Dose-Response: An International Journal

6-2013

EXTREME SENSITIVITY AND THE PRACTICAL IMPLICATIONS OF RISK ASSESSMENT THRESHOLDS

John Bukowski
WordsWorld Consulting

Mark Nicolich
Cogimet

R. Jeffrey Lewis
ExxonMobil Biomedical Sciences, Inc.

Follow this and additional works at: https://scholarworks.umass.edu/dose_response

International DOSE-RESPONSE Society

EXTREME SENSITIVITY AND THE PRACTICAL IMPLICATIONS OF RISK ASSESSMENT THRESHOLDS

John Bukowski, DVM, PhD □ WordsWorld Consulting

Mark Nicolich, PhD □ Cogimet

R. Jeffrey Lewis, PhD □ ExxonMobil Biomedical Sciences, Inc.

□ Traditional risk-assessment theory assumes the existence of a threshold for non-cancer health effects. However, a recent trend in environmental regulation rejects this assumption in favor of non-threshold linearity for these endpoints. This trend is driven largely by two related concepts: (1) a theoretical assumption of wide-ranging human sensitivity, and (2) inability to detect thresholds in epidemiologic models. Wide-ranging sensitivity assumes a subpopulation with extreme background vulnerability, so that even trivial environmental exposures are hazardous to someone somewhere. We use examples from the real world of clinical medicine to show that this theoretical assumption is inconsistent with the biology of mammalian systems and the realities of patient care. Using examples from particulate-matter air-pollution research, we further show that failure to reject linearity is usually driven by statistical rather than biological considerations, and that nonlinear/threshold models often have a similar or better fit than their linear counterparts. This evidence suggests the existence of practical, real-world thresholds for most chemical exposures.

Keywords: threshold, non-cancer health effects, human sensitivity, epidemiologic models, particulate matter, low-dose extrapolation

BACKGROUND

The traditional assumption in the field of quantitative risk assessment (QRA) has been that non-cancer health effects are associated with thresholds below which chemical exposures cause negligible risk (NRC 1983). This assumption forms the basis for the reference doses/concentrations within the Integrated Risk Information System (IRIS) maintained by USEPA (2011). But, there is an ongoing regulatory trend toward an assumption that exposure concentration-response functions may be linear (through the ordinate) for non-cancer health effects, including such diverse and complex outcomes as death, heart disease, and reproductive impairment. This trend is being driven largely by two concepts: (1) a theoretical assumption of extreme sensitivity within the diverse human population, and (2) an inability to detect thresholds in epidemiologic models.

Address correspondence to R. Jeffrey Lewis, PhD, ExxonMobil Biomedical Sciences, Inc., 1545 US Highway 22 East, Annandale, NJ 08801; Phone: 908-730-1107; Fax: 908-730-1192; Email: r.jeffrey.lewis@exxonmobil.com

Sensitivity and risk assessment thresholds

In the 2006 proposed rule for particulate matter (PM) regulation, the US Environmental Protection Agency (Federal Register 2006) acknowledged that "it is reasonable to expect that there likely are biologic thresholds for different health effects in individuals or groups of individuals with similar innate characteristics and health status," but that population thresholds are unlikely due to extreme differences in sensitivity between individuals. The Agency stated the following:

> "Individual thresholds would presumably vary substantially from person to person due to individual differences in genetic-level susceptibility and pre-existing disease conditions ... Thus, it would be difficult to detect a distinct threshold at the population level, below which no individual would experience a given effect, especially if some members of a population are unusually sensitive" (Federal Register 2006).

This idea is mirrored in the recent National Research Council (NRC 2009) report on advancing risk assessment at EPA, in which the authors state that "noncarcinogens can exhibit low-dose linearity, for example, when there is considerable inter-individual variability in susceptibility and each individual has his or her own threshold." A similar argument was made by members of a recent EPA workshop on low-dose extrapolation, in which a wide range of "individual thresholds" are assumed to be driven by similarly wide differences in "background risk" (White *et al.* 2009).

The idea of near-infinite variation in sensitivity echoes arguments posited within the environmental-justice literature, in which hypothesized extreme sensitivity is purportedly due to social/racial stressors from the environmental "riskscape" (IOM 1999; Morello-Frosch and Shenassa 2006). These stressors are said to act directly or indirectly through various vague mechanisms such as "weathering," allostatic load, chronic stress, and wear and tear (Geronimus 1992, IOM 1999; Morello-Frosch and Shenassa 2006). Researchers also speculate that "the body's defense mechanisms and ability to recover or detoxify have been compromised through prior exposure to harmful agents" (Morello-Frosch and Shenassa 2006).

A related argument suggests that even low-level exposures add to background risks, enhancing ongoing disease-causing processes in a linear manner (Crawford and Wilson 1996; White *et al.* 2009). For practical purposes this argument can be seen as an extension of the sensitivity argument posited above, in that these hypothetical background risks are thought to enhance individual sensitivity to other environmental exposures.

The other commonly posed argument for non-carcinogenic, low-dose linearity is that thresholds are difficult to detect in epidemiologic studies. The EPA uses this inability of common epidemiologic models to detect

low-dose thresholds as support for their linearity arguments, noting that "new epidemiologic studies have used different modeling methods to address this question, and most have been unable to detect threshold levels in the relationship between short-term PM [particulate matter] exposure (generally using PM_{10}) and mortality" (Federal Register 2006). The previously cited workshop panelists repeat this idea, stating that "exposure-response models ... [for] environmental toxicants with relatively robust human health effects databases at ambient concentrations (eg, ozone and particulate matter air pollution ...) do not exhibit evident thresholds" (White *et al.* 2009). The NRC (2009) repeats this argument yet again, noting that "There are multiple toxicants (for example, PM and lead) for which low-dose linear concentration-response functions rather than thresholds have been derived for non-cancer end points."

