number of different components as compared to the assessment of non-carcinogens. These include:

(1) An assumption of linearity at low dose versus a threshold dose response.

(2) An assumption that humans are equally susceptible to the carcinogen as is the animal model as compared to humans being 10-fold more susceptible than the animal model as employed in the assessment of non-carcinogens.

(3) The use of body surface area dose normalization for carcinogens as compared to a body weight normalization for non-carcinogens. The use of body surface area rather than body weight for dose normalization results in a 12 to 13- and 5 to 6-fold lower exposure for mice and rats, respectively.

The concept of hormesis indicates that the carcinogen dose-response displays a threshold as it passes into the hormetic zone. Consequently, the hormetic model directly conflicts with the assumption of linearity at low doses. Since the hormetic model acknowledges a threshold below which a reduction (below control values) in cancer incidence is expected, a risk management procedure could be adopted similar to that described for non-carcinogens. This would involve a rejection of the linearity model, and acceptance of the assumption that the humans display 10-fold greater susceptibility than the animal model as in the case of non-carcinogen risk assessment. The use of surface area vs. body weight has not been explored within an hormetic context to my knowledge.

DERIVATION OF A RFD FOR CARCINOGENS

The following section will provide an approach for deriving an RfD for carcinogens. This approach assumes that there are safe levels of exposure to carcinogens and that they are expected to display a threshold. As in the case for the RfD derivation process used by EPA for non-carcinogens it would be necessary to derive a NOAEL. Following the traditional EPA methodology UFs of 10 would be employed for the animal to human extrapolation and for human interindividual variability (10 x 10 = 100). However, in the current process it is assumed that a decreased tumor response will occur below the NOAEL of both the normal and high risk

segments of the population. The dosage range of the hormesis zone is assumed to be 100-fold below the NOAEL. This value is based on the belief that the human hormesis variability range would be larger than that observed in more homogenous experimental systems where the range is commonly 5 to 10-fold (Calabrese and Baldwin, 1999). In order to optimize the potential hormetic response for the high risk group an additional factor of 10 could be selected (10 x 10 x 10 = 1000) (Figure 2). In practical reality this would result in cancer risk assessment values about 100- to 200-fold higher than currently employed (Gaylor and Gold, 1998).

OPTIMIZING POPULATION RESPONSE

In many discussions of risk assessment, only two subgroups of the general population are considered: the "normals" and those at high risk because of some real or presumed genetic or other predisposition to disease. In essence, protecting the hyper-susceptible is the driving force for the Precautionary Principle and may be acceptable in that context; when formulating policy using hormesis as the underlying biological model, there are at least three sub-groups that should be considered: high risk, intermediate risk, and low risk. Figure 3 shows a hormetic dose-response curve for each sub-group. A, B and C are the points of optimal health (the lowest amount of disease associated with exposure to the agent) for the respective groups. A', B' and C' are the points where the disease frequency in each group is identical with the background disease frequency in the total population – roughly the NOAEL for each group.

The hormetic dose response curve for the total population combines the data from all three groups, producing a curve whose lowest point (X) represents the optimal state of health for the total population. Note that the NOAEL for the total population (X') approximates (at least in this figure) the NOAEL for the intermediate risk sub-group (B'). Note also in the figure, all the sub-groups are of equal size and the difference of susceptibility between those with high risk and intermediate risk is the same as that between those with intermediate risk and low risk. As a consequence, points X and B occur at a similar dose level in this figure.

In reality, it is highly unlikely in any free-living population that the sub-groups will be of equal size. If the high risk group were the largest, point X would shift left relative to points B and C. If the low risk group were the largest, point X would shift right of point B. If (as is likely), the intermediate group is the largest, X would center near the dose related to B, or slightly left or right depending on both the relative differences of the distance points A and C are from B – and the relative numbers of those in the high and low risk groups – i.e., the respective contributions of data from each outlying group to the total population curve.

