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Ideological toxicology: invalid logic, science, ethics about low-dose pollution

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If scientists rely on assumptions rather than logic, empirical confirmation, and falsification, they are no longer doing science but ideology – which is, by definition, unethical. As a recent US National Academy of Sciences report put it, "bad science is always unethical."[1] This article discusses several ways in which toxicologists can fall into ideology – bad, therefore unethical, science.

In part because of the increasing expense of pollution control, some toxicologists have been re-examining pollution dose-response curves that are non-monotonic, that is, curves in which the direction of some response changes with increasing or decreasing dose.[2] Ethanol is a classic example of a non-monotonic dose-response curve because moderate drinking is associated with lower risks of heart disease, whereas heavy drinking is associated with higher risks.[3,4] If some low-dose pollutants exhibit adaptive or "beneficial effects,"[5] this might suggest re-thinking pollution regulations which presuppose linear no-threshold (LNT) dose-response curves.

Overview

As illustrated by the case of ethanol, claim H is that for some biological endpoints, low-dose toxins and carcinogens exhibit hormesis, a "beneficial"[5] or "adaptive response characterized by biphasic dose responses" and resulting from "compensatory biological processes following an initial disruption in homeostasis."[6] From this uncontroversial claim H, however, the article argues that some toxicologists invalidly infer HG (that H is "generalizable across biological model, endpoint measured, and chemical class"[7]) and HD (that "a strong case can be made for the use of hormesis [H] as a default assumption in the risk-assessment process"[2]). Evaluating HG and HD, this article argues for five claims. While 1) H is true, 2) HG falls victim to several logical fallacies and therefore is logically, scientifically, and ethically invalid. 3) Because it relies on logical fallacies, confuses necessary and sufficient conditions, and violates at least five sets of ethical norms, HD is logically, scientifically, and ethically invalid. 4) Five remedies could help address HG-HD flaws and failure to adequately assess low-dose exposures. 5) Three objections to these criticisms of HG and HD are easily answered.

H is scientifically uncontroversial because of its limited scope

As many examples attest, claim H (that for some biological endpoints, some low-dose toxins and carcinogens exhibit hormesis – a "beneficial"[5] or "adaptive response characterized by biphasic dose responses" and resulting from "compensatory biological processes following an initial disruption in homeostasis"[6]) is both true and uncontroversial. H is true and uncontroversial, however, largely because it requires so little: at least one non-monotonic effect, on one endpoint, from one pollutant, for one period of time. H would be satisfied if a pollutant caused cancer (one endpoint) but increased fingernail growth (another endpoint).

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Thus, low-dose cadmium satisfies H in reducing some tumors in some species and increasing growth in some plants, although tests on 8700 adults showed that low-dose cadmium is associated with excess prediabetes and diabetes, and animal tests showed pancreas damage, glucose dysregulation, and kidney damage.[8] Likewise, moderate drinking of 1.2–2.2 drinks/day satisfies H because it reduces mortality, yet it increases breast-cancer risk.[8] The upshot? Given the minimalist definition of H, when low-dose responses are beneficial for some endpoints but harmful for others, the response nevertheless satisfies H.

Indeed, the Calabrese–Baldwin conditions for H are so minimal that they call responses "hormetic," [2] when a) alleged H responses do not satisfy criteria for statistically significant changes from control. Thus, a non-statistically significant change in incidence from 2 to 3, in a sample of 20, is called a 33% change, evidence of hormesis. Likewise, Calabrese–Baldwin used a study no-observed-adverse-effect level (NOAEL) to assess H. Because sample size, statistical power, data variability, endpoint measured, duration of exposure, route of exposure, rate of exposure, and so on affect study NOAEL, therefore b) alleged H responses can be merely artifacts of factors like small sample size or data variability.[3,9]

Because scientific criteria for H are minimalist, not scientifically rigorous, instances of alleged H responses are easy to find. Yet they reveal almost nothing about total responses, net beneficial effects, lifetime responses, or all-endpoint effects – factors that are crucial to reliably assessing the policy-relevance of alleged low-dose responses to toxins such as TCDD (dioxin). Consider four methodological flaws in a 2-year, low-dose TCDD test on rats, a test alleged to illustrate H, decreased tumor incidence.[10] First, the study covered only about two-thirds of the rats' life span, not the most vulnerable periods. If roughly 80% of human cancers are diagnosed in the last one-third of life[11] and if the rat analogy holds for human life span/cancers, the study may have captured only 20% of cancers induced by TCDD, not total cancers. Second, although liver, lung, tongue, and nasal tumors increased in this study, whereas pituitary, uterine, mammary, pancreas, and adrenal tumors decreased, the study invalidly aggregated all tumors. Because no individual tumor response was non-monotonic, the alleged H response seems an artifact of invalid aggregation. Third, the study also ignored early mortality and confounders like lower body weights when it calculated tumor rates, relative to controls. Fourth, there may be a replication problem because other TCDD studies (in primates) have shown a variety of low-dose adverse effects.[12] Despite these four methodological problems, the study has been used to allege H.[8,3]