In a recent paper, Rhomberg *et al.* (2011) evaluated these arguments and rebutted them on a theoretical basis. These authors noted that the extreme variability and sensitivity posited by proponents of linearity are hypothetical arguments that ignore the reality of biological and disease processes. That is to say, biological systems are highly regulated homeostatic entities, and toxic states generally result when control mechanisms are overwhelmed, leading to a cascade of events that cause disease. Therefore, at low concentrations, the impacts of potentially toxic exposures are both less common and less severe, producing negligible effects at levels well below the toxic/therapeutic range. Rhomberg *et al.* (2011) further point out that rather than being just theoretical assertions, their arguments are backed by repeated empirical observation.

In the current paper, we attempt to place these arguments in perspective by highlighting the empirical evidence from clinical medicine, and examining the practical limitations to the concept of extreme sensitivity within human populations. This discussion updates and expands upon an earlier paper (Bukowski and Lewis 2004). We also use mortality from PM air pollution as an epidemiologic case study, pointing out examples where thresholds have been detected, and the statistical limitations of assuming linearity in epidemiologic models.

THE CLINCAL REALITIES OF EXTREME SENSITIVITY

The non-threshold assumption is grounded in a belief that sensitivity to chemical exposure lies along an almost infinite distributional range, or at least that this range extends well beyond the 10-100-fold uncertainty factors for inter-individual human variability typically applied to QRA. This assumption implies that even trivial exposures are thought to present a risk to some person or group within this highly diverse population.

Extreme sensitivity is said to reside within groups that are not always addressed by traditional QRA, including children, senior citizens, poor/minority populations, and those with preexisting illness or impair-

ment. Factors that promote the enhanced sensitivity of individuals within these groups have been referred to as determinants of "background risk" (White *et al.* 2009; NRC 2009) or non-chemical "stressors" (Morello-Frosch and Shenassa 2006; NRC 2009). The NRC (2009) calls for a formal "vulnerability assessment that takes into account underlying disease processes in the population."

Acceptance of the above argument poses several unanswered questions, including: (1) are these groups inherently more sensitive to low-level environmental exposures, (2) does the range of this enhanced sensitivity encompass even trivial chemical exposures, (3) is such extreme sensitivity compatible with existence, and (4) are extremely sensitive individuals already protected from environmental exposures? We address these questions below.

Range of Variation

The extreme variation argument suggests that biological variability spans multiple orders of magnitude, so that even trivial perturbations of the homeostatic mechanism, as might occur from a few molecules of pollution exposure, could push someone somewhere over the edge into death or overt illness. Yet, this notion appears inconsistent with what is already known about pathophysiology.

As Rhomberg *et al.* (2011) note, "we do not see continuous and gradual gradation between people with normally functioning physiology (...adequate to maintain basic functioning) and those who cannot maintain internal states in the face of environmental fluctuation or... cannot carry out basic life processes." Put another way, mammalian physiology follows truncated rather than open-ended continuous distributions, with extreme variation being incompatible with life. This can be observed by examining basic clinical parameters (Table 1).

The normal ranges for clinical blood parameters do not encompass all healthy individuals, but these ranges do suggest limits that cannot be exceeded (Table 1). For example, a small minority of healthy people might have an oxygen partial pressure (pO_2) beyond the range of 80-100 mm/Hg, but no living person has a value of 8 or 1000, as suggested by the extreme variation/sensitivity argument. Similarly, blood glucose levels of 8 mg/dL, leukocyte counts of 400, and potassium levels of 0.5 (or 50) can be found only among those in danger of imminent death. Even for less critical parameters such as ALT or bilirubin, order-of-magnitude extremes are associated with clinical disease, not relative health. Rather than wide-ranging variation, we see that human physiology functions within relative narrow ranges, so that extremes of even 10-fold are rare and often incompatible with life.

J. Bukowski and others

TABLE 1. Range of normal values for selected blood parameters across major systems.[a]

Test parameter	Normal range
Liver/Digestive	
Alanine aminotransferase (ALT)	≤ 48 U/L
Alkaline phosphatase	20-125 U/L
Amylase	60-180 U/L
Total bilirubin	0.3-1.0 mg/dL
Kidney	
Blood urea nitrogen	7-30 mg/dL
Creatinine	<1.5 mg/dL
Cardiovascular	
Cholesterol	<200 mg/dL
Creatinine kinase (total)	≤ 235 U/L (male)
	≤ 190 U/L (female)
Low-density lipoproteins	<130 mg/dL
Immune System	
IgG	800-1500 mg/dL
Leukocyte (WBC) count	$4.3-10.8 \times 10^3$
Oxygen Metabolism	
Erythrocyte (RBC) count	$4.1-54.9 \times 10^6/mm^3$
pO_2	80-100 mm/Hg
Endocrine	
Cortisol	5-25 ug/dL (8 hour)
Fasting glucose	75-115 mg/dL
Reproductive/Endrocrine	
Lutenizing hormone	0.8-26 mIU/mL (female)
Acid phosphatase	≤ 2.5 ng/mL (prostate)
Follicle-stimulating hormone	1.4-9.6 (female)
Serum Electrolytes/Proteins	
Calcium	9-10.5 mg/dL
Sodium	136-145 mEq/L
Potassium	3.5-5 mEq/L
Plasma osmolality	285-295 mOsm/kg
Total protein	5.8-8.0 g/dL

[a]Values taken from Physician's Desk Reference (2010)

Extreme Sensitivity of Children

It is often assumed that children are more sensitive to pollutant exposures. In a recent report on cumulative impacts of environmental exposures, the California Environmental Protection Agency (CalEPA 2010) cites potential differences in kinetics and inherent sensitivity as explanations for enhanced risk among children. However, while it is certainly true that there are cases where this is correct, it is not clear that it is universally true, or that this heightened risk would be great enough as to approach extreme or near-infinite sensitivity.