The public health significance of this representation is that point X represents the point of optimal health for the population as a whole, but regardless of where X falls, it will not represent the point of optimal health for at least two and quite possibly all three subgroups. Furthermore, if the acceptable dose is set below the dose related to point A (the "conservative" strategy inherent to the Precautionary Principle), all three groups would be penalized. Their health, albeit better than background, would not be optimized. They would be subject to some amount of excess disease that could have been prevented. This excess disease (the amount of which could be appreciable if the high risk group were quite small relative to those in the other two groups) associated with the lower dose would be, in a sense, "caused" by the low dose. Irrespective of the semantics, that would be poor public health policy. If the calculations of Gaylor and Gold (1998) are a useful guide and the cancer risk assessment values are 100 to 200-fold more restrictive than necessary, the current regulatory practices that ignore hormesis by policy are putting the public at unnecessary risk. Prudence (aka a caution similar to the Precautionary Principle) would suggest that these policies need be modified.

THE ADVANTAGE OF THE HORMETIC DEFAULT FOR CARCINOGEN RISK ASSESSMENT

Risk Assessment

(1) Consistent with quantitative features of the dose response.

(2) Harmonizes non-carcinogen and carcinogen risk assessment since responses for non-carcinogens and carcinogens display quantitatively similar dose response relationships.

(3) Protects health by setting the acceptable dose level such that disease frequency in each group is below background.

(4) Optimizes public health by controlling this dose level only to that point where disease frequency of the total population is the lowest.

(5) As unlikely as it may be, even if the approach was completely wrong and the dose response followed a linear at low dose extrapolation the estimated risk would be $< 10^{-4}$ based on Gaylor and Gold, 1998. The net effect of this approach is that it would permit carcinogen risk assessment values to be about 100-higher than those guided by a 10^{-6} risk assessment value.

Societal

(1) Better regulations on more chemicals could be formulated and implemented faster. Current regulations are based in part on biology (e.g., the NOAEL) and in part on technology – the technologies of detection, control and remediation. While the former is fixed, the technologies are not. As technologies improve, the current approach coupled with the precautionary principle means acceptable exposure levels likely will have to be reduced still further. The process often gets locked into a continuous loop of public hearings, regulations and lawsuits related to

a limited number of agents. Since much time and energy is directed toward the same agents over and over again (e.g., dioxin) lower volume materials are typically addressed inadequately. Once a regulation on a particular agent is in place, the limited resources of all parties could be redirected to new agents.

(2) Control and remediation costs will be less because once adequate controls are implemented they won't have to be rapidly replaced by newer, more costly controls. Resources could be redirected to other agents or, once most of the agents of any particular company have been adequately controlled, to capital investments.

(3) Expenses related to environmental controls will be more predictable for industry.

(4) With acceptance of hormesis and the resulting acceptance both of thresholds for both carcinogens and non-carcinogens and also of the concept that optimal health can be achieved at levels of exposure well above zero, the tort liability problem will self-correct – at least to the degree that "fear of" and the "risk of even one molecule" will not longer be viable legal strategies.

CONCLUSION

The incorporation of the concept of hormesis and its quantitative features into the risk assessment process represents a data driven decision to make the process more toxicologically-based, with a formal recognition of the role of low dose adaptive responses as legitimate and expected components of the dose-response spectrum, something that is presently excluded by the U.S. EPA (EPA, 2004). In fact, a 2004 position paper by technical staff of the EPA states that "as the purpose of a risk assessment is to identify risk (harm, adverse effect, etc.), effects that appear to be adaptive, non-adverse, or beneficial may not be mentioned". It is not clear on what authority or logic that this definition of the purpose of risk assessment is based since it implies that the dose-response and risk characterization phases of the risk assessment process are constrained to permit a population-based response on a > zero percentage response. A risk assessment should be designed to assess a population-based response across the broad spectrum of possible exposures whether risks are increased, not affected or decreased relative to the comparison group. The risk manager then has the entire spectrum of possible population-based responses available upon which to consider various exposure options. Consequently, the stated goal of a risk assessment within the EPA document unnecessarily and improperly places constraints on the scientific features of the risk assessment, reducing the range of data available and limits possible options for risk managers, including the full range of toxicological perspectives added to the risk assessment process by the concept of hormesis.