Generalizing to hormesis claim HG: logically, scientifically, and ethically invalid

Given the lack of rigorous scientific conditions for (and thus the relative ease of) claiming an instance of H, there are obvious scientific problems with generalizations based on H. HG is the claim that H is "generalizable across biological model, endpoint measured, and chemical class,"[7] that "the hormetic model is not an exception to the rule [of linear no-threshold (LNT) dose responses] – it is the rule"[13]

One indicator of HG's potential problems is that the classic cases from which HG is most often inferred, those of Calabrese and Baldwin,[2] include no epidemiological or field studies.[3] Yet these types of studies are precisely those in which conditions best mimic real-world exposure and in which HG is most likely to be refuted.

Limited scientific information is another indicator of HG's problems. As a consequence, inferring HG that claim H is true, "generalizable across…endpoint measured" often commits the fallacy of appeal to ignorance. This fallacy occurs when people assume that because no evidence refutes a claim, therefore, it is true. They invalidly assume that the absence of some evidence (e.g., against HG) constitutes evidence of the absence (e.g., of data against HG). For instance, US National Academy of Sciences' studies have warned that despite known higher sensitivities of children to pesticides and herbicides and despite current regulations' not adequately protecting them, nevertheless data are inadequate to precisely define these higher sensitivities for children's neuro-developmental effects or endpoints.[14] Yet to posit HG, one must commit the fallacy of appeal to ignorance and assume that, despite scientific ignorance (e.g., about precise pesticide-herbicide effects on children's neuro-developmental endpoints), HG holds for all endpoints. Yet to confirm that HG holds, as adaptive across all endpoints, there must be evidence from large sample, long term, in-depth, all-endpoint studies. In the absence of such sophisticated studies – clearly not those typically used to assert H – HG proponents commit the fallacy of appeal to ignorance.

HG proponents also exhibit the inductive fallacy (also called the fallacy of invalid extrapolation or the fallacy of hasty generalization) when they generalize

or extrapolate to all endpoints, groups, and time-periods, on the basis of only a few endpoints, population subgroups, or time periods. The earlier cases of cadmium and ethanol illustrate why the HG extrapolation (to all endpoints) constitutes an inductive fallacy. HG extrapolation to all individuals and population subgroups likewise is problematic because of genetic and lifestyle differences, for example, certain medications can affect responses to toxins. HG extrapolation to all age groups is particularly questionable because of children's vulnerability. Some pharmaceuticals have half-lives that are 3–9 times longer in neonates than in adults, and neonates may have elimination half-lives that are more than 10 times longer than adults. In the case of alcohol, for example, while maternal drinking of 1.2–2.2 drinks/day may have beneficial effects on the mother, only 0.5 drinks/day have been associated with adverse behavioral and developmental effects on the fetus. Even apart from adult–child differences, among adults responses to pesticides, for example, may vary significantly because of factors like seven-fold differences in levels of detoxifying enzymes.[8]

Ignoring the endpoint/individual/age and other differences just illustrated, HG proponents' inductive fallacies are especially objectionable because they explicitly and harshly criticize those who extrapolate from high-dose to low-dose responses. Consistency therefore requires HG proponents to practice what they preach. They must avoid invalid extrapolations from some biological endpoints to all endpoints; from adult, pure-bred, homogenous animal populations of toxicological studies to non-adult, non-pure-bred, and heterogeneous members of human populations; and from some adaptive responses to net adaptive responses. They also must avoid extrapolating (purely on the basis of a simple, quantitative, low-dose measurement) to dose effects that are determined not only by quantity but also by when the dose is received, who receives it, what is her health and nutritional status, how it is received (e.g., the dose rate), and with what it is received, for example, other exposures. In using the inductive fallacy to extrapolate in all these ways, HG proponents not only "trim" the relevant dose data that are most likely to show HG false but also err in the same ways as those they criticize.

Apart from logic and scientific method, there are good biological reasons that individual, low dose, adaptive responses are unlikely to be generalizable, overall, as adaptive – as HG requires. One reason is that, as Calabrese and Baldwin recognize,[2] hormesis effects are likely "overcompensations in response to disruptions in homeostasis." But when organisms overcompensate to respond to threats or disruptions, they pay a price. There is no free lunch. The adrenalin rushes that are temporarily adaptive are, over the long term, maladaptive. Likewise, although overcompensatory responses to some toxin obviously have some adaptive benefits, they also obviously have metabolic costs, costs that, over the long term, may be harmful. HG proponents ignore these biological facts.