Several authors have examined differential sensitivity between children and adults and have concluded that although the physiology of children may differ from that of adults, these differences are not uniformly in the direction of increased sensitivity for children (Dourson *et al.* 2002;

134

Sensitivity and risk assessment thresholds

ECETOC 2005). In fact, children often have more rapid clearance of chemical exposures, suggesting decreased overall sensitivity (Renwick 1998; Dourson *et al.* 2002). Using chemicals for which clearance data were available for both children and adults, Dourson *et al.* (2002) concluded that the average child/adult clearance ratio of 1.8 favored children, suggesting that they were on average less sensitive than adults to these select chemical exposures. Furthermore, for those instances in which children were more sensitive, the 3.16-fold kinetic component of the default intraspecies uncertainty factor covered the variation of 91% of the chemicals tested (Dourson *et al.* 2002).

Premature infants do appear to have reduced clearance (Renwick and Lazarus 1998), but this is a group that exists in a highly protected hospital environment removed from exposures to airborne pollutants and most chemical contaminants. Furthermore, premature infants would largely lack the enzymes necessary to convert many potentially toxic chemicals into their active forms (Renwick and Lazarus 1998).

Given that most of the chemicals examined by Dourson *et al.* (2002) were pharmaceutical agents, it is possible to put these data in perspective by comparing the child and adult dosages for these drugs, as well as for others selected at random from the Physician's Desk Reference (2010). These dosages are based on clinical research, and encompass not only the pharmacokinetic data examined by Dourson *et al.* (2002), but often issues of absorption, distribution, and other pharmacodynamic factors as well. In general, child dosages are not necessarily lower than those given to adults (Table 2), which agrees with the findings of Dourson *et al.* (2002). Furthermore, child/adult variation rarely differs by more than several-fold, not the 10-100 factor used in QRA. This variation applies to highly toxic cancer chemotherapeutics as well as more benign antibiotics and antihistamines (Table 2).

On occasion, idiosyncratic effects from drugs like chloramphenicol and tetracycline limit their use in children. However, these mechanisms generally operate at therapeutic doses that are not relevant to the exceptionally low levels of exposure implied by extreme sensitivity. Allergic reactions also limit drug use, but even allergens appear to exhibit thresholds below which trivial exposures fail to elicit a reaction (Taylor *et al.* 2009).

Extreme Sensitivity of Other Subgroups

Other high-risk subgroups with background vulnerability are said to include senior citizens and those with "underlying disease processes" or poor "health status." Specific conditions are often not well defined, although respiratory, cardiovascular, and immune disorders have been mentioned as background risks that could greatly enhance sensitivity to environmental exposures (NRC 2009).

135

J. Bukowski and others

TABLE 2. Dosage instructions for common drugs used in children and adults.[a]

Drug	Adult (mg/kg/d)[b]	Child (mg/kg/d)	Additional information
Antibiotics			
Aztreonam	43-57	90-120	Dosages assume moderate-severe infection
			Halve dosage in moderate renal impairment
Cefotaxime	43-86	50-180	Child dose for 1 mos to 12 years (neonate 100-150 mg/kg/d)
			Halve dosage in renal impairment
Ceftibuten	6-9	9	Reduce adult dose to 2.25 mg/kg/d in moderate to severe renal impairment.
Ceftriaxone	14-29	50-75	Do not exceed 2000 mg/d if both hepatic and renal disease
Cephpodoxime	2.8-11	10	No adjustment needed for cirrhosis
			No adjustment needed in elderly
			Halve dosage if severe renal impairment
Ciprofloxacin	7-21	20-40	Similar safety/efficacy in elderly
			5-14 mg/kg/d in renal impairment
Trimethoprim	8	5	Given in combination with sulfa
			Dosage for urinary tract infection
			50% reduction with moderate renal failure
Antifungals/Antivirals			
Fluconazole	1.4-2.8	3-6	Dosage for esophageal candidiasis
			Halve dosage in moderate renal impairment
			5.7 mg/kg/d for prophylaxis in bone marrow transplantation
Valacyclovir	43 (for 7 d)	60 (for 5 d)	Treatment for herpes zoster (adult) or chicken pox (child)
			7-14 mg/kg q 12-24 hours (7-28 mg/kg/d) in renal impairment
Muscle Relaxants			
Atracurium	0.4-0.5 mg/kg	0.3-0.4 mg/kg	Given IV with anesthesia
			Pediatric dose for infants (older children given adult dosage)
			Similar safety/efficacy in elderly
Pipecuronium	70-85 mcg/kg	40-57 mcg/kg	Given IV with anesthesia
			50-70 mcg/kg in adults with renal impairment
Narcotics/Tranquilizers			
Alfentanil	0.13-0.24 mg/kg	0.03-0.05 mg/kg	Dosage for induction of analgesia
			Shorter half-life in children
			Longer half-life in elderly and those with hepatic disease
Buprenorphine	0.017	0.008-0.036	Halve dosage in "high-risk" patients (eg, elderly, liver disease, respiratory disease)
Chlorpromazine	0.57-2.1	2.2-3.3	Dose to control nausea
			Elderly started at lower range of dose
			Use with caution in those with kidney, liver, or cardiovascular disease
Hydroxyzine	200-400 mg/d	50-100 mg/d	Use cautiously in elderly and begin at lower therapeutic range
Anticancer/Immunosuppressive Drugs			
Busulfan	0.06	0.06	Induction dose for cancer
			Use cautiously in elderly and begin at lower therapeutic range