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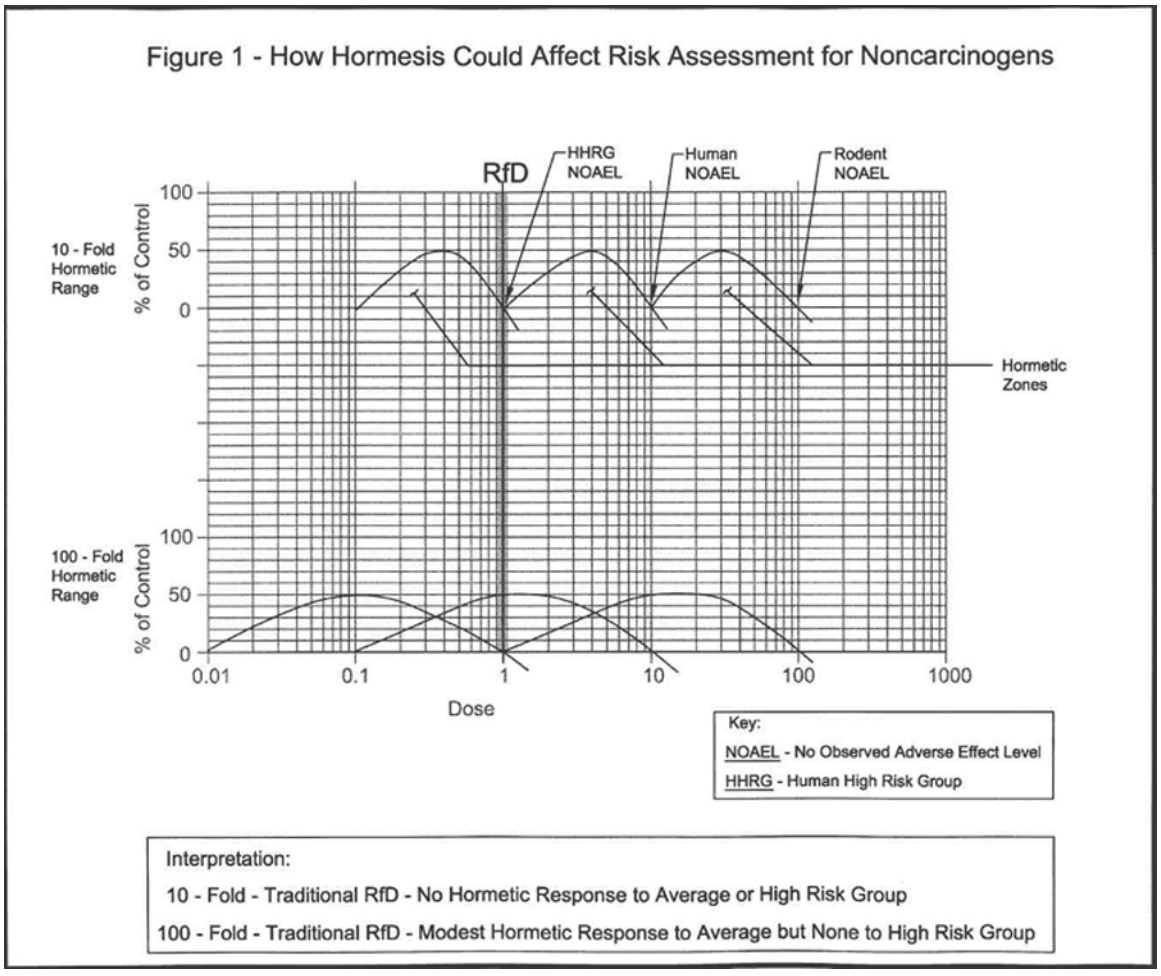
Table 1. Default Dose-Response Model Criteria