Because HG proponents fall victim to inductive fallacies and appeals to ignorance when they generalize to all endpoints, all responses, all subjects, all ages, and all exposure conditions, they beg the question of whether HG is true or not. Instead of offering detailed empirical evidence for all of these generalizing inferences, they merely assume it. Moreover, because HG is scientifically and logically invalid, it also is ethically invalid. A recent US National Academy of Sciences analysis made a similar point: "bad science is always unethical."[1] Discussing "studies in which people…make the case for setting a less stringent [pollutant] exposure standard," the academy authors warned that because "studies that do not meet the highest scientific and ethical standards" have great potential to mislead scientists and regulators, they "should not be…accepted…as input to the regulatory decision-making process."[1]

Using HD in regulation: logically, scientifically, and ethically invalid arguments

Consider the consequences of preceding arguments for the claim HD that "a strong case can be made for the use of hormesis [H] as a default assumption in the risk-assessment process."[2] Obviously, if the generalization HG is logically, scientifically, and ethically invalid, using it to infer HD is also invalid. Risk-assessment policy and regulation, such as HD, should not be based on invalid, therefore unethical, science.

However, even if HG were true for most endpoints (and there is much evidence that it is not) – this would not justify HD – that is, it would not justify using HG as a default position in risk assessment and regulation. For one thing, even if hormetic, adaptive responses to a pollutant held across most endpoints, as HG posits, this fact constitutes only necessary, not sufficient conditions for accepting HD. In addition, at least five other necessary conditions – ethical conditions – would have to be met to accept HD.

One ethical condition is a) that HD would have to represent an adequately health-protective stance, in the face of uncertainty about precise risks.[15–17] Because default rules like LNT and HD are used in situations of uncertainty, their acceptance is not a purely scientific decision. Rather, their acceptance is an ethical decision about how much risk people will accept, who should take those risks, whether the benefits are worth it, and so on – given uncertainty about the possible ramifications of the risks. Hence, promoting an essentially ethical/policy claim, HD, largely on the basis of an allegedly scientific argument, HG is invalid because HG-HD proponents attempt to deduce an ethical "ought" (HD) from a nonethical or allegedly scientific "is" (HG).[18] Yet, solely from what is the case, allegedly HG, it is never valid to deduce what ought to be the case, allegedly HD. To make this deduction is to commit the is-ought fallacy in ethics.

In addition to establishing HG scientifically and avoiding the is-ought fallacy in ethics, HD proponents would at least have to argue ethically b) that it is equitable, compensable, just, and so on, to impose HD's possible risks on citizens; c) that risk bearers should and would give informed consent to this HD default rule; d) that the rule is operationalizable; and e) that it satisfies basic rules of biomedical ethics.[17] No HD proponents have arguments meeting these five standard ethical conditions for risk imposition.

Moreover, several reasons suggest HD could not meet ethical condition (c) for consent. One reason is that people generally agree to bear uncertain risks, like those associated with a default rule, when they get something in return. Breast-cancer patients may take tamoxifen – despite its uncertain but excess risks of thrombosis, stroke, uterine hyperplasia, uterine cancer, and uterine sarcoma,[8] because they get something in return, reduced risk of breast-cancer recurrence. In fact, virtually all pharmaceuticals impose one risk, in exchange for reducing another risk. Ethics handle such mixed-risk pharmaceutical cases through informed consent.[17] Hence, even if people were adequately informed about HD risks, they likely would not consent, particularly if their children could be most at risk or if they received nothing in return. As later paragraphs show, if the main HD beneficiaries are polluters, not the people who would bear most of the risks, HD is unlikely to satisfy the consent condition.

