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LOW DOSE LINEARITY: THE RULE OR THE EXCEPTION

Introduction

A recently published paper by Martha Crawford and Richard Wilson entitled "Low-Dose Linearity: The Rule or the Exception? " in the journal *Human and Ecological Risk Assessment*, Vol. 2, No. 2, 1996 argued that low dose linearity of the dose response curve might be the rule rather than the exception. While the assumption of low dose linearity has been widely accepted in concept and implemented in U.S. federal risk assessment practices for radiation and chemical carcinogens, it has not been believed to apply to non-carcinogens that have been accepted without controversy as having thresholds below which no adverse effects would be expected. However, Crawford and Wilson contend that the concept of low dose linearity is broadly generalizable and should apply to non-carcinogens as well. Their article, which urges a reconsideration of how background response is considered in risk assessment, challenges not only the vast array of current assertions that low dose linearity is no longer appropriate for low dose cancer risk assessment but suggests that non-carcinogen risk assessment practices may need to be reconsidered as well.

While the BELLE initiative has focused on an assessment of the wide possible range of dose response relationships in the low dose zone, the BELLE Newsletter has published a series of papers that have challenged the notion of low dose linearity based on theoretical foundation, as well as experimental/epidemiological and mechanistic studies. Thus, given the potentially controversial, yet substantial, nature of the Crawford and Wilson paper, it was felt that there should be a broad discussion of this paper since it is at the heart of critical issues in the risk assessment process. Consequently, Dr. Richard Wilson was contacted and asked to prepare a shortened form (e.g., 10 pages down from over 30 pages) of the original article. He also agreed to consider and respond to the comments of a number of external experts that would be invited to offer independent commentary on this paper. The reviewers were sent both the original (longer) version and the shortened form which is now published in the Newsletter. We trust that you will find this discussion both challenging and enlightening.

If you have comments on the issue of the Newsletter please send them to the BELLE office. A decision will be made whether to publish selected individual responses in a subsequent issue of the Newsletter and/or to post them on the BELLE website.

If you are interested in obtaining a copy of the original publication of the Crawford and Wilson paper in the journal *Human and Ecological Risk Assessment* please contact CRC Press, LLC at 1-800-272-7737. Please use the prompt for journals customer service and ask to speak with Joyce Lucas.

LOW-DOSE LINEARITY: THE RULE OR THE EXCEPTION?

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ABSTRACT

In 1976, Crump, Hoel, Langley, and Peto described how almost any dose-response relationship for carcinogens becomes linear at low doses when background cancer are taken into account. This was used by the U.S. Environmental Protection Agency, USEPA, as partial justification for a regulatory posture that assumes low-dose linearity, although detailed calculations were not made. The argument depends critically on the assumption that the pollutant and the background proceed by the same biological mechanism. In a recently published paper (Crawford and Wilson, 1996), we illustrate the difference between assuming the same and different mechanisms by discussing the possible dose response relationship for the leukemia genic response to benzene exposure.We then showed that the same argument applies to non-cancer endpoints, as well. We discussed the application to a number of situations: reduction in lung function and consequent increase in death rate due to (particulate) air pollution; reduction in IQ and hence (in extreme cases) mental deficiency due to radiation *in utero*; reduction of sperm count and hence increase in male infertility due to DBCP exposure. After concluding that, although the biological basis for the health effect response is different, in each case low-dose linearity might arise from the same mathematical effect

discussed by Crump *et al.* (1976), we then examined other situations and toxic end points where low-dose linearity might apply by the same argument. Here we review the mathematical support for the argument of Crump *et al.*, and discuss the policy implications of the generality of their argument for environmental exposures. In closing, we urge that biologists and chemists should concentrate efforts on comparing the biological and pharmacokinetic processes that apply to the pollutant and the background.

INTRODUCTION

The idea that cancer incidence might be a stochastic process with the probability of incidence being proportional to dose dates back at least to the work of Jeffrey Crowther (1924), who formulated the theory that radiation -induced cancers occur when an ionized cell becomes malignant and proceeds to multiply. Even if we assume that most damaged cells are actually repaired by the body's defenses, linearity can still be maintained, if the fraction of cells repaired is constant with dose. Since that time, physicists have tended to accept Crowther's suggestion that cancer incidence is linear with exposure to radiation, but biologists and physicians have often continued to believe in thresholds.

Crump *et al.* (1976) and Guess, Crump, and Peto (1977) pointed out that if a pollutant produces cancer via the same mechanism by which background cancers occur, then there results a linear incremental response to the incremental dose. Even if the biological dose response mechanism has a threshold, or is non linear, the existence of the background cancers shows that the threshold is already exceeded by a background pollutant. Then when a small amount of the same pollutant, or to another pollutant operating in the same way as the first, is added, an incremental response linear with the incremental dose of pollutant can result, almost independently of the particular biological mechanism relating dose and response. This simple and elegant argument follows mathematically from the fact that the first derivative of a smooth curve is always finite. The idea was applied to cancer risks, and was used as a partial justification for the U.S. Environmental Protection Agency's (USEPA) default assumption of low-dose linearity for regulating carcinogens. Overall, however, the seminal paper of Crump *et al.* (1976) has received remarkably little attention, and few people (not even the EPA) have discussed how the idea should be applied in practice. At a minimum, the concept of incremental linearity should shift the focus of discussion from biological thresholds (which are almost impossible to verify at the levels of interest) to whether the pollutant and whatever causes the background cancers operate via the same biological mechanism.

An examination of the risk assessment literature published during the past twenty years, however, reveals that discussion has remained focused on trying to identify biological thresholds, rather than biological mechanisms, for given effects. At the same time, the EPA has continued to assume a nonlinear, or "threshold," dose-response relationship for regulating chemicals that are toxic, but not carcinogenic. In recent years, several researchers have suggested the inadequacy of this approach, demonstrating that the arguments made by Crump *et al.* about carcinogens may also be extended to non-carcinogenic toxins. For several non-cancer adverse health effects, a no-threshold dose-response mechanism has been suggested (Evans *et al.*, 1982, Pease *et al.*, 1992). Crawford and Wilson (1996) have demonstrated that the mathematical effect formulated by Crump *et al.* (1976) applies to an array of situations in which a pollutant causes a non-cancer, or toxic, adverse effect. The one requirement is that there exists a reasonably large background of the biological effect under consideration, and that the pollutant acts in the same way as the background. It is evident that this might be satisfied by a large number of biological effects and pollutants. The generality of the argument suggests that a linear dose-response relationship may be the rule, rather than the exception, at the low doses typical of environmental exposures, even for ordinary toxic (noncarcinogenic) effects.

INCREMENTAL POTENCY ARGUMENT

In this section we apply the argument of Crump *et al.* to any biological endpoint, using both an analytical and a graphical approach. For the sake of argument, we assume that the biological response to a dose of a substance is inherently non-linear, but monotonically increasing, such as depicted in Figure 1. It might for example be represented by a power law, $R = Ad^n$. (R is response, A is a constant, d is dose, n is an integer greater than one.) (If the dose response is not monotonic, or $n < 1$, the situation becomes more complex and needs more careful scientific and public policy discussion. This has not yet been the focus of regulatory discussion.) Figure 1 presents the particular case of a cubic ($n = 3$) power function. If there were no background incidence of the response in question, the dose-response relationship at low doses would be clearly non-linear, and an infinitesimal increase of dose would give a negligible increase in response.

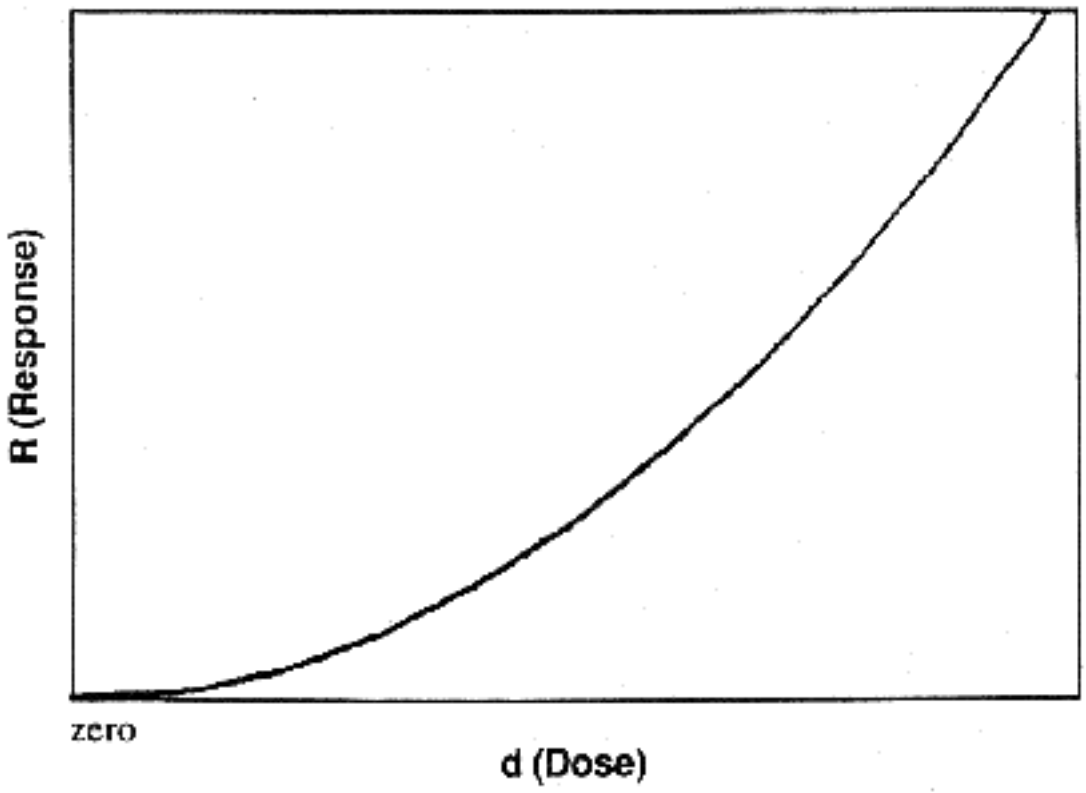

Figure 1. Typical nonlinear, "threshold", dose-response relationship ($R = Ad^3$).

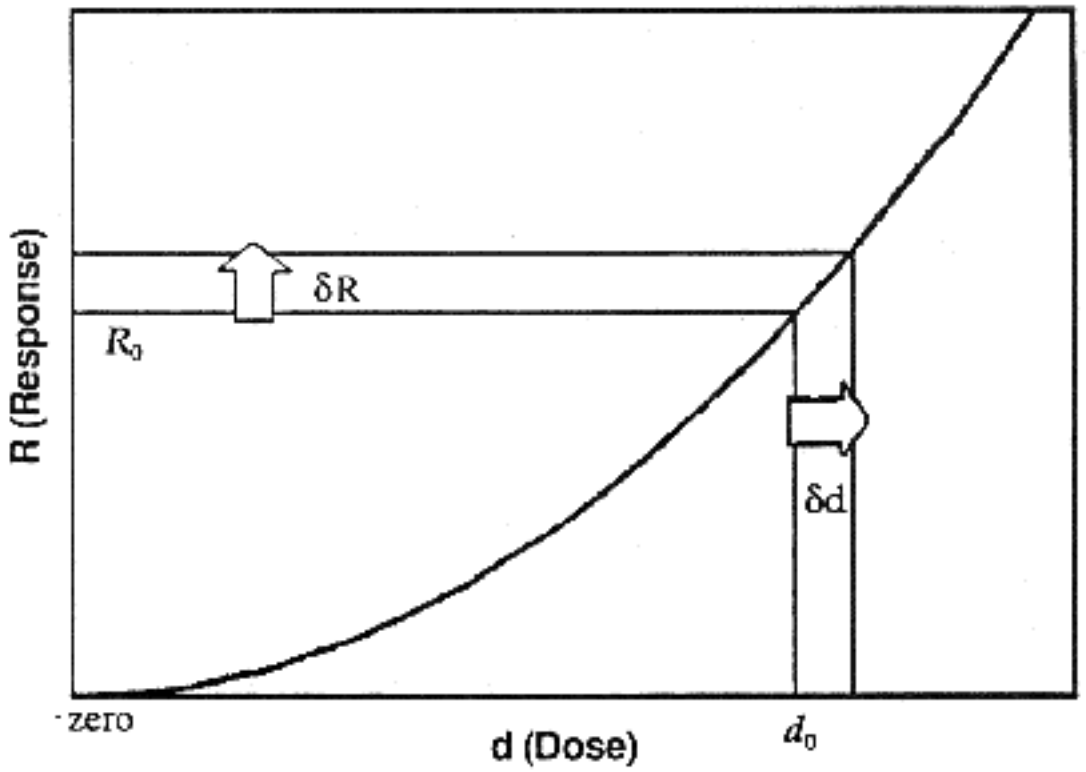

Figure 2. Threshold dose-response relationship ($R = Ad^3$) with axes shifted to R_0 and d_0. Note that ∂R_0 is proportional to ∂d_0.