continued…

136

Sensitivity and risk assessment thresholds

TABLE 2. Continued

Cyclophosphamide	40-50 (IV) 1-5 (oral)	40-50 (IV) 1-5 (oral)	Reduce if low WBC or if combined with other agents
Methotrexate	7.5 mg/week	4.5 mg/week (10 mg/m^2/wk)	Dosage for adult or 10 kg child with rheumatoid arthritis Elimination reduced with impaired renal function
Nelarabine	1500 mg/m^2 d 1,3,5	650 mg/m^2 d 1-5	Closely monitor if kidney or liver disease
Thioguanine	2	2	Use cautiously in elderly and begin at lower therapeutic range
Vinblastine	3.7-18 mg/m^2	2.5-7.5 mg/m^2	Induction dose Halve dosage in hepatic disease
Cardiac/Respiratory Agents			
Chlorpheniramine	16-24 mg/d	8-12 mg/d	Pediatric dose for 6-12 year old Use cautiously in elderly and begin at lower therapeutic range
Digoxin	0.002-0.007	0.01-0.015	Maintenance dose for adult or 2-5 yr. child 0.001.5-0.003 mg/kg/d if creatinine clearance < 40 mL/min
Fexofenadine	120-180 mg/d	30 mg/d (0.5-1 yr.) 60 mg/d (2-11 yr.)	Adult dose for child ≥12 yrs. Halve dosage in renal dysfunction
Theophylline	4.3-8.6	12-20	Pediatric dose for child <45 kg Do not exceed 400 mg/d among high-risk groups (eg, liver/kidney disease, elderly, or heart failure)

[a]Data taken from Physician's Desk Reference (2003, 2010) or appropriate package insert
[b]Units converted to mg/kg/d unless otherwise indicated

Liver and kidney disease

Drug dosage recommendations often include reduced dosages for those with liver or kidney disease (Table 2). However, most suggested reductions range from half to one quarter of the dose given to healthy adults, rather than the orders of magnitude reductions suggested by the extreme vulnerability argument used in QRA. Often, clinicians are admonished only to "use with caution" in those with potential organ impairment.

Senior citizens

Cautionary dosage statements are often applied to the elderly as well, not because of special vulnerability, but because seniors are more likely to have subclinical organ impairment compared to younger patients. As with children, older adults in good health do not appear to be inherently more susceptible to clinical drug effects (Table 2).

Variation in genetic polymorphism

Genetic polymorphism accounts for much of the variable impact in drug therapy, with enzymes such as those in the cytochrome P450

137

(CP450) family playing a major role in lack of response or adverse reactions (Johansson and Ingelman-Sundberg 2011). Between-person differences in individual CP450 enzymes can span 1-2 orders of magnitude (Zhou *et al.* 2009).

Although genetic differences influence idiosyncratic drug responses, they do not necessarily translate into wide-ranging differences in chemical toxicity among the general population. For example, recommended dosage ranges for pharmacotherapeutics rarely span orders of magnitude (Table 2). Furthermore, research has not necessarily shown wide variation in toxicity of common xenobiotics. One study of 14 drugs and chemicals that covered a wide range of toxicant classes found little variation in toxicity across 85 different human lymphoblast cell lines, except for two chemicals (perfluorooctanoic acid and phenobarbital) in which variability ranged from approximately 2-5 fold (O'Shea *et al.* 2011). Similarly, research among workers occupationally exposed to butadiene has shown little genetic variability in metabolism, with most results spanning a factor of two or less (Fustinoni *et al.* 2002; Albertini *et al.* 2001, 2003, 2007).

The impact of genetic polymorphism would also be greatly lessened within the context of extremely low doses. The high doses that produce therapeutic or toxic effects can kill cells, alter homeostasis, overwhelm repair mechanisms, saturate enzyme pathways, and deplete co-substrates. Genetic polymorphism forms an important modifying factor for these high-level processes (Slikker *et al.* 2004) but should have little impact on the orders-of-magnitude lower exposures implicated under the extreme sensitivity argument.

Background disease status and the impact of competing risks

Theoretical arguments in favor of extreme vulnerability suggest that those with existing disease conditions would be at greatest risk from low-level environmental exposures. In the real world of clinical medicine, recommendations for the management and protection of these most sensitive individuals are embodied within the formal practice guidelines and position papers developed by expert committees and professional associations. These cover conditions such as chronic obstructive pulmonary disease (COPD), immune suppression, chronic liver or kidney disease, and cardiovascular disorders (Table 3). Under the extreme sensitivity argument, such individuals would be the ones hypothetically most impacted from ever diminishing pollution exposure.

Expert guidelines on the management of important conditions such as cardiovascular disease (and associated risk factors), hepatitis, and immune suppression stress two main needs: proper treatment and modification of personal behaviors (Table 3). Proper treatment includes pharmacotherapy, surgical interventions (eg, procedures to control heart rate in atrial fibrillation), and adjunct therapies (eg, oxygen for COPD). Behavioral modification involves education and support for weight reduc-

Sensitivity and risk assessment thresholds

TABLE 3. Summary of major practice guidelines for management of selected chronic diseases.