Likewise, HD proponents seem unable to meet ethical condition (d) because operationalizing and applying HD to the real world is impossible. Yet by the "ought implies can" rule, people can never be required to do what is impossible for them to do.[19] People cannot be required to spread their wings to fly, to rescue someone in the ocean, because it is impossible for people to spread their nonexistent wings. To say they "ought" to perform such a rescue implies they "can." If they cannot, logically they have no obligation to do so. Calabrese, Cook, and Baldwin forget this fundamental ethical rule – and its logical consequence.[1,13,20] Instead they repeatedly urge regulatory and risk-assessment changes so as to take account of what is impossible for most people viz., having total effects that are low dose. But regulators and assessors need/ought not make such changes to HD because they cannot. They cannot for two reasons, i) because each person's exposure cannot be titrated to achieve a total exposure that is narrow and low dose and ii) because typical multiple doses of pollutants drive total exposures beyond low doses. To see these impossibilities, consider that Calabrese and Baldwin claim that maximal low-dose hormetic response occurs on average at a dose fivefold below the NOAEL.[21] If so, it logically follows that simultaneous exposure to five equally potent hormetic agents, each at one-fifth the NOAEL, could move the victim from the low-dose range to that of adverse effects. Yet it would be impossible, given a lifetime of fluctuating exposures and concentrations, to titrate each person's exposure to achieve a narrow, hormetic-exposure range.[8] Repeated US Environmental Protection Agency and Centers for Disease Control studies have shown that all US citizens have received doses of hundreds of chemicals whose residues are measurable in their blood or tissue.[8,3] Immunological evidence also shows that the combination of many low-dose effects is not always additive but synergistic as when people are exposed to TCDD and numerous dioxin-like compounds, or to radon and smoking, to asbestos and smoking, to alcohol and smoking; more and more exposures add to the total immunologic and estrogenic burden.[22]

Likewise, although Calabrese and others repeatedly claim (HG) that low-dose radiation is adaptive, hormetic, or beneficial,[4,21,23,24] their claim contradicts all classic, consensus-position radiation studies, like those of the US National Academy of Sciences, which affirm LNT. (Only radiation studies whose authors have obvious conflicts of interest, like those of the French, reject LNT, but these conflicted studies are rejected by the global scientific community).[25,26] Yet even if HG were true for radiation, HD would not be operationalizable in the radiation case, any more than it is for the chemical case. Because all scientists agree that ionizing-radiation doses are cumulative, by the time a child is born,

she has already received more than a low dose.[26] Thus, even if HG were true, because of the impossibility that most people's total doses of radiation or chemicals were low, and because of the impossibility of titrating such low-dose exposures, the ought-implies-can rule means that HD cannot meet (d) the operationalizability problem. HG is thus an irrelevant artifact, inapplicable to HD's real-world policy-making. That is, apart from its ethical problems, the inference from HG (about low doses) to HD (about total real-world responses that are almost never low dose) commits the logical fallacy of irrelevant thesis and therefore is also unethical.

HD proponents likewise are unable to meet ethical condition (e), adherence to basic norms of biomedical ethics, as set out in classic statements like the Nuremburg Rules, the Belmont Report, the Helsinki Report, and the Common Rule of the US.[17] These all require that, before any risk is imposed on a subject, she must give free informed consent to that risk, part of which involves full risk disclosure and full risk understanding.[27,28] Yet the lack of data on many pollutant risks (e.g., earlier National Academy warnings about data gaps for childhood neuro-developmental effects of pesticides-herbicides)[14] militates against the disclosure and understanding conditions for informed consent. People do not receive right-to-know disclosure forms either distributed in their neighborhoods by industries responsible for toxic releases or available when they purchase pesticide-laden foods. They are likewise unaware, for instance, that their children are at much higher pesticide risks than adults. Consequently, public consent to imposed industrial and agricultural risks like pesticides (from which people receive far less benefit than do polluters) is much less likely than in the case of medical consent, for example, to some drug, from which they are more likely to benefit. Because such consent is less likely, anything that increases pollutant exposure (as moving from LNT to HD would do) exacerbates ethical problems with consent and hence is ethically worse.

Can HD meet the second basic requirement of all classical codes of biomedical ethics that subjects bearing some imposed risk have an acceptable risk-benefit ratio?[17,28] This rule requires medical experiments and societal uses of toxins to satisfy norms of distributive equity so that most benefits of risk imposition do not go to risk imposers or even to society as a whole, whereas most risks are borne only by a subset of people. In other words, it is unethical to use some risk victims as means to the end of others, even the end of benefits for all of society. Especially, it is unethical to use some risk victims as means to the end of greater benefits for risk imposers, such as pesticide-herbicide manufacturers. Yet as mentioned earlier, if the National Academy is right, then current pesticide-herbicide regulations fail to have an adequately protective risk-benefit ratio for children.[14] Because accepting HD (instead of LNT) would make children's risk-benefit ratios, at least for pesticide-herbicide responses, even worse, HD would exacerbate violations of this second key rule of biomedical ethics and thus create a worse ethical situation.