In general, if it is assumed that a particular background effect is caused by a mechanism similar to that caused by the pollutant in question, it follows that there must exist an "equivalent background dose", d_0, to create this background response, corresponding to $R_0 = Ad_0^n$, as shown in Figure 2. This "background dose" may be a background of a different substance so that it would not normally be considered, but it might be a substance that acts via the same biological mechanism as the pollutant under discussion. If the dose is increased by an amount ∂d due to anthropogenic (pollutant) activity, the response will increase by an amount ∂R, so that:

$$R_0 + \partial R = A(d_0 + \partial d)^n, \quad \text{(Eq 1)}$$

where A is a constant greater than zero.

Expanding this for ∂d small (which is typical of most environmental exposures), we find:

$$R = R_o + \partial R = A\ (\partial d + d_0)^n = \qquad \text{(Eq. 2)}$$

$$Ad_0^n + nA\ (d_0^{(n-1)})(\partial d) + \text{Order of } (\partial d)^2$$

Solving Equation (2) for dR, we find:

$$\partial R = nAd_0^{(n-1)}(\partial d) \quad \text{(Eq. 3)}$$

The incremental potency of the toxin, βinc, is then equivalent to the slope of the dose-response curve, or:

$$\beta_{inc} = (nAd_0^{(n-1)}) \quad \text{(Eq. 4)}$$

If the dose-response curve is "anchored" by a measured acute response R_h, corresponding to a high dose d_h (including background dose d_0), as is typical of data gathered through laboratory experimentation, then $R_h = Ad_h^n$.

The straight line potency, βsl, is derived by drawing a straight line from the response at the high anchoring dose to the origin:

$$\beta_{sl} = R_h / d_h = A d_h^{(n-1)}$$

whereas the incremental potency at dose d_0 is

$$\text{is } \beta_{inc} = nA d_h^{(n-1)} \quad \text{(Eq. 5)}$$

The ratio of the incremental to straight line potency is then:

$$(\beta_{inc} / \beta_{sl}) = n (d_0 / d_h)^{(n-1)} \quad \text{(Eq. 6)}$$

The incremental potency at the anchoring dose is greater than the straight line potency by the factor $n(d_0 / d_h)^{(n-1)}$. In general, if the dose is close to the background dose (as is typical for environmental exposures) the incremental potency will be less than the straight line potency (as determined by data at the higher dose), as seen in Figure 3. It is important to realize that the coefficient of low dose linearity (the slope of the curve, starting from $R = R_0$ at $d = d_0$) will not generally be the same as the coefficient of high dose linearity, as derived from laboratory studies at acute doses d_h. Moreover the low-(incremental) dose slope depends not only upon the biological dose-response curve but also upon the background dose level. The value of the ratio is shown as a function of dose in Figure 4.

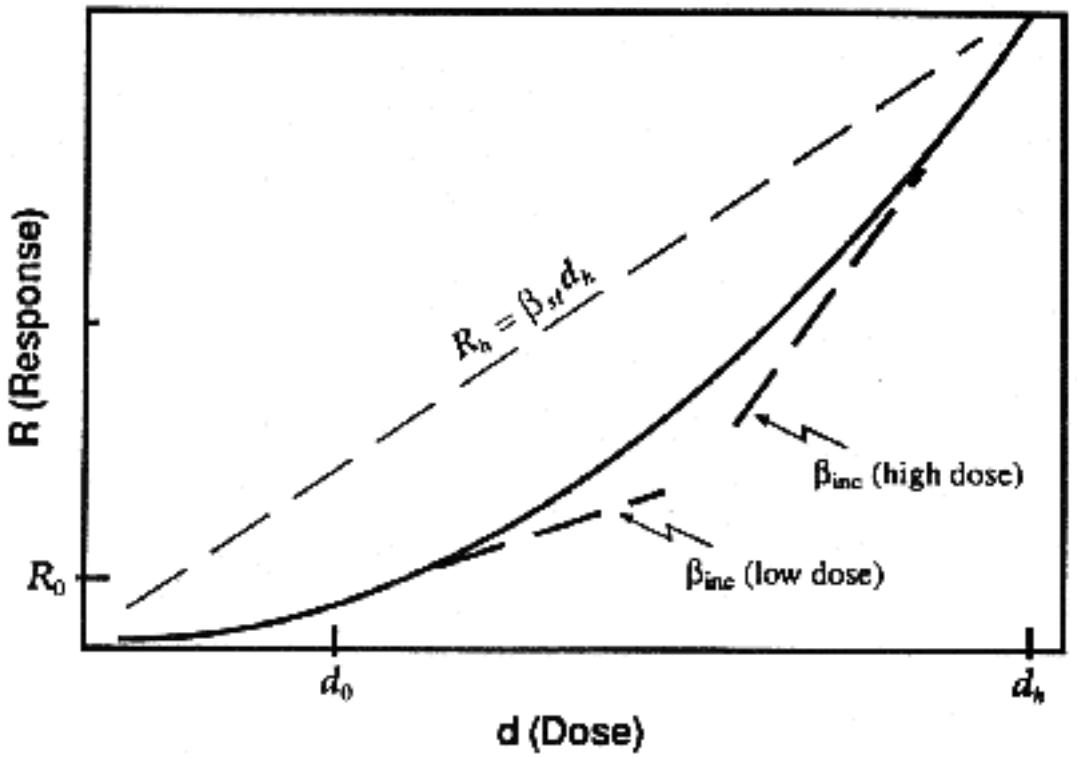

Figure 3. Comparison of slope derived from incremental response model, β_{inc}, and that derived by extrapolation from high-dose laboratory data, β_{sl}. Note that often $\beta_{inc} < \beta_{sl}$.

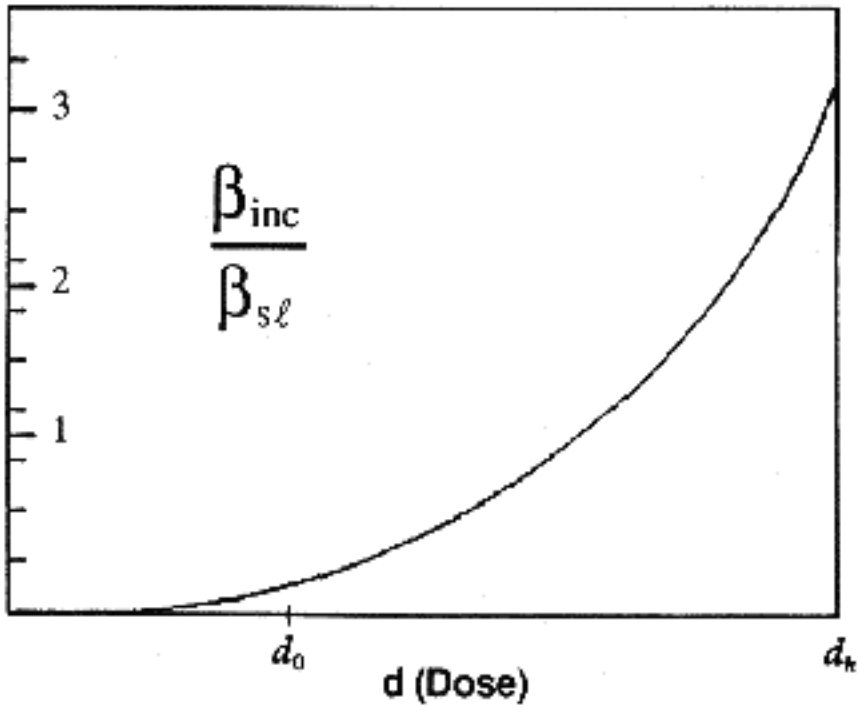

Figure 4. Incremental dose, d_i versus Risk Ratio (RR). At low doses, when $d_i = d_0$, incremental potency is less than the straight line potency.

If the response under consideration is the probability of developing a particular cancer, the above argument is essentially the argument of Crump *et al.* But the argument is also applicable to non-cancer responses, as we recently showed in detail in Crawford and Wilson (1996). In application to non-carcinogens, the normal curve might describe the population variability with regard to some biological capacity, such as fertility or lung function, which is compromised by the effects of a pollutant (Dockery *et al.*, 1983; Beck, Doyle, and Schachter, 1981; Links, Kensler, and Groopman, 1995). We argue that, if the resultant deficiency occurs naturally via the same basic biological mechanism as that through which the pollutant exerts its effect, then even a small increase in pollutant increases the number of people with the deficiency. Thus the pollutant elicits an incremental (and possibly linear) response with even the lowest dose, irrespective of the biological details of the dose-response relationship, provided that it monotonically increases. It should be clear, however, that non-monotonic cases, which might exist if the distribution of the effect in the population were discrete or bi-modal, would need different treatment.

Often, an epidemiological measurement from an acute exposure, or a laboratory measurement from a high-dose experiment, fixes a risk ratio (RR), the ratio of the effect at the dose where it is measured d_h, to the background effect at the assumed background dose d_0. Then:

$$RR = (Ad_h^n / Ad_0^n) \text{ and } d_h / d_o = (RR)^{1/n} \quad \text{(Eq. 7)}$$

Eliminating the values of the doses from these equations, the ratio of the incremental potency to the straight line potency becomes:

$$n(d_0 / d_h)^{(n-1)} = n\ (RR)^{-(n-1)/n} \quad \text{(Eq. 8)}$$

The general requirements for this model are easily seen: (1) the original, biologically derived, dose-response curve must be smooth and monotonic; and, (2) the background agent and the pollutant must act by the same mechanism or receptor in causing the effect. As a restriction upon the generality of the argument, we note that this argument involves the dose applied to the organ of concern. Any non-linearity in the pharmacokinetic relationship between exposure and organ dose remains.

As an example of the incremental potency argument, consider how the regulation of benzene might be modified if we assume a non linear biological dose response with two alternative assumptions about the background. The limited data on leukemia in humans suggests that benzene carcinogenicity proceeds via a non-linear dose-response mechanism with toxic effects manifested via metabolites (Lamm *et al.*, 1989; Thorsland *et al.*, 1988; Paustenbach, Bass, and Price, 1993). Furthermore, benzene is not a direct mutagen, rendering linearity even more unlikely. We here assume that the dose-response is a cubic (n = 3) function, but also make the usual assumption that benzene produces leukemias in the same way that background leukemias are produced. The risk ratio, at the dose where the data on benzene are anchored, is given by RR = 12. Then the incremental potency (near the background dose) is

approximately 3/5 of the straight line potency (as shown in Figure 3). An argument similar to this has been given for the risk of leukemia from benzene by Thorsland *et al.* (1988). To the best of our knowledge this was the first quantitative discussion using the Crump *et al.* (1976) idea.