Default Dose-Response Model Criteria
Generalizability by biological model, endpoint measured and chemical class/physical agent.
Frequency in the toxicological literature
Application of dose-response model for endpoints of relevance to risk assessment.
Capacity for false positive and negative estimates.
Impact of model on hazard assessment study requirements.
Capacity to estimate risk quantitatively.
Ability to validate risk estimates.
Capacity to assess public health implications.



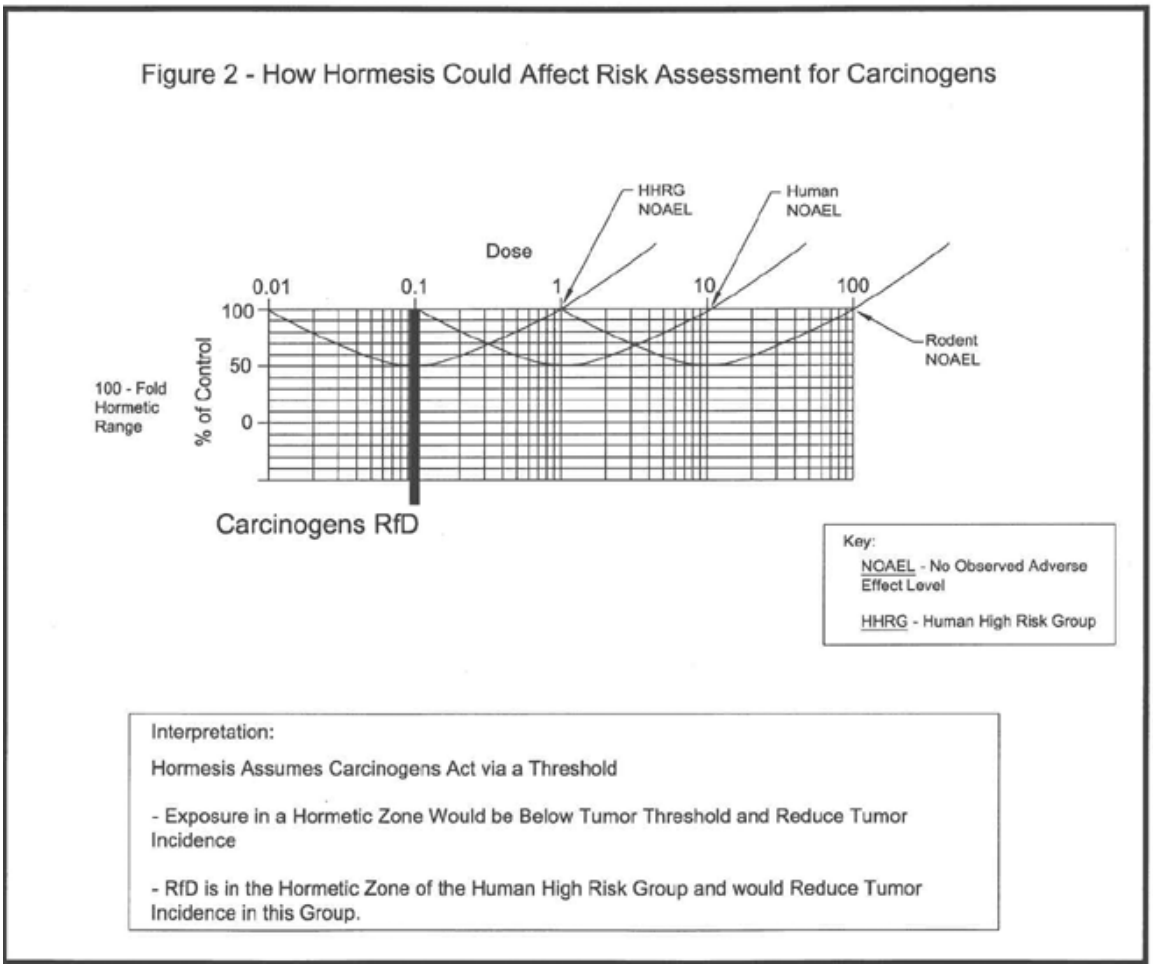
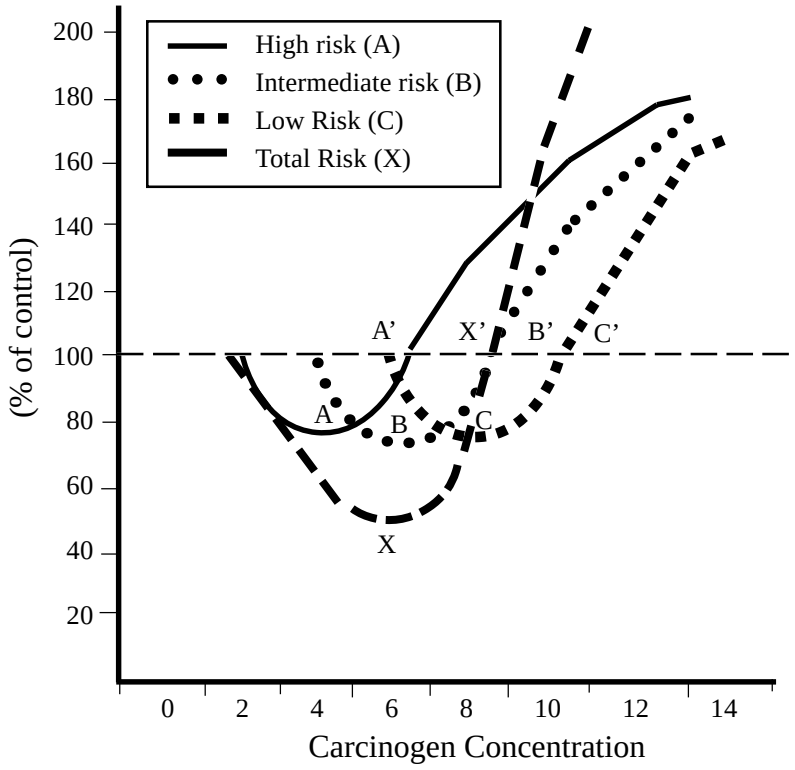