Can HD meet the third important norm of biomedical ethics that no risk impositions, whether of medical subjects or victims of toxins like pesticides-herbicides, should result in targeting a special group of people who will bear significantly higher risks?[17,28] At least for the case of herbicides-pesticides, it is clear that their most damaging effects are borne by children. If so, weakening these already defective herbicide-pesticide standards (by accepting HD instead of LNT, as Calabrese proposes) would result in an even worse targeting of a vulnerable group, children, and hence would result in an ethically worse situation.[29]

If the preceding arguments are correct, HD proponents fall victim not only to logical fallacies like irrelevant thesis and confusing necessary and sufficient conditions but also to at least five different sorts of ethical errors. As a consequence, HD is logically, scientifically and ethically invalid. Why is this invalidity sometimes unrecognized? Perhaps because researchers commit the fallacy of equivocation, for example, using the same term, "hormesis," to refer to three logically distinct claims, H, HG, and HD. Cook and Calabrese commit this fallacy when, under the heading "FDA Regulation of Hormesis," they refer to themselves as "proponents of hormesis" and talk about "regulation of hormesis."[4] Obviously they should have said "proponents of HD" and "regulation via HD" because H is not controversial (virtually everyone is a proponent of H) and because only invalid claim HD, not valid claim H, is specifically relevant to FDA regulation. Similar fallacies of equivocation occur when HG-HD proponents attempt to answer critics who attack HG and HD as invalid. For instance, after Thayer, *et al.*[3] attack HG and HD, Cook and Calabrese respond to these attacks by using equivocation to defend H; they say "hormetic dose-response curves have been observed for a large number of individual agents."[4] Thus, Cook and Calabrese appear to be correct, but only because they use a logical fallacy of equivocation to defend a claim, H, that is not at issue. HG and HD are at issue, but because they do not (and perhaps cannot?) defend these adequately, they mislead

the reader about the nature of the argument – by focusing on H.

Five reforms to help promote accurate and ethical analysis of low-dose responses

Given conflicting claims about H, HG, and HD, there are at least five ways in which low-dose debates and relevant research could be logically, scientifically, and ethically improved. As just suggested, the first needed improvement is 1) to distinguish claims H, HG, and HD in all research and writing so as to avoid logical, scientific, and ethical fallacies arising from confusing three quite different claims of quite different logical and scientific validity. For instance, in their first paragraph, Cook and Calabrese say that "the concept of hormesis….has not been without its detractors. One paper critical of the concept was published last year in this journal (Thayer, *et al.*, 2005)."[4] Yet here Cook and Calabrese commit the fallacy of equivocation and confuse H, HG, and HD. Contrary to their claim, the Thayer, *et al.* paper is not critical of "the concept of hormesis," H. Rather, as is obvious from their paper, Thayer, *et al.* are critical of HG and HD.[3] As this example illustrates, often when critics challenge HG and HD, their proponents erroneously allege that the critics are challenging H. HG-HD proponents thus fail to respond to their critics' charges because they commit the logical fallacy of falsely attributing straw-man arguments (against H) to their opponents. Because straw-man arguments are far weaker than what opponents actually argue (against HG and HD), using these erroneous arguments appears to (but does not really) defeat opponents.

The fallacy of equivocation also occurs, for instance, when Cook and Calabrese say "the hormetic model also provides decision makers in regulatory agencies with a much broader array of options in the risk assessment process."[4] If this is a claim about H, it is obviously false because H is not generalized, yet only generalized science is relevant for regulation. Likewise, if this is a claim about HG, it also is obviously false because regulatory options require satisfaction of at least five democratic and ethical conditions (see earlier remarks) like informed consent, whereas HG is a purely scientific claim. Hence, the quoted remark appears to be saying that HD would theoretically provide regulatory decisionmakers with more options – a claim that requires extensive ethical support, not given by the authors, along the lines argued in the previous section. By thus equivocating by using H for HD, proponents are not obviously wrong when they fail adequately to support HD. Yet if the authors are to avoid logical fallacies, and if they mean HD, they should say HD, not the vague "hormetic model" – which could mean either H, HG, or HD.

The second improvement, in analysis of H, HG, and HD, also was defended earlier. It is 2) to treat low-dose toxins and carcinogens as pharmaceuticals, so that they might be fully tested, then regulated by the US Food and Drug Adminstration.[3] Obviously there is no reason to expose the entire US population to chemotherapeutic agents having a favorable benefit-risk ratio only for cancer patients, not most of the population. Partly because of rights to equal treatment and to self determination, similar arguments hold for low-dose pollutants and the population subsets they might harm or benefit.[29] Thus, without harming others, those who seek chemotherapy or low-dose-pollutant benefits can obtain them through proper individual dosage.