In general, the ratio of incremental potency to straight line potency is on the order of one, when ($3 < RR < 30$) and ($2 < n < 5$), which can justify the present regulatory approach. However, to the best of our knowledge, this simple justification has never been given before. Statistical limitations make it usually impossible to determine directly the dose-response relationship at the low doses of interest to environmental regulators. However, it may be possible to determine the linearity (or otherwise) of the intermediate biological response and this analysis suggests that is a good place for biological attention.

The usual assumption that background- and pollutant-induced biological effects proceed by the same biological mechanism may not be correct in the case of benzene. There is some evidence that benzene-induced leukemias are always preceded by pancytopenia, which does not occur naturally in the population to any appreciable extent. If this is the case, background leukemias must be produced by an entirely different mechanism than benzene-induced leukemias, and the Crump et al (1976) argument does not apply. Then the ratio of the incremental potency at a typical environmental dose of 1/50 of where the straight line potency is anchored becomes $3 \times (1/50)^2$, or about 1/800 (assuming a cubic dose-response). *This emphasizes that it is important not only to measure the magnitude of the biological dose-response relationship, but also to have some understanding of the underlying biological mechanism(s) in particular, whether the mechanisms are the same for pollutant- and background-induced effects.* It is also clear that even if the background and the pollutant effect operate by the same mechanism, the slope of the dose-response function at low doses can be much lower than the slope at high doses *if* the background itself is small.

In Crawford and Wilson (1996), we further illustrated the incremental potency argument by applying it to a range of cases: 1) exposure to particulate air pollutants, cigarette smoke, and coal dust, causing a reduction in lung function which can lead to premature death; 2) exposure to DBCP, causing a reduction in sperm count which can increase incidence of male infertility; 3) exposure to radiation *in-utero*, causing a reduction in IQ and hence increased incidence of mental deficiency among children. In each of these cases others have suggested a linear dose-

response relationship, but have not related their suggestion to the general principle elucidated by Crump *et al.* In each case it seems plausible that there is a linear relationship between an environmental (typically low-dose) exposure and an intermediate biological response which itself leads to an effect on health. If the biological model is "plausible", even though possibly not completely understood, we argue that the calculated risk must be taken seriously (Crawford and Wilson, 1996; Evans, Ozkaynak, and Wilson, 1992; Hill, 1965). Indeed, if plausibility is taken to require that every step in the mechanism leading to the toxic effect be clearly understood, we will fail to describe (and hence predict and prevent) many risks to health. Even so, we must ensure that a hypothesis is rooted in available data and knowledge, and be willing to modify our statement of plausibility if and when new data appear, or we might spend time and money in fruitless chases.

Conclusions

The yearning for binary ways of coping with risks (yes it is safe/no it is dangerous) finds its way into scientific discourse. Thirty years ago, although carcinogens were suspected of displaying linear dose-response relationships, there were few chemicals known to be carcinogens. In this context, when the EPA was created, the simplest solution seemed to be to ban those which were known carcinogens (Coulston, 1977), and if one or two turned out to have net benefits for society, to cope with these exceptions separately. In recent years, with the availability of more sensitive detection instruments, it has been shown that about half of all chemicals tested in animals cause cancer at some dose. Also, some known carcinogens have been shown to have benefits for society (for example-saccharin or alar). So today the simple banning solution seems inappropriate. Our extension of this approach to non-carcinogenic endpoints (Crawford and Wilson, 1996), using the argument of Guess, Crump and Peto (1976), underscores the inadequacy of this approach to the regulation of environmental pollutants. In our view, there is no alternative to openly discussing what level of risk is acceptable and possible.

Since it is economically and physically infeasible to identify and avoid exposure to all harmful agents, we must settle for protecting against the most harmful and the least beneficial. It is intrinsically distasteful to consider that the health or life of certain individuals will be sacrificed for economic gain, even though the sacrifice would be random. It is much more comfortable to espouse the doctrine of zero risk, and call for biological models. But as has been discussed widely (Coulston, 1977; Gorman, 1993) the first makes regulations unwieldy and impractical, and often diverts scarce regulatory funds to protect against relatively insignificant risks, while the second is ducking the issue, since "zero risk" is unattainable and a complete biological model for every pollutant unrealistic. As a society, we

must accept and live with the idea that a necessary part of health risk assessment involves weighing benefits against costs.

The number of situations where there is a linear dose-response relationship is likely to be much greater than that given by carcinogens alone, and suggests a more careful analysis of what risks are acceptable. The EPA, for example, has set regulations to protect individuals from low levels of carcinogen, and set an "acceptable" or "*de minimis*" level of risk of one in a million per lifetime. If EPA tries to regulate the many non-carcinogenic end points to the same standard, the system could well be choked. A re-examination may well be necessary. We have argued that low-dose linearity may be a common situation for environmental toxins of interest to public health, rather than the rarity that has historically been assumed. Any biological endpoint is likely to display this linearity, in proportion to the extent that this particular endpoint exists in a subsection of society. The public policy issues that are raised by this argument are inextricably linked to societal approaches to especially sensitive groups (Devlin 1993).

In fact, a precedent exists for the application of this type of "acceptable risk" approach. The Coal Mine Health and Safety Act (U.S. Congress Public Law 91-173, 1969) requires that each miner working at the coal face be tested once every five years for early signs of CWP. If any sign is detected, the miner is reassigned to a work site closer to the surface, where exposure to coal dust is lower. In this way, individuals with greater susceptibility to lung damage are identified and only allowed to be exposed to a level of acceptable risk. Clearly, this law recognizes the inter-individual variability which leads to differences in response. This inter-individual variability is what leads to there being a response at the population level for any level of exposure.

Terminology contributes to the traditional bias toward consideration of individual thresholds rather than of linearity for the response of a group. When biologists discuss "low doses," they usually mean low absolute doses, not low incremental doses. Whereas, when we speak of "low environmental doses," we think of low incremental doses. Since our mission is to define a dose-response relationship relevant to environmental doses, attempts to understand the relationship at the origin of the dose-response curve (as pictured in Figure 1), may be irrelevant from a regulatory point of view. Instead we should strive to understand the relationship at the "background dose". In short, any changed paradigm for regulation of environmental pollutants should not discuss thresholds without discussing backgrounds at the same time

The arguments in this paper should not be construed to imply that the authors reject biologically based models. On the contrary, we welcome biological models, and suggest, by means of the macroscopic arguments, where a good biological understanding can be most useful. A biological model is often taken to mean a full understanding of how a particular "end point," be it lesion or tumor, is produced by the agent (pollutant) at issue. In situations where we are discussing an "end point" that occurs naturally with considerable frequency, we suggest that an emphasis on the more limited questions of whether the pollutant acts in the same way as the background may be more tractable and therefore more fruitful. Also, the distinction between the regulatory treatment of carcinogens and non-carcinogens ‹ that only the former has a linear dose-response relationship ‹ is probably incorrect.

We also reopen the issue of the default assumptions for regulatory procedure. Although it is usually hard to find a scientific reason for a particular regulatory assumption, the default assumption that a carcinogen has a linear dose-response relationship is often considered plausible. We argue that for many end points it is plausible that a pollutant acts in the same way as a background, and therefore that low dose linearity applies for these - although the slope of the dose response at low doses is not a simple extrapolation from high doses.

Many scientists would consider it to be plausible (in the absence of contrary evidence) that a pollutant contributes to many end points. If plausibility is all that is required for regulation, then including non-cancer end points in the regulatory scheme in this way could increase the regulatory load many fold, and emphasizes the need for a logical way of prioritization.

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INVITED COMMENTARIES TO THE HEITZMANN AND WILSON ARTICLE

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In this paper Prof. Richard Wilson and his colleague, Martha Crawford Heitzmann, have provided us what the profession expects from him, a provocative treatise on risk management soundly based on fundamental physical science. The only hazard posed by articles such as this is that readers may take as science arguments for a sound policy. This paper advocates assuming that adverse effects from stressors such as airborne particulates add to background processes, and are thus justifiably treated for risk management purposes as being estimated by a linear-through-zero approximation.

Given valuing protection of people's health, this policy strikes me as sensible, absent information to the contrary. As science, however, it does not pass muster.

A philosophical introduction: we should take as "science" our humble attempts to describe as perfectly as we can the material world and its manifestations. The English physicist and philosopher John Ziman argues that society values science because it provides reliable knowledge about the material world (Ziman, 1978). We value this

reliability because it reduces the uncertainty surrounding decisions we need to make.

Thus it is important for those of us whose work consists of interpreting science for policy makers to distinguish our attempts to provide "best estimates" of reality from policy advice that is conditioned by our understanding of the relevant values and policy frameworks.

I suggest that in this paper Drs. Heitzmann and Wilson are proffering policy advice.

I have several reasons for concluding that this is the role they have adopted.

First, as a scientific proposition, the hypothesis described by the title cannot be tested. A scientific proposition would have to be more complex, in order to contain and explain both the examples of additivity they cite and the exceptions (of which they cite only one). The very concept of "the rule" is thoroughly value-laden: In whose eyes might something be the one or the other? Under what circumstances? The authors allude to the circumstances in which these questions have answers; these circumstances concern policy decisions.

Second, their conclusion rests on a mathematical analysis of a special case and a few examples, one an obvious ‹ and acknowledged ‹ exception. For *science*, the proof of their proposition is not persuasive. Third, their extension of Crump's proposition repeats an important, simplifying initial condition that effectively turns their argument into a syllogism. They, and Crump and his co-workers (Crump, *et al.*, 1976; *cf*. also Krewski, *et al.*, 1995), begin by postulating that the curve describing the relation between exposure and effect is continuous and monotonically increasing. A relation that is discontinuous ‹ a step function, for example ‹ will obviously not produce a straight line when added to any background process. The result will still be a step function. Heitzmann and Wilson note that such a case has not received adequate discussion in the science policy community. I wholeheartedly agree, and call to the attention of *BELLE's* readers some relevant papers by Seiler and Alvarez (1994) and myself (Wilson, 1996). Both Seiler and Alvarez and I assert that uncertainty ‹ "noise" ‹ in the measurements frustrate empirical testing of the Crump/Heitzmann and Wilson proposition of low-dose linearity. Seiler and Alvarez go on to argue that predictions of "risk" smaller than the measurement-noise limit cannot be reliable guides for policy ‹ and certainly not useful decision-criteria. I have concluded that the weight of biological evidence favors the proposition that, for individuals, the exposure-response for non-mutagenic carcinogens will more closely resemble a step function than a ramp with

its toe at [0,0]. The argument rests on the observation that for all non-mutagenic carcinogens, the rate-limiting step consists of inducing proliferation in cells in the target organ, a process that is very tightly controlled, physiologically. The ability to exert control is capacity-limited; only when the control capacity is exceed will adverse effects be possible.

Thinking about discontinuous functions leads us into thinking about some interesting details of biological plausibility, biological processes, and what our representations of exposure-response actually mean. We know, for instance, that actual exposures to any pollutant or stressor vary with time, yet we represent them as being constant. Even the dirtiest, smokiest cities of China or Mexico have fine days and nasty ones. We infer that breathing nasty air causes lung damage by comparing the results of doing so with the results of living where the air is sweet. By definition, breathing nice air causes no damage. Does one nasty day in one thousand cause damage? Not so we can tell. One in one hundred? Ditto. One in ten? Experts think it may. What is the appropriate way to represent "risk" ‹ likelihood of injury, given predicted conditions ‹ when the putatively damaging exposures are occasional but the measure of effect integrates many such exposures? Do the effects really simply add, or is the true representation some complex function of stress and repair? Biology suggests the latter.