COPD
(O'Donnell *et al.* 2008; Qaseem *et al.* 2007)
    Smoking cessation
    Prevention of respiratory infection (vaccination, etc.)
    Spirometry to monitor progression
    Adherence to appropriate pharmacotherapy
    Avoidance of allergens and respiratory irritants
    Oxygen therapy for hypoxia
    Pulmonary rehabilitation (exercise, diet, weight control, behavioral modification, etc.)
Chronic Hepatitis (Hep B or C virus)
(Dienstag and McHutchison 2006; Wejstal *et al.* 2003; Weinbaum *et al.* 2008; Lee *et al.* 2010)
    Limitation or discontinuation of alcohol intake
    Smoking cessation
    Caution in using new drugs or herbals that may harm liver
    Education on behavioral modification and reducing the risk of transmission through sex, blood products, etc.
    Adherence to appropriate treatment with antivirals and immune stimulants
    Hepatitis A vaccination
    Management of comorbid conditions (eg, HIV, immune suppression, etc.)
    Periodic exams and monitoring of viral levels
    Screening for liver cancer
Chronic Kidney Disease (including post-transplant)
(Hogg *et al.* 2003; Burden and Tomson 2005; Chan *et al.* 2011)
    Diagnosis and treatment of comorbid conditions (eg, hyperlipidemia, cardiovascular disease, hypertension, and diabetes)
    Adherence to appropriate pharmacotherapy
    Dialysis to replace kidney function
    Monitoring kidney function with glomerular filtration rate and proteinuria levels
    Nutritional support to combat anemia, osteoporosis, diabetes, dyslipidemia, and hypertension
    Exercise and weight control
    Smoking cessation and limiting alcohol intake
    Psychosocial support
Heart Disease (and related factors)
    Metabolic Syndrome (Novo *et al.* 2008; Graham *et al.* 2007; Grundy *et al.* 2005)
        Patient education as to weight loss, increased exercise, and other behavioral modifications
        Control of hyperlipidemia and hyperglycemia through diet and medication
        Smoking cessation
    Chronic Stable Angina (Gibbons *et al.* 2003)
        Adherence to appropriate pharmacotherapy (eg, aspirin, ACE inhibitors, and beta blockers)
        Lifestyle changes such as weight loss, increased exercise, and improved diet
        Appropriate pharmacotherapy to manage risk factors such as diabetes, hypertension, and hyperlipidemia
        Surgical revascularization (if appropriate)
Heart Failure
(Jessup *et al.* 2009; Mant *et al.* 2011)
    Management of comorbid conditions such as hypertension and diabetes
    Adherence to appropriate pharmacotherapy (eg, ACE inhibitors and beta blockers)
    Advanced electrical therapy (if appropriate)
    Exercise rehabilitation with psychosocial and educational support
    Ongoing monitoring of disease progress
    Smoking cessation and alcohol reduction
continued…

139

TABLE 3. Continued

Immune Suppression (bone-marrow transplant)
(Ogden *et al.* 1990; Kruger *et al.* 2005; Dadd *et al.* 2003; Yokoe *et al.* 2009)
    Initial protective isolation (rooms with HEPA filtration, laminar flow, positive pressure, etc.) if appropriate based on neutropenia
    Reverse isolation procedures that stress hand washing and face masks
    Appropriate prophylactic antibiotics, antifungals, and antivirals
    Initial restriction of visitors and screening out those with rash, colds, etc.
    Strict hand hygiene after preparing food, bowel movements, touching animals, going outdoors, and other activities associated with bacteria
    Avoidance of gardening, excavation sites, or other soil exposures
    Avoidance of or limiting exposure to animals or their feces (eg, farming, grooming, veterinary practice, cleaning litter)
    Avoidance of water from lakes, ponds, or private wells (municipally treated water okay)
    Avoidance of undercooked meat, fish, and eggs
    Low-microbial diet that restricts certain foods such as raw nuts
    Water filtration/boiling to avoid cryptosporidium
    Safe sex

---

tion, proper nutrition, increased exercise, smoking cessation, alcohol reduction, and other factors that improve organ function and reduce the risk of further damage.

Practice guidelines do not include any caution about exposure to low levels of pollution, trace chemicals, or disinfection byproducts. In fact, chemical disinfectants are widely used to guard against infection. In cases of serious respiratory diseases such as COPD, avoidance of irritants is recommended, but this refers to combustion products and chemical irritants at levels high enough to cause frank respiratory irritation, not the low-level ambient exposures suggested by extreme sensitivity arguments.

In extreme immune suppression, isolation under conditions of sterilization, HEPA-filtered air, and limited access to outside people may be recommended, but this is to limit transmission of pathogens or opportunist organisms, not pollutants (Dadd *et al.* 2003; Sehulster and Chinn 2003). In fact, mortality rates for patients in strict isolation under HEPA filtration and positive pressure are similar to those associated with less stringent approaches that mainly limit visitors and stress hand washing and face masks (Ogden *et al.* 1990; Dadd *et al.* 2003). This suggests that completely removing all air pollution exposure is of no apparent benefit, and that most of the risk among highly vulnerable immune-suppressed patients resides with endogenous microorganisms and close contacts, not exogenous exposures.

Guidelines for extreme immune suppression may also restrict food and water, including avoidance of certain foodstuffs. These again are based on concerns for microbiological exposure, not chemical contaminants. In fact, highly processed foods and juices, and highly disinfected municipal drinking water, are all acceptable despite the fact that such consumables contain numerous chemical byproducts. In some instances,

140

Sensitivity and risk assessment thresholds

water filtration or boiling is suggested, but only to remove the risk of *Cryptosporidium* infection (Yokoe *et al.* 2009).