A third improvement needed for accurate scientific and ethical analysis of low-dose responses is 3) to encourage those who would benefit most, financially, from weakened pollution laws to fund research on H, HG, and HD. Although Calabrese, Baldwin, and Cook make important points about not ignoring hormesis, responsibility and fairness dictate that those who would profit most from regulatory implementation of H, HG, and HD should either bear most of this research burden or fund independent, non-conflicted groups to do it.[29] For example, if organophosphate and related pesticides "comprise the majority of cholinesterase inhibitors that are offered by the hormesis proponents as examples of chemicals that may be beneficial at low doses,"[8] chemical companies should fund the relevant research because they would profit most from HD.

A fourth improvement, needed to reliably analyze H, HG, and HD – and to follow research ethics[16,30] – is 4) to urge hormesis researchers to reveal all sources of funding, thus all potential conflicts of interest. Such revelations are especially needed as Calabrese and Baldwin note that "the external influence of the enormous cost of environmental cleanups and the proper allocation of limited societal resources have strongly encouraged a…reexamination of… hormesis."[2] Others say something similar about chemical-industry motives regarding low-dose exposures.[31,32] A recent US National Academy of Sciences' report warned "pesticide manufacturers" and other "economically interested third parties" are funding and conducting studies "to justify reducing" chemical-safety standards "thereby increasing the acceptable or safe human exposure

level…that might otherwise have been precluded under [current] …safety standards."[1]

Likewise, the US military, long acknowledged as the nation's worst polluter, has obvious potential (financial) conflicts of interest regarding low-dose pollutants. It is responsible for more than 15 million contaminated US acres, including 10% of all the worst US pollution sites (those having Superfund designation). Among more than 2300 contaminated military sites, 39 states have 130 heavily polluted military bases, all Superfund sites. One contaminant is rocket fuel, whose main ingredient is perchlorate. Especially dangerous to children's IQ, hearing, speech, and motor skills perchlorate from military bases in Arizona, California, and Nevada alone contaminates the drinking water of 20 million people.[33] Yet because of costs, the US military has fought to reduce cleanup. The Pentagon wants to cut $4 billion/year in environmental cleanup (<1% of the annual US military budget), and since 2001, the US military has failed to implement 70 federal-cleanup agreements for military bases. Yet 1 in 10 US citizens – 29 million people – live within 10 miles of military Superfund sites, and the 1986 Defense Environmental Restoration Program requires full cleanup. Many state attorneys-general as well as city- and state-government water and waste-management agencies have sued the military to force clean-up – which mostly has not occurred. Denver's Lowry Air Force base presents a typical case of military noncompliance with environmental-health laws. Partly because it claims low-dose pollutants are not harmful, the Air Force has refused to meet a state order to clean the 22 Lowry acres it still owns, and it has refused to reimburse the Colorado redevelopment authority for the $15 million cleanup that was necessary to protect homeowners from dangerous Lowry wastes left on other land by the Air Force.[34–37]

Besides the chemical industry and the military, the nuclear industry likewise has potential financial conflicts of interest regarding low-dose pollutants. President of the International Commission on Radiological Protection, Roger Clarke admitted that costs for reactor decommissioning and for radioactive waste cleanup ($1 trillion for US nuclear-weapons facilities alone), not science, are driving proposals to weaken low-dose radiation protection.[38]

Substantiated by US-government oversight agencies, Congress, and National Academy reports (see above), such claims suggest that chemical, nuclear, and military interests, all have potential conflicts of interest regarding low-dose pollutants and would gain from weakened regulations. One obvious way to address this conflict, analogous to what major environmental-health journals like *Environmental Health Perspectives* have done, is to require those who publish anything anywhere, on low-dose exposures, to reveal (in their publications, on their websites, and in their resumes) all funders of their research. Many publications of those who argue for HG and HD, for instance, are funded by groups having conflicts of interest. Calabrese acknowledges long-term US Air Force funding,[7,2,4] and Cook acknowledges consulting with Dow Chemical, a major pesticide manufacturer.[4,20] Two Calabrese reports are listed as publications of the Texas Institute for Advancement of Chemical Technology,[39,40] which is funded by Dow, BASF, Bayer, Shell Chemical, and Syngenta.[8] Such acknowledgements deserve praise, but they are incomplete. For instance, in Calabrese's online resume, 3 of 9 sources of "current research support" are not listed, yet these unlisted sources are responsible for a total of $810,000 given to Calabrese.* Q3