And how nasty, how dirty must air be to do damage? Will the smoke from one cigarette in the middle of the South Atlantic harm us? Evidence exists that agriculturists in dry and sandy areas suffer some lung damage from the dust they breathe over a lifetime; clearly our species is not perfectly adapted to living in such conditions. But how far should we go, how stress-free should we strive to become?

I have gone beyond science. As they did, I have strolled into that domain in which the dispute over values can no longer be much informed by science, because here science has past its limits. As science, the proposition they describe can be given no better than "not proved." As a policy tool, it has valuable utility in certain contexts.

So, in closing, a comment on that context.

It is possible crudely to divide chemical/ environmental decisions into two kinds. One kind of decision can be made on the basis of a "screening" or "safety" analysis. The other requires a complex analysis including evaluation of

competing benefits, risks, and interests. In the first kind, the "safety" decision, we as a society have reached general agreement on how to balance risks and benefits. In the second, in what might conveniently be called, "value-balancing" decisions, we have not reached such agreement.

"Safety" decisions include approval of food additives (FDA) and "Pre-manufacturing Notices" (EPA / TSCA), establishing standards for drinking-water contaminants and tolerances for pesticide residues in food, and screening decisions such as the "no action" decision option in Superfund remedy selection. The analyses done for these decisions rely very heavily on "default" assumptions and positions. Heitzmann and Wilson's proposal fits very nicely among these assumptions and positions. For such purposes it is quite appropriate to adopt a risk-averse and uncertainty-averse position such as they advocate. We are, after all, very leery of accepting a median position when uncertainty is high (absent compensations of some kind); our usual practice is to "be safe rather than sorry."

The "value-balancing" decision class includes all the high-stakes environmental decisions, such as ambient air quality standards (for particulates, ozone, etc.), "major" rules such as regulating categories of emission sources under either Clean Air or RCRA, Superfund site remedy selections, revoking pesticide licenses, and so on. These decisions require tough tradeoffs among costs and benefits, to both the public and various parts of the private sector. People who live in Los Angeles do want cleaner air, which a lower ozone standard would force, but they also want to continue to drive their cars. People who live near Superfund sites want them cleaned up, but also, often, don't want thousands of loads of dirt trucked past their houses. Those who are affected by these high-stakes decisions deserve and need to know, as best as science can tell them, what the risk management tradeoffs represent. Just because we in the risk analysis profession have been very tardy in providing this information, in most cases, doesn't obliterate our obligation to do so.

For these conflicted-value decisions, the kind of "reasonable worst case" default proposed by Heitzmann and Wilson is useful only as part of a first-iteration screen. Yet for that kind of purpose, it's useful; we should adopt it.

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Heitzmann and Wilson correctly emphasize the importance of considering background phenomena and their relationship to the assessment of human health risks. There are four fundamental points that I wish to make; namely, (1) the authors are making two critical assumptions, (2) numerous (if not most) biological situations fail to satisfy these assumptions, (3) even if the assumptions were satisfied, they do not justify the current practice of using high-dose slope values as low-dose slope values, and (4) interspecies extrapolations should (but currently frequently do not correctly) incorporate background phenomena.

Assumptions

As the authors themselves note, the relationship between the shape of the dose-response relationship at high doses and at low doses is highly dependent upon the two "critical" assumptions being made by the authors. First, the background dose and the "pollutant" are assumed to have exactly the same mechanism of action (that is, that the background dose and the pollutant dose are additive in the dose-response relationship). For example, this means

not just that the background dose and pollutant both cause liver tumors, but also that they both affect the same cell types, affect the same stage in a multistage process, and cause the same type of cellular activity (e.g., both cause the same adducts, both inhibit the same repair processes, or both impact cell proliferation or apoptosis in the same way).

Second, the authors assume that the dose-response relationship is monotonic (strictly increasing in dose).

Biological Reality

There are numerous biological situations in which the two critical assumptions made by the authors are not satisfied, and their argument in favor of low-dose linearity is not applicable. Because cancer and noncancer health effects are often complex biological processes involving multiple components and multiple stages, the likelihood that the first assumption of a common mechanism is satisfied is small. Even if the first assumption is satisfied, the second assumption of monotonicity may not be satisfied. In an earlier Belle Newsletter (Stevenson *et al.* (1994)) and several follow-up papers (Sielken *et al.* (1995) and Sielken and Stevenson (1997 a,b)) examples of several mechanisms are given which do not have monotonic dose-response relationships. In some cases, the non-monotonicity is due to the interaction between multiple dose-dependent components, such as cell birth and death rates. In cases in which health is a dynamic balance between "invaders" and "defenders", there is a large range of dose-response shapes that are possible, including non-monotonic ones like "hormesis" (the potential for beneficial effects over certain dose regions). For example, if small increases in dose above the background dose stimulate (either directly or through feedback) the defense mechanisms sufficiently, a hormetic non-monotonic dose-response relationship can easily occur. The recent Third Belle Conference was wholly devoted to toxicological defense mechanisms and their impact on the shape of the dose-response relationships.

Practice

Even if the authors' two critical assumptions are met, the slope of the straight line from the risk at the background dose to the risk at a high dose may be much different (usually much greater) than the slope of the straight line from the risk at the background dose to the risk at a small incremental dose above background. This can be easily illustrated using the authors' own example in which the probability of a slope of the response follows a power law, $R=Ad^m$. In this case, the straight line from the zero risk at dose zero to the risk at a high dose d_h is Ad_h^{n-1}; the slope

of the incremental risk at a background dose d_0 is nAd_0^{n-1}, and their ratio is

$$(Ad_h^{m-1}) / (nAd_0^{m-1}) = (d_h/d_0)^{m-1}/n.$$

This ratio can be easily quite large. For example, if the high dose $d_h=10d_0$ and n=3, then the slope of the straight line from the zero risk at dose zero to the risk at the high dose d_h is more than 33 times greater than the slope of the incremental risk at the background dose d_0. Similarly, if the high dose $d_h=100d_0$ instead of $d_h=10d_0$, then the high-dose slope would exceed the low-dose slope by more than 3000 fold.

Thus, even when the critical assumptions are met, there is no scientific justification for the common policy (default) of assuming that the slope of the straight line from the risk at the background dose to the risk at a high dose is a good estimate or surrogate for the low-dose slope. It is bad enough that the assumptions used to justify the theoretical possibility of low-dose linearity are often not carefully considered or critically evaluated in practice. What may be even worse is the common practice of using the value of a high-dose slope as the value for low-dose slopes.

Interspecies Extrapolations

There are at least two current practices related to interspecies extrapolation that are not discussed by Heitzmann and Wilson but which fail to properly incorporate background phenomena. Interspecies extrapolations of cancer potencies (or dose-response relationships in general) should incorporate interspecies differences in background doses and especially interspecies differences in background transition rates from stage to stage in multistage processes.

The current method of calculating the upper bound on the cancer potency (q_1^*) from the linearized multistage model assumes that the background transition rates from stage to stage in a multistage carcinogenic process in humans are exactly the same as they are in the bioassay animals. Because several tumorigenic responses in mice and rats occur in organs with a much higher background rate than in humans and, hence, higher background transition rates,

the failure to incorporate the interspecies differences in these transition rates often leads to a significant overstatement of human risk. Sielken and Stevenson (1994) discuss this flaw and its mitigation.

A second common malpractice occurs when the dose-response relationship is not strictly linear and there are interspecies differences in the background doses. Agencies usually convert the animal bioassay dose levels to so-called "human equivalent doses" (HEDs) by dividing the animal dose levels by an interspecies conversion factor (e.g., based on body weights to the 3/4 power). After dividing the animal doses by this conversion factor, the human dose-response model is supposedly obtained by fitting the animal response frequencies against these HEDs. Unfortunately, because the animal dose assigned to the controls is zero and not the actual background dose and the zero HED assigned to the controls during the dose-response model fitting fails to reflect any interspecies differences in the background doses, the supposed human dose-response relationship fails to reflect any interspecies differences in the background doses. This problem can be overcome by fitting the animal response frequencies to the animal doses and then extrapolating the fitted dose-response relationship to humans and incorporating the differences between human and animal background doses in that extrapolation (Sielken, 1989).

Discussion

While the explicit quantification of low-dose risks would facilitate cost/benefit analyses and regulatory prioritizations, the frequent misuse of theoretical arguments supporting low-dose linearity in special situations as a general license to practice low-dose risk assessment by using high-dose slopes to characterize low-dose risks results in frequently biased characterizations of those risks. Furthermore, because the magnitude of the bias can vary by several orders of magnitude from one chemical to another or from one situation to another, the bias makes it virtually impossible to even reliably rank the relative risks or differentiate significant risks from de minimis risks. This leads to exactly the misallocation of limited health protection resources that the authors wish to avoid.

The problems associated with past cancer risk characterizations based on a default assumption of low-dose linearity and the faulty use of high-dose slope values as low-dose slope values are a good reason for the public to be concerned about any extension of these flawed quantitative cancer risk assessment techniques to noncancer health effects.

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Heitzmann and Wilson use two assumptions to conclude that though biologic dose-response relationships are

probably non-linear, the biological incremental responses of risk of cancer or other illnesses to low doses of radiation or chemical pollutants are linear.

The two required assumptions are:

1. The biologic response to a dose of substance is inherently non-linear, but monotonically increasing. Example: $R=Ad^n$
2. There exists a reasonably large background of a particular biologic effect (response) that is caused by a mechanism similar to that caused by the pollutant in question.

The linear adverse biological responses to low-dose pollutant increments are logically derived by a simple mathematical analysis of these assumptions.

The authors' emphasize, "...*that it is important not only to measure the magnitude of the biological dose-response relationship, but also to have some understanding of the underlying biological mechanism(s) - in particular, whether the mechanisms are the same for pollutant-and background-induced effects*." Their two assumptions concerning: 1) the biologic dose-response relationship $R=Ad^n$, and 2) the similarity of underlying background and pollutant mechanisms of inducing negative health effects, need examination to determine whether they are upheld by significant scientific data.

The first assumption is not supported by any statistically significant quantitative data. U.S. National Council on Radiation Protection (NCRP) 121, November 30, l995 states, "...essentially no human data can be said to prove or even provide direct support for the concept of collective dose [based on the linear nonthreshold "(LNT) theory] with its implicit uncertainties of nonthreshold, linearity, and dose-rate independence with respect to risk."[1] Efforts to present low-dose data that support the LNT theory, i.e. a monotonically increasing risk of cancer, have led to misrepresentation of their data by the authors of three studies: 1) the 1989 Canadian Fluoroscopy Study,[2] 2) its 1996 revision in which the 0.10-0.19Sv and 0.20-0.29Sv dose groups are missing,[3] and 3) the IARC Occupational Workers Study.[4]

Another effort to support the LNT theory was made in November 1996. The ICRP and the French Society for Radioprotection under Chairman Roger Clarke, reviewed the 1996 RERF Life Span Study of Atomic Bomb Survivors Report 12 which includes the 1985-1990 mortality data.[5,6] The ICRP claimed, though the authors of the Life Span Study did not, that their analysis of this new data showed a statistically significant increased solid cancer mortality at doses as low as 5 rem. According to Warren Sinclair, president emeritus of the NCRP and chairman of the ICRP Committee 1 which analyzes results of health-effects studies, the new results "vindicate" previous recommendations to lower permissible dose limits to 2 rem/year for occupational workers and to 0.1 rem/yr for the general public. "The combination of more data points and a more precise analysis, Sinclair said, allowed the RERF researchers to state with confidence that excess cancer risk due to radiation was observed at doses as low as 50 mSv."[6]

Statistical analysis of the excess solid cancer deaths following exposures of 5 rem (P=0.11) and 15 rem (P=0.42) demonstrate that they are not statistically significant; the lowest significant DS86 dose for increased solid cancer mortality is 35 rem. The correct dose for this significant increase is considerably greater than 35 rem since the revised DS86 dosimetry used gives estimates for neutron radiation from the Hiroshima atomic bomb that are lower by an order of magnitude than both the original T65D dosimetry and the experimental values obtained from neutron activation measurements at the distances from the hypocenter that correspond to low-dose exposures.[7]

While no statistically significant data support the assumption of monotonic increased risk of cancer with increased low-dose radiation, in recent decades there has accumulated a considerable body of contradictory scientific epidemiologic data.