It is tempting to ignore the import of practice guidelines under the notion that healthcare professionals deal with clinical situations and would therefore be unaware of the more subtle effects of environmental exposures. But rather than ascribe ignorance to the practitioner, we need to recognize that doctors and nurses must deal with the realities of patient care, in which important competing risks dwarf the hypothetical impact of trace-level environmental exposures.

Clinicians recognize that immune-suppressed individuals are most likely to succumb to infection or some other aspect of bone-marrow depression (eg, bleeding disorders or anemia), matters unrelated to low-level exposures to chemical pollutants. By the same token, it is much more important for those with COPD to stop smoking, limit exposure to high-level irritants, and guard against weight gain, malnutrition, anemia, heart disease, and other comorbid conditions associated with disease progression (O'Donnell *et al.* 2008). Similarly, adherence to proper treatment, nutritional management, exercise, control of hypertension, psychosocial support, and many other factors are much more important in the management of chronic conditions such as heart disease and kidney failure (Table 3).

Based on the clinical guidelines, it would seem that low-level environmental exposures have negligible impact on patient health in the face of important known risks for disease progression. Put another way, real-world competing risks tend to trump concerns about hypothetical trace-level exposures to pollutants. That is to say, it is very unlikely that someone would be healthy enough to survive the gauntlet of major competing risks, only to be felled by trace-levels of ambient $PM_{2.5}$ or ozone.

Clinical Protection of those at Highest Risk

Justification for the extreme sensitivity argument requires a population of excessively debilitated individuals who would be most vulnerable to even minor environmental exposures. This would include patients with severe respiratory impairment or immune dysfunction. Yet, best clinical practice tends to incidentally minimize pollution exposure in these very individuals. For example, those with advanced COPD are maintained on oxygen for most of the day, limiting exposure to ambient air (Qaseem *et al.* 2007; O'Donnell *et al.* 2008). Of even more relevance, patients at highest risk from immune suppression, such as those undergoing bone marrow transplants, may be kept in protective isolation that includes HEPA filtration, laminar flow, and positive pressure (Dadd *et al.* 2003; Sehulster and Chinn 2003). Premature infants are similarly isolated. An extreme example would be a so-called "bubble boy" existence, in which an individual with severe immune depression lives in an artificial environment devoid of outside contact (Guerra and Shearer 1986). Such protective practices would remove all

141

J. Bukowski and others

or most ambient exposures, so that those at highest hypothetical risk of effect would be at lowest actual risk of exposure.

Even if severe protective practices were not in place, it is doubtful that very low-level pollution exposures would negatively affect even the most vulnerable described above. Referring again to the switch from restrictive isolation practices to less restrictive "reverse isolation" procedures, restrictive HEPA filtration and positive air pressure essentially remove exposure to all ambient pollution, yet switching to less stringent procedures has produced little difference in patient mortality. This highlights the fact that the main risk to those with severe immune dysfunction is from endogenous organisms and close contacts, not external exposures (Dadd *et al.* 2003).

STATISTICAL CONSIDERATIONS FOR THRESHOLD DETECTION IN PM STUDIES

Interpretation of the data from risk assessments almost always involves statistical evaluation. In this section we discuss how statistical considerations such as model choice can influence identification of nonlinear relationships, and how these considerations may have combined to obscure thresholds in air pollutions studies of acute or chronic mortality. A more in-depth discussion of statistical issues involved in model choice can be found in Nicolich and Gamble (2011).

Model Choice

Regulatory agencies often base safety standards on interpretation of statistical models. However, different models applied to the same data can lead to different conclusions, highlighting the importance of choosing the appropriate model. Reliance on inappropriate models can lead to either overly lax standards that jeopardize health or overly stringent ones that suppress economic benefits by requiring expensive, but needless, remediation and prevention strategies.

Some agencies apply models based on the concept of a Threshold of Toxicological Concern (TTC) which is "a pragmatic risk assessment tool that is based on the principle of establishing a human exposure threshold value for all chemicals, below which there is a very low probability of an appreciable risk to human health" (Kroes *et al.* 2004). This approach has been adopted (for some applications) by the US Food and Drug Administration (FDA) and several European agencies (Kroes *et al.* 2000, 2004, 2005; EFSA 2004). Some agencies apply models based on a related concept called the Threshold of Regulation (TOR), which posits that there is a de minimis risk level below which regulation is unwarranted. The EPA has proposed applying the TOR rules to pesticide regulation (Federal Register 2002). Both concepts (TTC and TOR) recognize the practical existence of a threshold without necessarily committing to a functional threshold model.

142

Sensitivity and risk assessment thresholds

However, air pollution standards developed by the EPA are generally based on strict linear no-threshold concentration-response (CR) models from epidemiologic studies, rejecting or ignoring thresholds unless the assumed linear relationship can be proven wrong (USEPA 2009; OAQPS 2005). Therefore, one reason that the EPA and its advisers may fail to detect thresholds is that they begin with models that do not address the existence of a threshold.

In essence, the approach used by EPA assumes a linear, no-threshold relationship unless proven otherwise. In this case, the "proof" relies on statistical tests that have weak power to detect nonlinearity in the typical situation with few observations in low-concentration range of the CR model. This makes it difficult to reject the no-threshold assumption even in the face of apparent nonlinearity (Li and Li 2008). Such an approach also ignores a basic tenet of traditional hypothesis testing, which cautions against accepting the null assumption simply because you failed to reject it (Daniel 1991).