Figure 3. Schematic Optimized Population Response to Carcinogen Exposure Based on Hormetic Dose Response Concept



COMMENTARY, CAN HORMESIS BE A DEFAULT FOR DOSE-RESPONSE

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Since the 1920s, interest in hormesis has peeked and ebbed. Hormesis had been a forgotten theory until recent investigation by Dr. Ed Calabrese at the University of Massachusetts, along with others, resurrected it from obscurity. This renewed interest is demonstrated by recent articles in prestigious scientific journals such as Nature and Science as well as the popular press (Discovery, US News & World Report and newspapers such as the Boston Globe). Currently, a strong interest in this theory of dose response (which predicts contrasting effects at low versus high does) exists and is explored in this issue.

This issue of the BELLE newsletter explores whether hormesis applies to a variety of chemicals in a high enough percentage of times to allow it to become a default for traditional dose response. In many cases, a beneficient effect at low dose will dip the dose response curve about 30% imparting a U or J shape to the overall curve. In some cases, 30% can have a profound impact (see Calabrese & Cook, this issue, 2005). For example, a drug that is protective at high relative dose may, if it has a long half-life, be present in the body at low levels for a significant timeframe. If these lower levels are toxic, then care must be taken by the prescribing physician. In another example, if a radiologic moiety is used at a certain dose to treat cancer, what is the effect of that dose before it reaches a cumulative body dose administration and what is the effect over time. If different concentrations result in a variety of effects these questions are vital and underlay the importance of understanding individual chemical hormesis.