Increased longevity and decreased cancer death rates have been observed in populations of the U.S., China, India, Austria, and the United Kingdom exposed to high natural background radiation.[7] Several recent epidemiologic studies with high statistical significance have reported that exposure to low or intermediate levels of radiation are associated with *decreased* mortality and/or *decreased* incidence of cancer:

- Persons living in the Eastern Urals after radiation exposure from a thermal explosion.[8]
- Atomic bomb survivors and residents of an urban area with radon spas in Japan.[7]
- U.S. populations exposed to high residential radon concentrations.[9] Figure 5 shows with high statistical significance, the strong tendency for lung cancer incidence to decrease with increasing radon exposure in sharp contrast to the incidence expected from the LNT theory.
- Occupationally exposed U.S. nuclear shipyard workers.[10,11] Table 1 shows a highly statistically significant decrease in death rates for exposed nuclear workers compared with unexposed non-nuclear workers (1mSv=0.1r). Nuclear workers also had lower death rates from leukemia and from lymphatic and hematopoietic cancers but these were not statistically significant.
- Canadian women who received repeated diagnostic lung fluoroscopy.[2] Figure 6 shows a statistically significant decrease in breast cancer deaths in women exposed to 15r(0.15Gy) with a typical U-shaped response to low-dose radiation.

Table 1. Standardized mortality ratios for selected causes of death among shipyard workers in the United States[11]

	Standard mortality ratio (95% CI)		
Cause of Death	≥5 mSv	<5 mSv	Non-Nuclear radiation workers
All Causes	0.76 (0.73,0.79)	0.81 (0.76,0.86)	1.00 (0.97,1.03)
Leukaemia	0.91 (0.56,1.39)	0.42 (0.11,1.07)	0.97 (0.65,1.39)
Lymphatic and haemopoietic cancers	0.82 (0.61,1.08)	0.53 (0.28,0.91)	1.10 (0.88,1.37)
	5.11	5.75	

Mesothelioma	5.11 (3.03,8.08)	5.75 (2.48,11.33)	2.41 (1.16,4.43)
Lung cancer	1.07 (0.94,1.21)	1.11 (0.90,1.35)	1.15 (1.02,1.29)

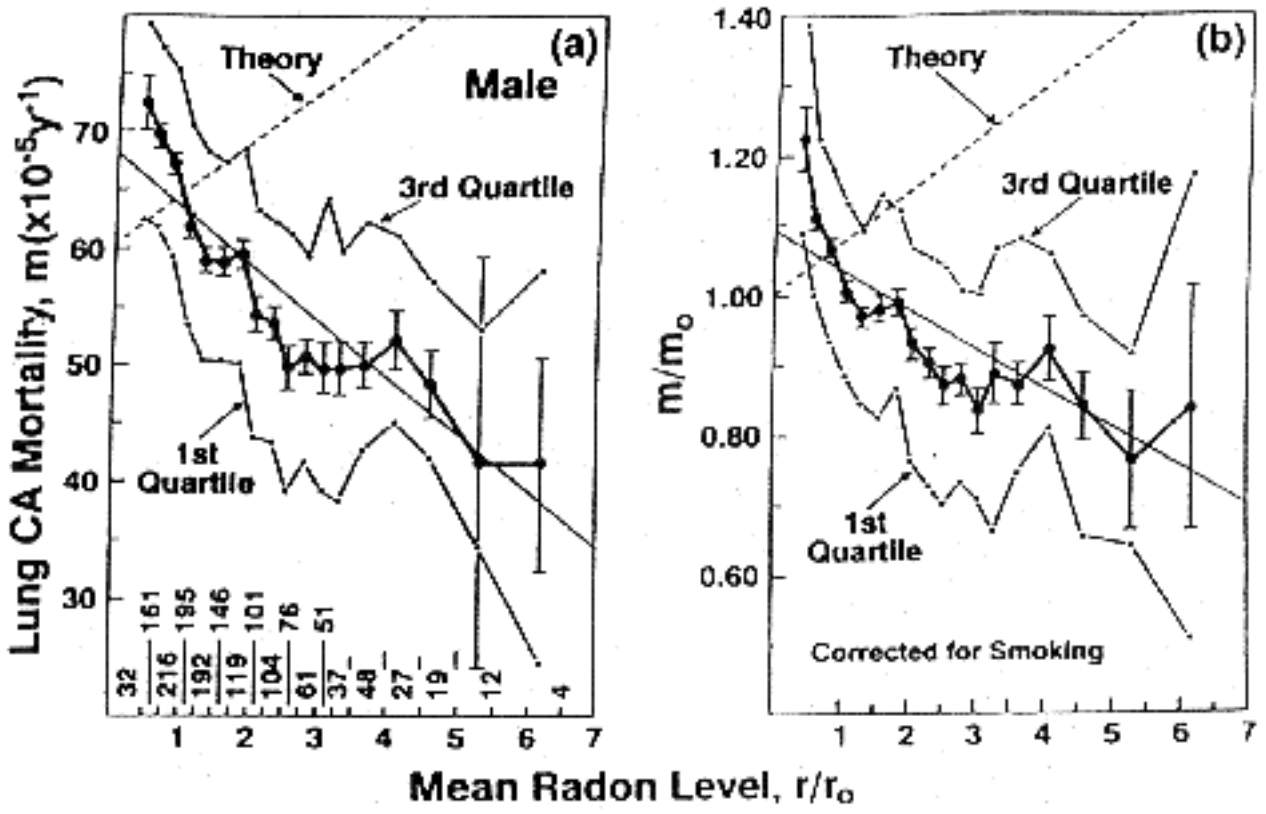

Figure 5. Lung cancer mortality rates vs. mean radon level r_0=l pCi/L. in homes for 1601 U.S. counties. Figure b incorporates the effects of smoking.[9]

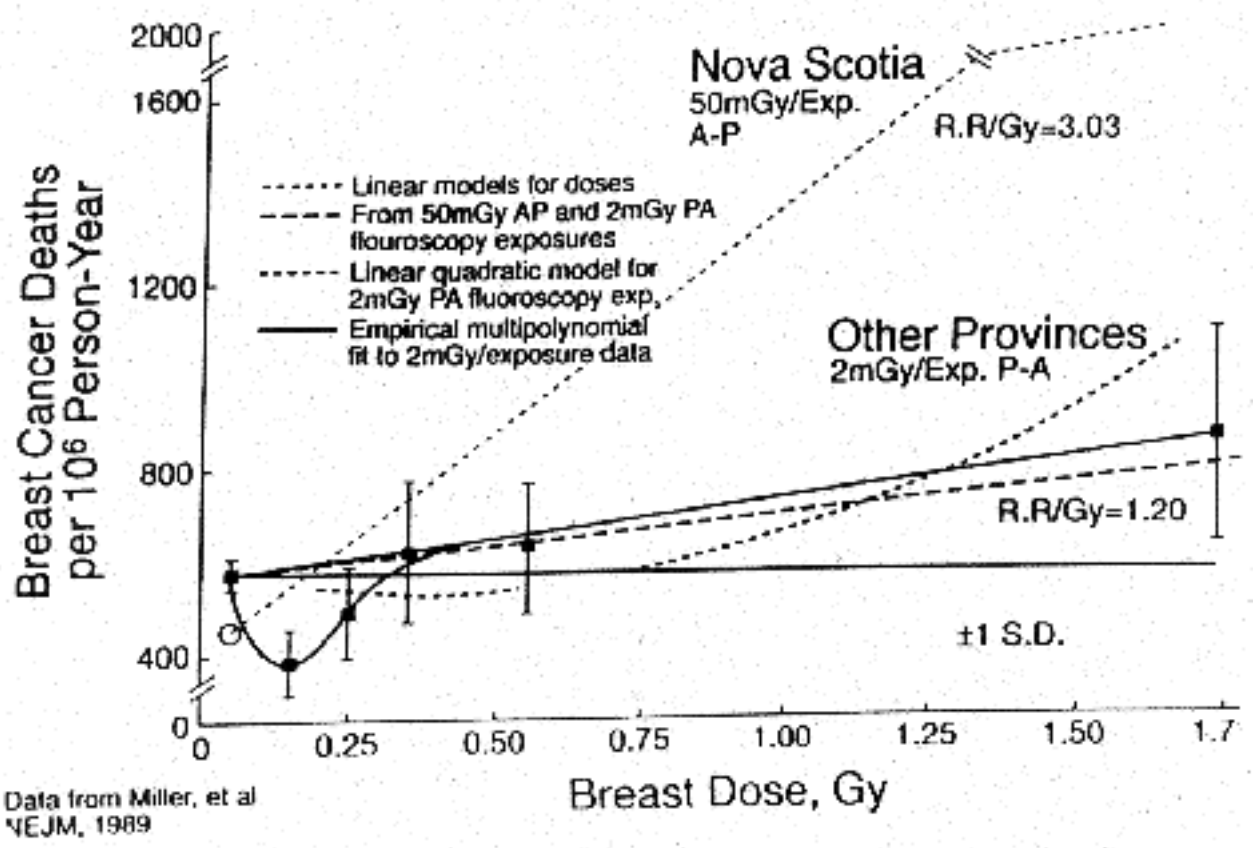

Figure 6. The Canadian Tuberculosis Fluoroscopy Study of Miller et. al. A graphic plot by E.W. Webster of the study data showing the authors' "best fit" linear model and linear-quadratic model relationships. The empirical least-squares best fit is added and shown.2

Despite almost 40 years of intensive search, the first assumption of a monotonic biologic dose response ($R=Ad^n$) to radiation is not supported by any statistically significant quantitative low-dose (e.g. ²20 rem) data. On the other hand, this assumption is contradicted by the emergence during the past 2 decades of significant data demonstrating risk *decrements* in response to low-dose radiation "pollutant" exposures. Risk *increments* in response to high doses (e.g., ³100 rem) are well documented. The authors correctly state, "If the dose response is not monotonic, or n<1, the situation becomes more complex and needs more careful scientific and public policy discussion. This has not yet been the focus of regulatory discussion."

The importance of the second assumption for the incremental potency argument for low-dose linearity is stated by the authors. "The one requirement is that there exists a reasonably large background of the biological effect under consideration, and that the pollutant acts in the same way as the background." The biological effect of most concern to radiation protection organizations and the public is cancer mortality; curiously, not mortality from all causes. Cancer mortality in the United States is 25% of mortality from all causes, satisfying the requirement of a large background. But does the "pollutant" radiation act in the same way to produce cancer as the background?