A final ethical reform needed in H, HG, and HD research is 5) to address higher public health and ethical priorities first.[17] Consider several facts. A) The classic report of the US National Academy of Sciences says current pesticide regulations do not adequately protect children.[14] B) The World Heath Organization says "only a small fraction of all childhood cancers" is associated with heredity, genetics, infections, and viruses; instead environmental pollutants appear "to play a major role," and air pollution alone is associated with up to half of all childhood cancers.[41] C) US National Institutes of Health and National Academy of Sciences studies estimate that industrial and agricultural toxins cause about 60,000 annual US premature, fatal cancers, or about 10% of total cancer deaths.[42,43,29] D) A 2002 *New England Journal of Medicine* study put the figure even higher. In its long-term study of 90,000 twins, it distinguished infection- and genetically-based from environmental cancers then concluded: "the overwhelming contribution to the causation of cancer in the population of twins that we studied was the environment."[44] E) It is a public-health truism that the vast majority of potentially harmful chemicals in use – tens of thousands of them – have never been adequately tested. F) Another public-health truism is that almost no multiple-chemical exposures, as occur in the real world, have been tested. Given the situation indicated by (A)–(F), what should be society's higher public-health priority? Should it be testing individual pollutants for low-dose beneficial effects (having little real-world applicability, given the preceding arguments)? Or should it be tracking down causes of environmental death and disease, most of which have not been adequately identified or tested? With valid arguments,

HG and HD proponents might be able to make a case for the first priority. Because of their invalid arguments for HG and HD, public health easily dictates the second priority.[a]

Objections

In response to the preceding arguments (that although claim H is obviously true, claims HG and HD are logically, scientifically, and ethically invalid), several objections might be made. These include objections that i) because hormesis is not defined as beneficial, it does not fall victim to some of the counterexamples given earlier; ii) that proper allocation of societal resources argues for HG and HD; and iii) that, contrary to earlier claims, HG and HD proponents do deal with low-dose effects on sensitive populations. Consider these objections in order.

First, HG and HD proponents like Calabrese object that "beneficial/harmful [thus adaptive] effects should not be part of the definition" of hormesis.[4] However, this response is logically invalid for two main reasons. First, if HG-HD proponents like Calabrese contradict their earlier claims and say H does not, by definition, involve beneficial or adaptive effects,[5,6] they thereby beg the question of changing pollutant regulation because of H. Only accounts of H as adaptive or beneficial would justify the regulatory and risk-assessment changes they propose.[45] A second problem is that HG-HD supporters face a logical dilemma. On one hand, if they say H is not defined as beneficial or adaptive, as just noted, they beg the regulatory question. On the other hand, as argued earlier, if they say hormesis is beneficial or adaptive, they cannot generalize to HG because their claims are inconsistent with scientific evidence showing low-dose responses are often beneficial for some endpoints but harmful for others. For example, although Calabrese and Baldwin say low-dose cadmium decreases testicular tumors in rats,[5] others report increases in prostate tumors.[45] HG and HD proponents thus have a choice between begging the question of regulatory applicability (H not defined as beneficial adaptive) or making claims that are inconsistent with replicated scientific findings (H defined as beneficial adaptive).

HG and HD proponents like Calabrese also object that their position is justified ethically on grounds of "proper allocation of limited societal resources,"[2] so that "the limited resources of all parties could be redirected to new agents. Control and remediation costs will be less because…resources could be redirected to other agents or…to capital investments."[20] This objection begs the question of whether cost-effectiveness arguments are ethically legitimate reasons for HG-HD. After all, one could not use cost effectiveness to ethically justify murder-for-hire, racial discrimination, or human-rights violations because cost-effectiveness arguments presuppose the prior ethical acceptability of the cost-cutting methods they sanction. Murder-for-hire obviously is not an ethically defensible method. But if not, HG-HD proponents must provide arguments for HD's ethical acceptability, as discussed earlier, not presuppose or beg it. Because HD proponents beg this ethical question, in appealing merely to cost effectiveness, they presuppose the ethical validity of free-market environmentalism. This is the view that pollution ought to be controlled by the market, not regulations, and that pollution ought to be allowed whenever it is not cost effective for polluters to reduce it.[29] But free-market environmentalism is ethically invalid because it takes no account of who causes the pollution, who benefits from it, who suffers from it, whether victims consent to it, whether it is distributed equitably and compensated, whether it results from polluter negligence or irresponsibility, and so on.