The dose response curve, sigmoid shaped, is shown in Figure 1 with increasing effect on the y-axis and increasing dose on the x-axis. If this curve is generated for a chemical, the "threshold" where a negative effect may begin is as the curve rises from the x-axis. Thus, the severity of effect increases with increasing dose, yet an area exists where no effect is observed. A threshold, a no effect level, is found when the response is initiated. The question asked in hormesis is whether there is a portion of the curve that dips below zero (Figure 2) demonstrating a positive effect. Figure 2 demonstrates an equally possible dose response J-shaped curve where a hormetic range (a beneficial effect) is located below the abscissa and a threshold exists where the curve crosses that x-axis. The question asked in hormesis is whether, in most cases, there is a portion of the curve that dips below zero demonstrating a positive effect. However, Figure 2 also shows the linear correlation which is typically extrapolated by the US Environmental Protection Agency (EPA) as a default to determine low dose toxicity as a carcinogen approaches zero dose. It is evident from an examination of these 2 curves shown in Figure 2 that the hormetic curve would dramatically influence any inference drawn from the linear slope.

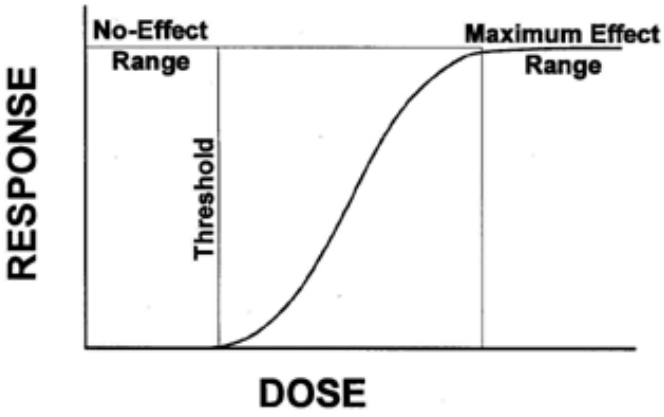

Figure 1

In the first manuscript of this issue, Calabrese and Cook (2005) have asked whether hormesis should be the default model in risk assessment and how it could be utilized. This question has not yet been addressed by risk assessment toxicologists and agencies but is surely a subject for debate. Jayjock (this issue, 2005) suggests a method for answering this question that includes development and use of genomic and proteonomic criteria while Rozman (this issue, 2005) suggests use of structure

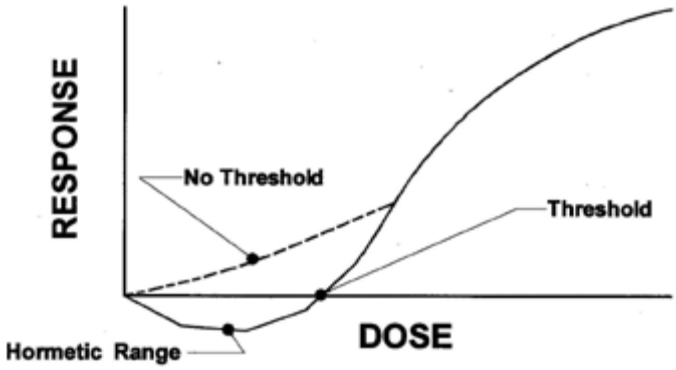

Figure 2

activity and time relationships. These new molecular tools should provide more specific information in human tissue response than the use of animal assays. Thus, as described in many of the papers in this issue, the No Observed Adverse Effect Level (NOAEL) may be a level, which tends to divide only one effect from another.