The complex cell circuitry signaling for growth, division, and death includes both extracellular factors and transcription factors. "...the extraordinary detail and duplicate functions of these circuits are designed so that single disruptions here and there do not create malignant growth. A cell divides without restraint only when its circuitry has been disrupted at a number of key points: multiple [persistent] mutations are required."12 Intrinsic mutations, i.e., mis-unrepaired DNA alterations occurring in an environment free of mutagens, occur with very high frequency. "...by fundamental limitations on the accuracy of DNA replication and repair, ...in a lifetime, every single gene is likely to have undergone mutation on about 10^{10} separate occasions in any individual human being..."[13] The additional relentless continual damage of DNA by reactive oxygen metabolites $(O_2^{\cdot}\blacksquare, \cdot OH, H_2O_2)$, comprising 2-3 percent of all oxygen consumed, and thermal instability, increases this number to about 10^{11} mutations per gene.[14,15]

"From this point of view, the problem of cancer seems to be not why it occurs, but why it occurs so infrequently. Evidently, the survival of mammals must depend on some form of double-or more than double-insurance in the mechanisms that protect us from being overrun by mutant clones of cells that have a selective advantage over our healthy normal cells; if a single mutation in some particular gene were enough to convert a typical healthy cell into a cancer cell, we would not be viable organisms."[13]

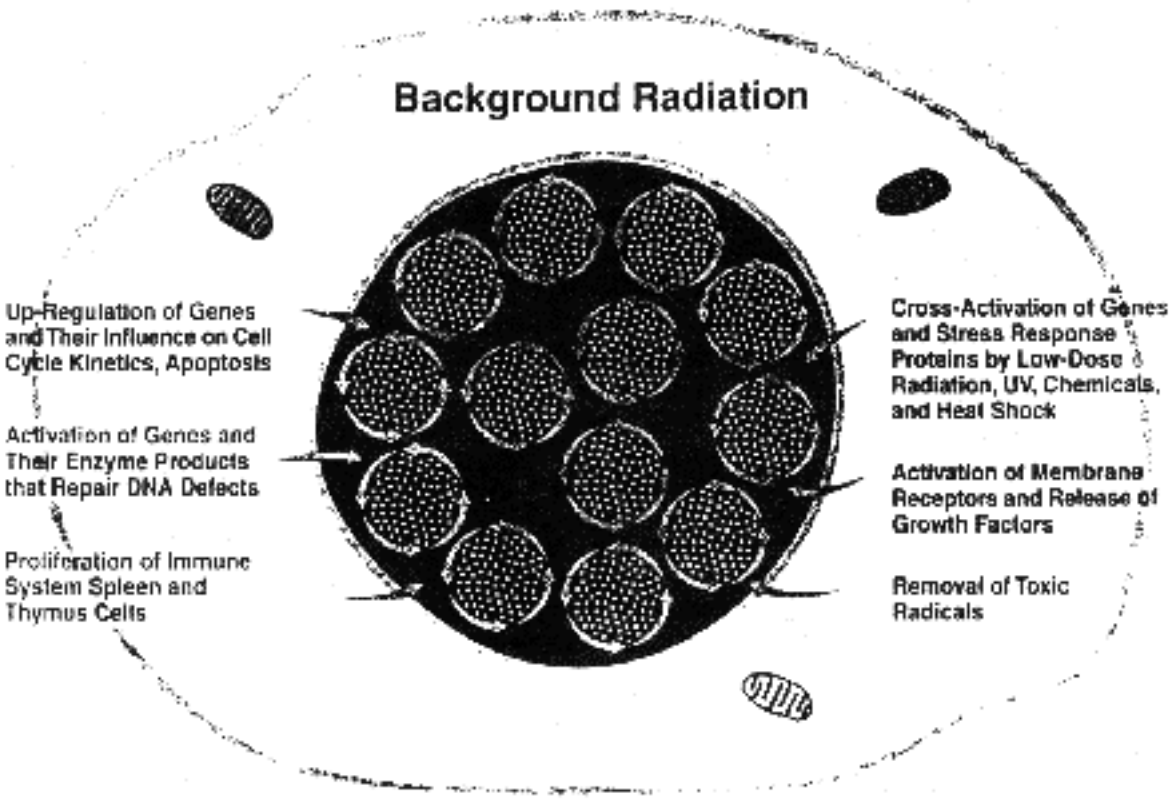

Figure 7. DNA damage control biosystem. Multiple adaptive responses prevent, repair and remove the $2.4X10^5$ potential mutations/cell/d produced in humans by reactive oxygen metabolites ($O_2^{\bullet-}$, $\cdot OH$, H_2O_2) and thermal instability, and each day remove about 10^{13} whole body mutations. The length of the arrows indicate schematically the level of adaptive response activity occurring at average background level of radiation during youth. The dots inside the nucleus represent the numerous potential mutations that are successfully prevented, repaired, and, if still persisting, removed by the adaptive responses controlling them.

Our survival is dependent upon effective defense mechanisms that prevent (anti-oxidants, cell cycle control), repair (DNA repair enzymes) DNA damage, and *remove* about 10^{13} mutations *daily* by cell cycle control, programmed cell death (apoptosis), necrosis, and the immune system (Figure 7).[11,15] The relatively rare occurrence of cancer under the age of 50 is usually associated with genetic defects of the biosystem controlling DNA damage. The progressive

age-related decline of biosystem effectiveness is associated with an exponential increase in the incidence of cancer with the third to the fifth power of age.[13,16-20]

A whole body radiation background of 0.1r/year produces about 109 mutations/day.[15,21] Exposure to 20r/year would produce about $2x10^{11}$ mutations/day. Though this is insignificant compared to the intrinsic metabolic background of 10^{13} mutations/day,[15] a very small linear incremental risk of cancer would result theoretically, *assuming that the effectiveness of the biosystem controlling DNA damage remains constant*. Heitzmann and Wilson state, "Even if we assume that most damaged cells are actually repaired by the body's defenses, linearity can still be maintained, if the fraction of cells repaired is constant with dose." During the past 15 years studies have shown that the fraction of cells repaired is not constant, but is increased by low dose radiation and decreased by high dose radiation. Though the activity of the DNA damage-control biosystem is decreased by high dose (e.g., ^{3}100r), high-dose-rate (e.g., ^{3}20r/min) radiation, it adaptively responds with increased activity to low-dose (e.g., ^{2}20r), low-dose-rate (e.g., ^{2}1r/min) radiation as well as to low-dose toxic chemical agents.[11,16,22]

Low-dose linearity ($R=Ad^{n}$) and LNT theory (n=1, R=Ad) applied to the risk of cancer are based on two assumptions: 1) the biological response of cancer to radiation dose is monotonically increasing, and 2) all mutations, whether induced by ionizing radiation or other agents, pro

duce a corresponding increase in the risk of cancer, assuming the fraction of cells repaired is constant with dose. These assumptions are invalid for they are contradicted, without any support, by statistically significant low-dose epidemiologic data and they ignore the operative effect of ionizing radiation on the DNA damage control biosystem. Emphasis is placed on the relative difficulty of repairing infrequent double strand breaks (0.4/cell/r low-LET radiation)[21] and if unrepaired, ignoring their daily *removal*, together with trillions of other environmental and spontaneous mutations, by the adaptive responses of cell cycle control, self programmed cell death (apoptosis), necrosis, and the immune system. Disregarded are the extremely high number of spontaneous mutations and the adaptive responses to radiation that, until they diminish with age, very effectively prevent, repair, and *remove* both the spontaneous and the few low-dose, low-dose-rate environmental mutations.

Contrary to the increased risks associated with injury to the DNA damage-control biosystem by high-dose radiation, this biosystem is stimulated by low-dose radiation to function even more effectively and *decrease* the risks of mortality and cancer. These observations of fundamental *biologic* cellular functions contradict the theoretical assumptions based on *biophysical* concepts and *exclude* a LNT dose-response relationship.

Scientific understanding of the positive health effects produced by adaptive responses to low-level radiation would result in a realistic assessment of the environmental risk of radiation. Instead of adhering to non-scientific influences on radiation protection standards and practice[23] that impair health care and research and waste many billions of dollars annually for protection against theoretical risks, these resources could be used productively for effective health measures and other benefits to society.

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The paper by Crawford and Wilson focuses attention on the "additivity-to-background" argument for low-dose linearity that was first advanced in Crump *et al.* (1976). Given that a general belief in thresholds remains common among scientists, and the enthusiasm that exists toward the creation of biologically-based dose-response models, it is useful to reconsider this simple argument for low-dose linearity. Crawford and Wilson are absolutely right in their basic assertion that it applies equally well to all heath effects, although Crump *et al.* originally presented it in the context of cancer.

Crump *et al.* argued that if the background response of a health effect (cancer or otherwise) is caused by a mechanism similar to that by which a pollutant causes the health effect, then it should be possible to represent the background response as a response to an equivalent background "dose", d_0, applied to a generalized dose response that incorporates both the background dose, d_0, and the dose, d, of the pollutant, i.e., the dose response of the pollutant can be expressed as $R(d_0 + d)$, where R is the generalized dose response function for the health effect produced by the common mechanism, whether due to the pollutant or to the effective background dose, d_0. Although Crawford and Wilson restricted attention to the case in which R is monotonically increasing, useful insights can be gained by considering the case in which R is assumed to have a threshold at some dose, T (Figure 8). If the background health effects are occurring by the same mechanism as that through which the pollutant acts (i.e., if $d_0 > T$), then the response will be approximately linear with response (i.e., the slope of the dose response curve will be positive) at low doses. On the other hand, if $d_0 < T$ there will be a threshold in the observed dose-response at the pollutant dose of $d_T = T - d_0$.

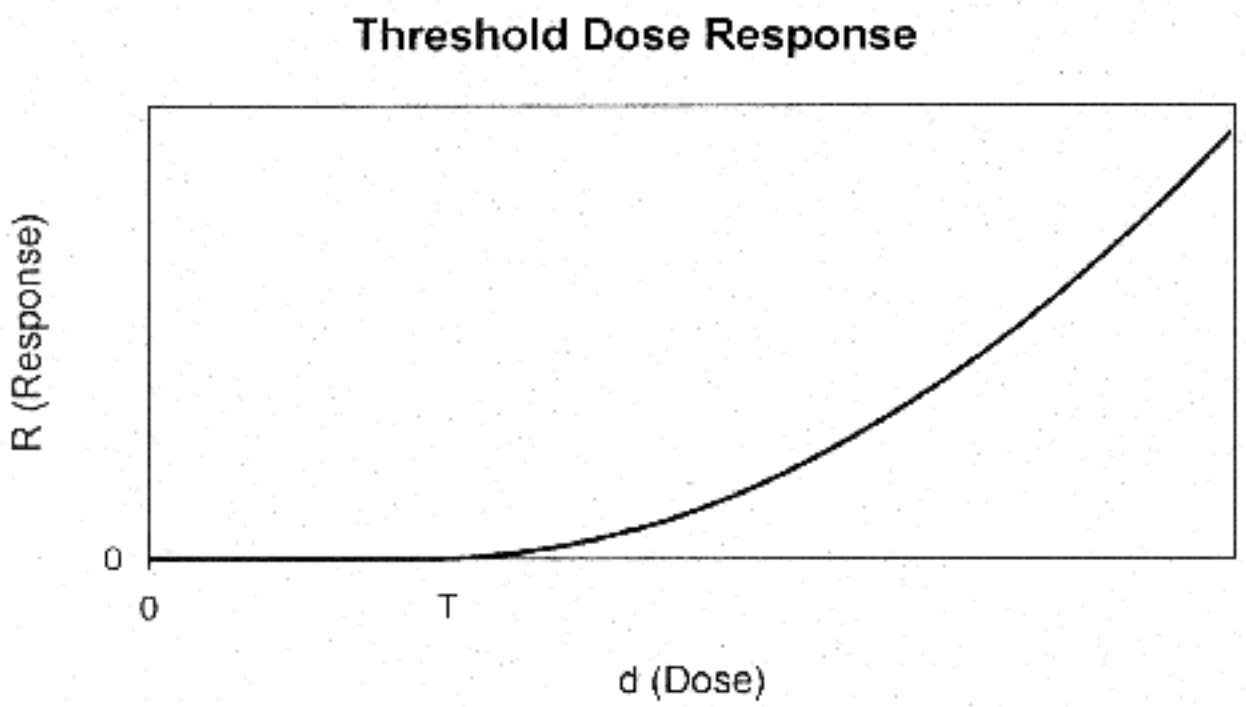

Figure 8. Threshold Dose Response

One important consequence of this argument is that non-linear, non-threshold responses are effectively ruled out. Note that the only plausible way the low dose can be non-linear and still non-threshold is for the generalized dose-response R to be non-linear (e.g., $R(d) = Ad^n$, $n > 1$) and for $d_0 = 0$. Assuming there is a non-zero effective background dose, d_0, then the low-dose response must be either threshold or linear; a non-linear non-threshold dose response cannot occur.