Exposure misclassification, which is a common problem in environmental epidemiology, also tends to obscure thresholds. In air pollution studies, exposure assessment typically relies on area-wide measurements that are not highly correlated with personal exposures. Using time-series data, Brauer *et al.* (2002) demonstrated that the resulting exposure misclassification tends to obscure the presence of a threshold when it exists.

The importance of using the correct CR function is widely acknowledged as "a critical component in interpreting health risks associated with ambient PM concentrations" (OAQPS 2003), which is "important from both an etiologic and regulatory perspective" (Abrahamowicz *et al.* 2003). In fact, the EPA has stated that the "single most important factor influencing the uncertainty associated with the risk estimates was whether or not a threshold concentration exists below which PM-associated health risks are not likely to occur" (OAQPS 2003). Therefore, a search for the correct model should include looking for nonlinearity rather than simply assuming linearity.

Choosing the appropriate model can be difficult given the typical situation in which there are relatively few data points in the low-exposure region wherein thresholds typically lie. Applying a linear model to such data will greatly overestimate risk at low concentrations and underestimate the risk at higher concentrations (Figure 1). Under this typical situation of few data points below the threshold, hypothesis tests will usually fail to reject linearity (Robins and Greenland 1986).

Thresholds in Acute-Mortality Data

Much of the support for a significant effect from low-level exposure to PM and other pollutants resides within time-series (TS) studies that use complex linear models to link daily fluctuations in pollution to daily mor-
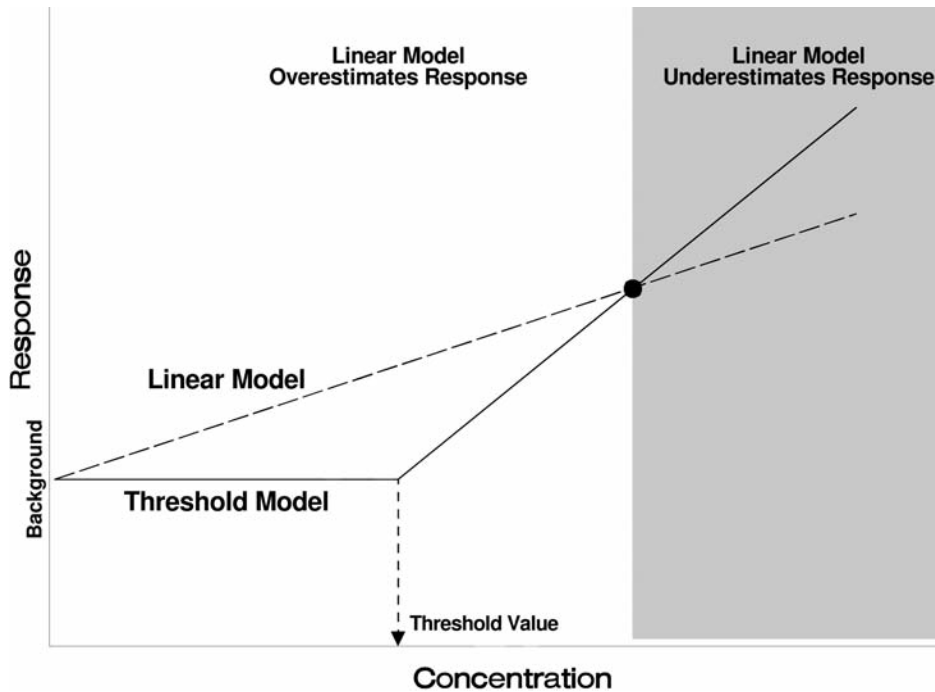
143

J. Bukowski and others

FIGURE 1. Overestimation of risk when a linear model is applied to non-linear, threshold data.

tality. In a number of instances, investigators have reanalyzed these data and shown that nonlinear models produced as good or better fit than the original linear ones, and that thresholds could often be statistically demonstrated (Table 4).

Mortality displacement

One concern in TS models of acute mortality is so-called harvesting or mortality displacement, wherein exposure hastens the deaths of a frail subset of the population that already has a short life expectancy, independent of exposure to PM. Most studies investigating this concept have concluded that mortality displacement would have only a small impact on the relative effects of PM (Dominici *et al.* 2003; Murray and Lipfert 2010; Murray and Nelson 2000; Schwartz and Zanobetti 2000; Smith *et al.* 1999; Zanobetti *et al.* 2000; Zeger *et al.* 1999). However, Roberts (2011a, b) showed that in some situations, mortality displacement can alter the shape of the CR curve so as to mask a mortality threshold. Although further work needs to be done, these initial findings suggest that apparently linear, no-threshold effects may in some cases be an artifact of mortality displacement.

Thresholds in Chronic-Mortality Data

The effects of PM have also been explored with cohort studies of chronic-disease mortality. Some of these have found consistent and sig-

Sensitivity and risk assessment thresholds

TABLE 4. Time-series studies of PM mortality that have been reanalyzed using nonlinear/threshold models.