Another problem with Calabrese's cost-effectiveness objection is its committing a fallacy of aggregation. Alleging that accepting HG-HD would allow "proper allocation of limited societal resources,"[2] objectors like Calabrese aggregate and call resources "societal," when they are mainly resources of polluters. If polluters are responsible for and profit from pollution, they ought to spend

[a] Calabrese, E.J. Faculty. University of Massachusetts Intercampus Graduate School of Marine Sciences and Technology, 2006, available at http://www.umassmarine.net/faculty/showprofs.cfm?prof_ID=30 and accessed 11-22-06; this was the most up-to-date resume found on the internet for Dr Calabrese, and it was copyrighted 2006, by his employer, as an "official page/publication of the University of Massachusetts. © 2006"; this same resume (with the same material), accessed January 30, 2007, appears again as an "official page/publication of the University of Massachusetts. © 2007." Although an older, more complete resume ("Edward J. Calabrese, Ph.D., Curriculum Vitae, April 2002") appears on the University of Massachusetts website, with a 2002 date, at http://people.umass.edu/nrephc/EJCCVApril02.pdf (accessed 30 January 2007), it has more than $3 million in grants/contracts whose sources of funding are not named; some named sources include Exxon, ARCO, Dow Chemical, Reynolds, Rohm and Haas. Even an out-of-date or shortened resume should not selectively reveal funding sources, both because readers will be mislead, because readers expect that state-university employees, in particular, reveal their funding sources and because most science-ethics groups endorse full disclosure.

money to control it, money that is private and not public. In invalidly aggregating and confusing private and public (governmental) resources, these objectors invalidly allege that society will save resources in adopting HG-HD. In reality, however, the main beneficiaries would be private, polluters, whereas those most harmed, the greatest losers, would be the public – victims like children.

Apart from its fallacy of invalid aggregation, this second objection ignores distributive equity, fairness, and responsibility for one's actions (e.g., polluting). To see why it unethically gives polluters a free ride, at the risk of public health, consider an analogous case. Suppose someone says "proper allocation of limited resources' requires setting most murderers free, since most never strike again, their threat to society is extremely low, and trial-incarceration is extremely costly." If society should never allow the costs of a murderer's prosecution and incarceration to trump ethical considerations of justice, fairness, responsibility, and compensation, society likewise should not assume that alleged polluters' costs can always trump the same ethical considerations.

A third problem with the second or cost-effectiveness objection is that HG-HD may not actually save costs overall. Obviously weakened regulations save polluter costs, but the cost-effectiveness objection begs the question (alleges, without evidence) that HG-HD implementation would save "societal resources."[2] If one counts pollution's market and non-market costs, including those to ecosystem services, individual health, work days, and so on, HG-HD likely would raise total societal costs.[46] Regardless, objectors need to empirically substantiate, not beg, the question of whether HD saves "societal resources."

A third objection from HG-HD proponents might be that their arguments do take account of sensitive groups, such as children. Regarding studies of high-risk groups, Calabrese and Baldwin admitted i) "that in about 20% of the cases, a hormetic response was not seen."[4,47] They also claim ii) that if society protected these high-risk groups – by continuing to follow a LNT, rather than HD, default rule – "the general public likely could suffer an increased risk to a preventable burden of disease."[4]

Contrary to the preceding claims (i) and (ii) do not support HG-HD, as Calabrese and others maintain. If 20% of cases illustrate no hormetic effect, then LNT, not HD, better protects this 20%. But if so, this argues against HD because it contradicts two major claims of HD proponents. First, LNT's superior protection of the 20%-high-risk group (claim i) contradicts HG, the claim (on which HD relies) that H is "generalizable across biological model, endpoint measured, and chemical class."[7] Second, LNT's superior protection of this 20% (claim i) also contradicts allegations that "the hormesis model clearly outperforms" either T or LNT models.[48] Thus, if objectors' claim (i) is true, it follows that it has refuted two of the objectors' own HG-HD arguments.

What about claim (ii) that if society protected these high-risk groups – by continuing to follow a LNT rather than HD default rule – "the general public likely could suffer an increased risk to a preventable burden of disease"[4]? Here the objectors provide no empirical documentation, whatsoever, to support claim (ii). Thus, they again beg the question. Moreover, claim (ii) also is highly implausible, given the earlier arguments that additive and synergistic effects of multiple exposures together yield exposures that are no longer low dose. By begging the question of (ii) and ignoring empirical data on total doses and synergistic effects, HG and HD proponents again appear to be doing ideology, not science and not ethics.

Conclusion

Analysis of low-dose pollution effects is important and ought not to be ignored. If it is to be accomplished with logical, scientific, and ethical rigor, however, at least five reforms are needed. These include 1) avoiding logical fallacies like equivocation by distinguishing claims H, HG, HD, rather than using only "hormesis" labels; 2) protecting informed consent by assessing and regulating low-dose exposures as pharmaceuticals; 3) ensuring fairness and responsibility by having those, who would profit most financially, pay for H, HD, and HG research; 4) following research ethics by having researchers' reveal all potential conflicts of interest; and 5) protecting rights to equal protection by first pursing research that is more important to public-health priorities. Becuase many researchers do not follow (1)–(5), they bear the burden of proof to defend both their ethics and their reasons for not accomplishing (1)–(5).

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