All of the above observations continue to apply if the generalized dose response, R, is U-shaped (Figure 9), provided the definition of "threshold" is broadly interpreted to include a beneficial response, and the threshold, T, is associated with the low point of the generalized dose response. If $d_0 < T$, the response is beneficial, and if $d_0 > T$, the response is adverse and linear at low doses. In either case (threshold or u-shaped dose response) the basic argument for low dose linearity is still valid; if background responses are occurring through the same mechanism as the dose-related responses (i.e., if $d_0 > T$), the low-dose response is linear.

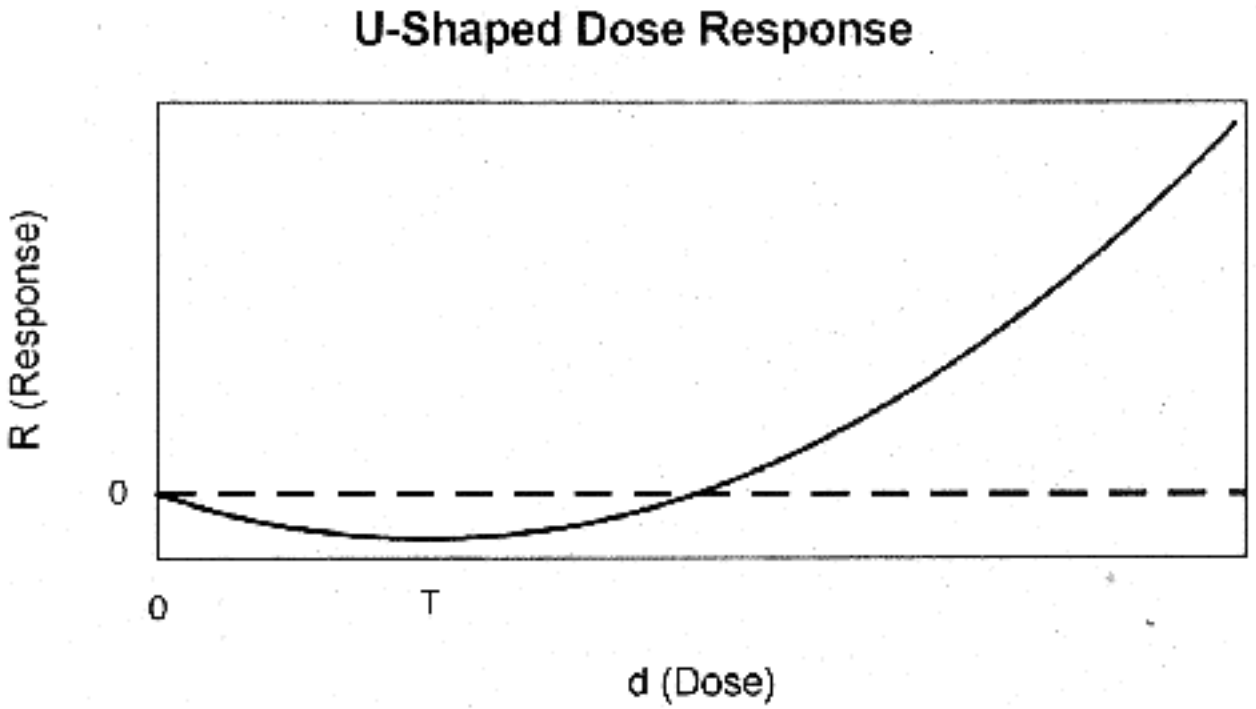

Figure 9. U-Shaped Dose Response

Crawford and Wilson caution that the argument for low-dose linearity involves the internal dose, and any "non-linearity in the pharmacokinetic relationship between exposure and organ dose remains". However, Richard Peto pointed out a number of years ago in his testimony on the OSHA cancer policy that the pharmacokinetic relationship between exposure and internal dose should also be linear at low exposure levels. This observation is consistent with all pharmacokinetic models (at least all of which I am aware) that have been developed for specific pollutants. Consequently, the argument for low-dose linearity applies, not just to the internal dose-response relationship, but to the exposure-response relationship as well.

The fact that this simple argument for low dose linearity applies equally to carcinogenic and non-carcinogenic responses suggests that EPA's former practice of applying fundamentally different risk assessment approaches to cancer (assuming a linear dose-response) and non-cancer (assuming a threshold exists) may not be justified (Crump, *et al.*, 1996). Although EPA's draft cancer guidelines (EPA, 1996) specify an approach for cancer that is

nearer to the approach generally applied to non-cancer, important differences remain. In a recent issue of *Belle*, Crump *et al.* (1996) proposed that carcinogens and non-carcinogens be regulated using a common approach that minimized the use of low dose extrapolation.

Even if low-dose linearity truly is the rule rather than the exception, as suggested by Crawford and Wilson, this does not necessarily mean that linear extrapolation from high doses is always the best approach to risk assessment. Actually, the argument for low-dose linearity imposes no bounds (other than zero) on the response at any dose. Estimates of the low-dose slope obtained by linear extrapolation from high doses could be seriously in error in specific situations.

Based on the additivity-to-background argument, in order to justify a biologically-based model of underlying mechanisms that predicts a non-linear low-dose response, it is necessary to rule out completely the possibility that non-pollutant-related responses could ever occur via a common mechanism. This would appear to be a difficult task in many ‹ perhaps most ‹ situations. The argument also suggests that the shape of the dose

response curve at low doses is inherently determined by the relationship between background responses and responses induced by the pollutant. This idea seems to have been largely ignored by researchers in designing and interpreting experiments with the goal of understanding low dose risk. Perhaps a fruitful line of research would be to develop data that could be used to better understand (and perhaps refute) the additivity-to-background argument for low-dose linearity.

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Heitzmann and Wilson usefully illustrate the critical roles of interactions with background pathological processes/mechanisms in forming expectations about the likely effects of incremental exposures to toxicants at relatively low environmental levels. They also show that one can at least begin the process of estimating likely low dose effects quantitatively if one has a reasonable amount of information about the potential for interactions and human interindividual variability in specific cases.

If I have any complaint about their summary and their more extensive earlier paper (Crawford and Wilson, 1996), it is that they have chosen a mathematically tractable power law dose response formulation for their illustrations, rather than something like a probit‹which is more directly interpretable in terms of lognormal variability in susceptibilities to toxic action (and/or) a lognormal distribution of functional reserve capacities in our diverse human population. The probit dose response model, long used by toxicologists to analyze acute animal lethality data, is based on the assumption that there will be a lognormal distribution of individual thresholds for a specific response. A lognormal distribution would be expected if there are relatively numerous sources of individual variability in susceptibility that tend to have multiplicative interactions. For example, one could well expect individual differences in the fraction of chemical taken up by a particular medium, rates of metabolic activation or elimination, and the baseline reserve capacities for key physiological functions affected by the chemical to all tend to interact multiplicatively in determining the dose of chemical needed to produce a specific non-cancer effect in a specific individual. In practice, models incorporating lognormal susceptibility distributions often describe population dose response data quite well (Hattis, 1996, 1997) (e.g., see Figures 10 and 11).

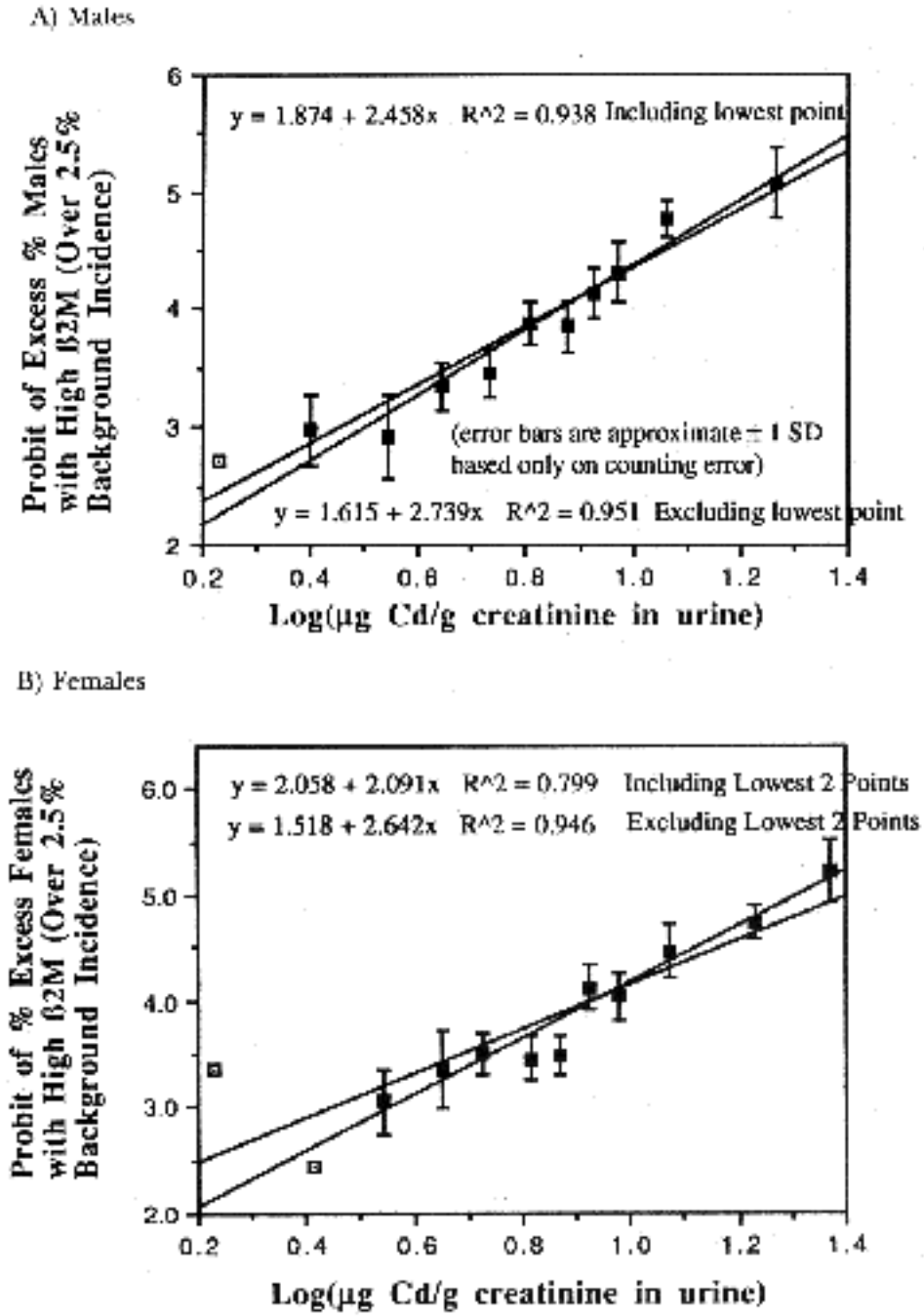

Figure 10. Traditional Log Probit Plot of the Excess % With High β2 Microglobulin Urinary Excretion (Data of Nogawa et al., 1992) Source: Hattis, 1997.