Pickrell and Oehme (this issue, 2005) suggest that Calabrese and Cook (this issue, 2005) have already answered the question of using hormesis as a default i.e. hormesis will be adopted "only if it offers improved explanations or means to solve problems" since it fits many datasets. In addition, these authors provide a clear concept of hormesis using nutritional essentiality and vitamins. On the other hand, they note that there appears to be no safe blood lead concentration for neurotoxic effects measured by IQ. Of course, some scientists might counter that we have not yet found a safe threshold for blood lead. Pickrell and Oehme (this issue, 2005) also note that lead's effect on erythrocytes might be beneficial and uncomplicated; they suggest a mechanism of action. Thus, with this chemical, hormesis could be dictated by effect. Clearly, these authors see a hormetic response for many chemicals, and suggest that hormesis provides more complete information (than other dose response paradigm).

In contrast, Kitchin and Drane suggest that hormesis will never be a default assumption, nor should it be considered as such. Since all dose-response curves are not hormetic, such a default would not be useful. It is clear to other authors, however, that all curves are not sigmoidal (and linear at low dose); however these assumptions are frequently used as defaults. Rozman suggests that these currently used linear risk assessment models are obsolete and scientifically indefensible. Kitchin and Drane suggest several options to account for the apparent hormetic effects found for certain chemicals and suggest that receptor-ligand, threshold, one hit, and multi-hit theories do much better at identifying the scientific data needed to build sophisticated dose response models. Such options should be investigated before changing a paradigm in risk assessment that is obviously flawed but probably protective.

Is the linear extrapolation scientifically correct in some or all cases? Evidence is accumulating that this may not be true in all cases. In 1971, the National Center for Toxicological Research attempted to determine how to develop the dose response curve by means of an animal study (the Megamouse study). Plans were scaled to a practicable level and the results published in the Journal of Environmental Pathology and Toxicology. A special committee of the Society of Toxicology (SOT) addressed the results of the research in a 1981 Fundamental & Applied Toxicology report. In this report, SOT states that the statistical model used (for extrapolating to low doses) "provides statistically significant evidence that low doses of a carcinogen are beneficial". The low doses described are from the chemical 2 – acetylaminofluorene and its relationship to bladder cancer. In another example, the significant reduction in the cancer incidence for Taiwanese citizens residing for years in cobalt-60 contaminated apartments demonstrates the presence of a protective low level effect (Bauer, 1995). Finally, the dose response curve of vitamins clearly demonstrates a hormetic process. For example, Vitamin A has been shown to exhibit developmental effects at higher than FDA recommended daily dose.

Rozman, in his paper on Hormesis and Risk Assessment, states that "the accumulated evidence has now reached a critical mass sufficient to postulate that at low doses all chemicals have hormetic effects (Rozman & Doull 2003). …This makes currently used linear risk assessment models obsolete…". However Kitchin and Drane disagree with this hypothesis assuming that problems such as the unknown prevalence of hormetic dose-response curves, and the random chance occurrence of hormesis and the unknown degree of generalizability of hormesis, exist. They assume the task of demonstrating that hormesis is true is too challenging, difficult and time consuming. However, many common risk assessment assumptions are challenging and time consuming. For example, the establishment of a cancer slope factor (CSF) takes two years in the laboratory (and more time for analysis) and is indeed time consuming.

It is imperative that proponents of this newer theory of hormesis answer the questions of those who do not accept it. Thus, science has forever been a push-pull in opposite directions until enough evidence exists to prove one point or the other. The "critical mass" to Rozman and Doull has not yet been proven to Kitchin and Drane.

Regardless of the number of studies showing positive hormetic results, the possibility of hormesis with essential nutrients and some pharmaceuticals (Crump, 2001) is important enough to generate further research.

Finally, the existence of hormesis is doubted by some scientists. Others appear confident enough in hormesis that they would not hesitate to replace a flawed process in current risk assessment methodology with this dose-response theory. Still another group are constrained by a lack of evidence that may be decided by new data like genomic and proteonomic studies and a further look at structure activity and time relationships. As this issue highlights, for all involved in the debate, we live in interesting times.

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