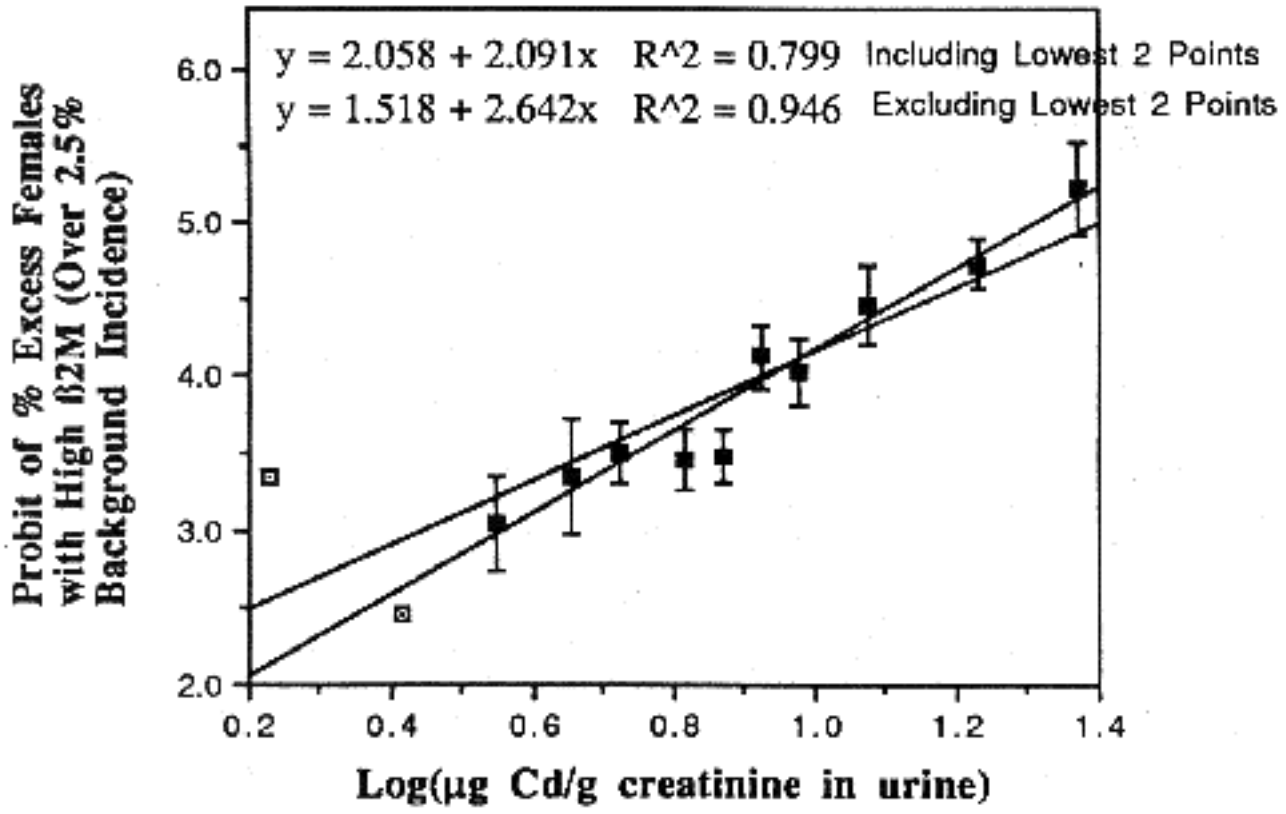

Figure 11. Log Probit Plot of the Percentage of 102 Tested People Who Gave Positive Skin Patch Tests for Chromium (VI) (Data of Nethercott et al., 1994) Source: Hattis, 1997.

In part because the field of quantitatively estimating non-cancer effects has been relatively neglected there is a rich potential for the creative future development of basic scientific information on individual variability and risk assessment modeling. In recent work (Hattis, 1997), I have suggested several different strategies for research and analysis for different responses, depending on

- The distinction between quantal vs continuous outcome data.

- Whether the causal models appropriate for a specific response are stochastic vs deterministic on an individual basis.
- The needs/opportunities to use one-step (simple input-output) models vs multistep models with intermediate parameters.

Table 2 briefly illustrates these different strategies.

Table 2. Strategies for Assessing Variability in Susceptibility and Predicting Risks

Outcome Parameter	One-Step vs Multi-Step	Deterministic vs Stochastic Process	Example(s)
Quantal	One-Step	Deterministic	Traditional log probit dose response analysis of the percentage of people showing hypersensitivity responses to dermally applied chromium(VI) solution is interpreted as a direct measure of the percentage of people who have thresholds below different doses.
Quantal	Multi-Step	Deterministic	Overall interindividual variability in susceptibility is modeled as a combination of the variability of component processes-uptake, pharmacokinetic, pharmacodynamic. E.g. Fish ingestion-methyl mercury uptake-methyl mercury blood levels-risk of fetal/developmental impairment.
	One-		Change in FEV_1 from short term exposures to ozone; Change in measures of kidney function

Continuous	One-Step	Deterministic	ozone; Change in measures of kidney function from long term exposure/uptake/ urinary excretion of cadmium.
Continuous	Multi-Step	Deterministic	Lead in house dust-blood lead-impaired development of IQ in children or elevated blood pressure in adults.
Quantal	Multi-Step	Stochastic	1. Changes in mortality as a function of cadmium-induced kidney damage; 2. Changes in male fertility as a function of toxicity-induced changes in sperm count and other sperm quality parameters. 3. Changes in infant mortality as a function of toxicity-induced changes in birth weight.
Continuous	One-Step	Stochastic	Number and severity of automobile injuries as a function of blood alcohol levels.
Continuous	Multi-Step	Stochastic	Number and severity of automobile injuries as a function of defined changes in hazard recognition and response times induced by alcohol and other neuroactive substances in experimental subjects.
Source: Modified from Hattis, 1997.			

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It is interesting to see both the continued application of the original Crump *et al*. (1) paper to cancer risk and its extension to other biological endpoints. As one of the original authors of the low-dose linearity paper, I am less enthusiastic than Crawford and Wilson are over its usefulness. The original paper was written some twenty years ago without benefit of much of today's biology. What is of concern is whether or not the original simple idea of background additivity is consistent with today's biology and whether the concept, if true, has any value for quantitative risk estimation. Crawford and Wilson appear to answer yes to these two questions.

The biological complexity is illustrated by the authors' benzene leukemia example. Pathologists now subdivide

leukemias using the French American British classification. During epidemiological studies, we are beginning to see differences in the effects of chemicals on these particular subtypes of leukemia. For example, for acute myelogenous leukemia Sandler *et al*. (2) reports a relationship with cigarette smoking and subtype M2, while Crane *et al*. (3) reports a high relative risk for subtype M4 from benzene exposure. Further, in the Taylor *et al*. (4) study of acute leukemia, approximately 15% of the human leukemia cases had an activated ras oncogene. They found that a history of occupational exposures to solvents increased the risk of ras activated acute leukemias but not for non-ras acute leukemia.

The example of benzene induced acute leukemia in man illustrates the existence of multiple pathways and the possibility that an agent may affect only a particular pathway. The question becomes whether or not the existence of multiple pathways matters in the linearity argument. If it does not, then the rarity of an effected pathway should matter.

With regard to basic cancer dose-response, Ames *et al*. (5) argues that many chemicals tested in the NTP animal cancer bioassay induce increased cancer incidence through cellular proliferation. The idea follows that if this is the sole biological basis for the cancer increase the carcinogenicity will not apply at low-dose where the proliferation is not induced by the chemical. Since cells will die spontaneously the additive background argument would say that there is low-dose linearity for cellular proliferation. This, I find difficult to accept.

The next issue at low-doses is the question of hormesis or adaptive response. Wolff (6,7) has shown with radiation that presumably repair induction at low-doses will modify the low-dose linearity assumption. This again illustrates the complexity of the biology and the speculative nature of the low-dose linearity assumption.

From a quantitative standpoint, I showed many years ago (8) that very simple pharmacokinetic considerations can modify risks estimates at low-doses by several orders of magnitude. It seems then that the additive background argument of Crump *et al*. (1) 20 years ago creates a false sense of scientific security in low-dose extrapolation. What should be said is that low-dose linearity is speculative and it is a reasonable assumption for public health purposes in those instances where there is no scientific evidence to the contrary.

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We are pleased by the positive note of the responses to our paper.

Dr James Wilson is right in his assertion that we "are proffering policy advice". Indeed the whole issue of low dose linearity is a policy issue, and has been ever since the International Commission on Radiological Protection suggested it as a Prudent Public Policy in 1928. But we do not understand his contention that "as science it does not pass muster". Does he mean this, as we think he should, to apply to all discussions of possible low dose behavior? If not, we have a serious disagreement. One of our conclusions is that the underpinning for low dose linearity for carcinogenesis is not appreciably better than for other medical end points. A prediction based on indirect data is not as good as a prediction based on direct data, but it can none the less be a scientific prediction particularly if a statement of uncertainty is attached. This may just be semantics; but in the communication of policy recommendations from the scientist to the managers, the precision in use of words is important.

While we admit that our title was meant to be more provocative than descriptive, Dr Pollycove has, in our view correctly gone further. He restates the two assumptions under which low dose linearity can follow: a monotonically increasing dose response and an understanding of whether the background and the pollutant act by the same mechanism. He then explains why in his view radiation, the first agent for which policy makers assumed a linear dose response does not satisfy these assumptions. It is just this reexamination that we urge on those responsible for radiation protection. There is still, of course, another possibility that the basic biological mechanism of radiation carcinogenesis has a linear dose- response. Pollycove criticizes those who fail to reexamine radiation carcinogenesis. For example recent (otherwise excellent) papers by Lubin and Boice (1997) and Riordan (1996) on radon risk assume (without comment) low dose linearity and in addition many studies assume that indirect evidence from uranium miners applies to residences. They discount the direct data at low doses by Cohen (1995) because

Cohen made an "ecological" study. We agree with Pollycove that these assumptions need reexamination. We urge that the presently sitting BEIR VI committee on radon hazards in residences at low exposures discuss these assumptions very carefully and also consider James Wilson's question: are they addressing science or merely policy? To the extent they are addressing policy, they should note that any errors in Cohen's arguments can only arise because other causes of lung cancer (such as smoking) much outweigh the small effect of radon.

We agree with and welcome the mathematical detail supplied by Crump, Hattis and Seilken. Indeed we might well have chosen the probit model as a practical example of a monotonically increasing dose-response relationship. But James Wilson is wrong when he says that a step function (a threshold) will not produce a straight line when added to a background process that acts by the same mechanism. It is not possible to have a finite population background with a step function dose response unless there is a distribution of sensitivities (perhaps only a narrow distribution). If that distribution is normal, then the result is the probit distribution mentioned by Hattis to which the general argument applies.

The most important comment is that of Dr. Hoel who argues that pharmacokinetic considerations can modify the dose response at low doses. We agree, but note that this is a discussion of the relation between

organ dose and applied dose which is another matter entirely. As Crump points out this may also be linear at low doses. But there can be a change in slope. This can be crucial if such changes in slope are different between animal (where there are data) and man where often there are no data. It is also true that the low dose slope extracted from high dose behavior can be overstated if the background is small.

We would leave the reader with three important ideas; one is that low dose behavior of any agent acting on any medical end point can only be indirectly derived and is to that extent an unproven assumption not a fact. This is as true for carcinogenesis as for non carcinogens; and another that the focus of discussion of the mechanisms that provide the indirect data should be on the relative behavior of pollutant and background. Finally that the mechanism being discussed only applies when there is a background, and the risk so derived is a small fraction of background. This is the situation in most environmental policy issues today.

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