City/Data Set	Results
Philadelphia, PA	Kelsall *et al.* (1997) reported a significantly increased relative risk (RR 1.01) for subjects ≥75 years of age, with no apparent threshold. Nicolich and Gamble (1999) reported that a threshold model better fit the data and produced a threshold around 125 mg/m^3 total suspended particulates (TSP).
Birmingham, AL	Schwartz (1993) reported a linear trend, no evidence of a threshold below 20 μg/m^3 PM$_{10}$, and a non-significant test for nonlinearity (p=0.70). Samet *et al.* (1995) used a categorical approach and reported a nonlinear trend with increased risks only at concentrations above 40-60 μg/m^3. Smith *et al.* (2000a) reported possible thresholds of 55-75 μg/m^3 using four different modeling approaches.
St. Louis, MO	Dockery *et al.* (1993) reported a 1.6% linear increase in total mortality for each 10 μg/m^3 increase in PM$_{10}$. Samet *et al.* (1995) reanalyzed the data by quintile and found no overall pattern of increasing mortality with increasing PM$_{10}$.
Utah Valley, UT	Pope *et al.* (1992) reported a significant linear association between daily mortality and PM$_{10}$ in Utah Valley between 1985-1989. Test for nonlinearity and thresholds were not significant. Samet *et al.* (1995) reported that the most plausible model produced a no-effect threshold.
Chicago, IL	Samet *et al.* (2000) performed a linear analysis that suggested a 0.05% increase in mortality for each 10 μg/m^3 increase in PM$_{10}$. Smith *et al.* (1997) found a nonlinear (but biologically implausible) relationship between PM$_{10}$ and mortality. Using piecewise linear analysis, Roberts (2004) could not reject linearity on statistical grounds, but found that "graphical presentations strongly suggest the existence of thresholds." Using statistically smoothed CR functions with varying lags, Moolgavkar (2003a) reported that the most plausible model comparing PM$_{10}$ to mortality had an obvious threshold at about 60 μg/m^3.
Phoenix, AZ	Mar *et al.* (2000) reported a weak linear association between total mortality and coarse PM (PM$_{2.5-10}$), but no associations with PM$_{2.5}$. Smith *et al.* (2000b) reported a significant linear relationship between mortality and coarse PM (PM$_{10-2.5}$) but not PM$_{2.5}$. In a second analysis similar to that used for the Birmingham data, Smith *et al.* (2000a) found nonlinear associations. Daniels *et al.* (2004) used a Bayesian model that suggested a PM$_{10}$ threshold at approximately 60 μg/m^3.
Los Angeles, CA	Moolgavkar (2003b) reported significant linear associations between PM$_{10}$ and mortality 2-4 days after exposure, and for PM$_{2.5}$ exposure on the day of death, but data suggested possible thresholds of 50-70 μg/m^3 for PM$_{10}$ and 45-65 μg/m^3 for PM$_{2.5}$. Daniels *et al.* (2004) reported a nonsignificant linear association between mortality and PM$_{10}$, but his Bayesian model suggested a threshold at or above approximately 75 μg/m^3 PM$_{10}$.
20 largest cities in NMMAPS	Daniels *et al.* (2004) report no evidence of a threshold for total or cardiovascular/respiratory mortality down to 10 μg/m^3 PM$_{10}$. Stylianou and Nicolich (2009) used validated alternative models on 9 of the 20 cities and reported that effects were not uniform across the nine cities, and that many models exhibited thresholds of approximately 25–45 μg/m^3 PM$_{10}$. Smith *et al.* (2009) report evidence of nonlinearity over 0-40, 40-60, and 60-80 ppb O3 intervals for 98 cities with coefficient significance shifts within a 25-40 ppb threshold range.

J. Bukowski and others

nificant associations between PM and death (Dockery *et al.* 1993; Pope *et al.* 2002), whereas others have not (Abbey *et al.* 1999; Lipfert *et al.* 2000). However, results from the American Cancer Society (ACS) cohort, which is the largest and most influential study, suggest significant association between PM exposure and either cardiopulmonary, lung-cancer, or all-cause mortality (Pope *et al.* 2002).

Cohort analyses typically rely on the Cox proportional hazards (PH) model, which considers time to an event (eg, death) under the influence of an outside exposure concentration (eg, PM). This model is built around the hazard function, which is based on the probability that the event will occur in the next short interval of time *t* (assuming it has not yet occurred). Mathematically, the time to the event is directly related to the hazard function, so that changes in the hazard directly affect survivorship. The Cox model is robust and effective for this type of analysis because it does not make assumptions about the form of the hazard function; only that exposure has a proportional effect on hazard. This allows considerable flexibility regarding the form of baseline survivorship, and direct estimation of covariate effects (assuming that covariates also have a multiplicative effect on the hazard function) (Harrell 2010).

An unfortunate limitation of the Cox model is that its standard form is not compatible with thresholds, because there is a basic assumption of proportional hazard across exposure concentrations (ie, the hazard function increases at all concentrations above zero) (Harrell 2010). Therefore, it is not surprising that thresholds have not been readily identified in cohort studies, given that a basic assumption of the standard modeling approach does not permit them. Additional research has also raised concerns about the Cox assumption of proportionality over the range of PM concentrations in the ACS study, suggesting the possibility of a threshold (Abrahamowicz *et al.* 2003).

Graphical evidence

In some instances, the USEPA and study investigators have failed to acknowledge nonlinearity that was statistically insignificant, but graphically evident. This highlights a key problem of relying on weak statistical tests as the sole arbiter of linearity/thresholds.

For example, results from the ACS cohort study are used to support the USEPA's stance that PM is linked to mortality in a linear fashion without an apparent threshold. Based on Cox PH results, authors of the ACS study reported significantly increased risks for PM that "were not significantly different from linear." However, nonparametric smoothed graphs showed apparent departures from linearity, primarily in the region of lowest exposure (Pope *et al.* 2002). This is mirrored in graphs taken from an earlier iteration of the study (Figure 2), in which the Health Effects Institute noted departures from linearity during flexible analyses (Krewski *et al.* 2000). In all cases there was evidence of apparent thresh-

146

Sensitivity and risk assessment thresholds

All Cause Mortality (Excluding Boise City, Idaho)

Cardiopulmonary Disease Mortality (Excluding Boise City, Idaho)

Lung Cancer Mortality (Excluding Boise City, Idaho)
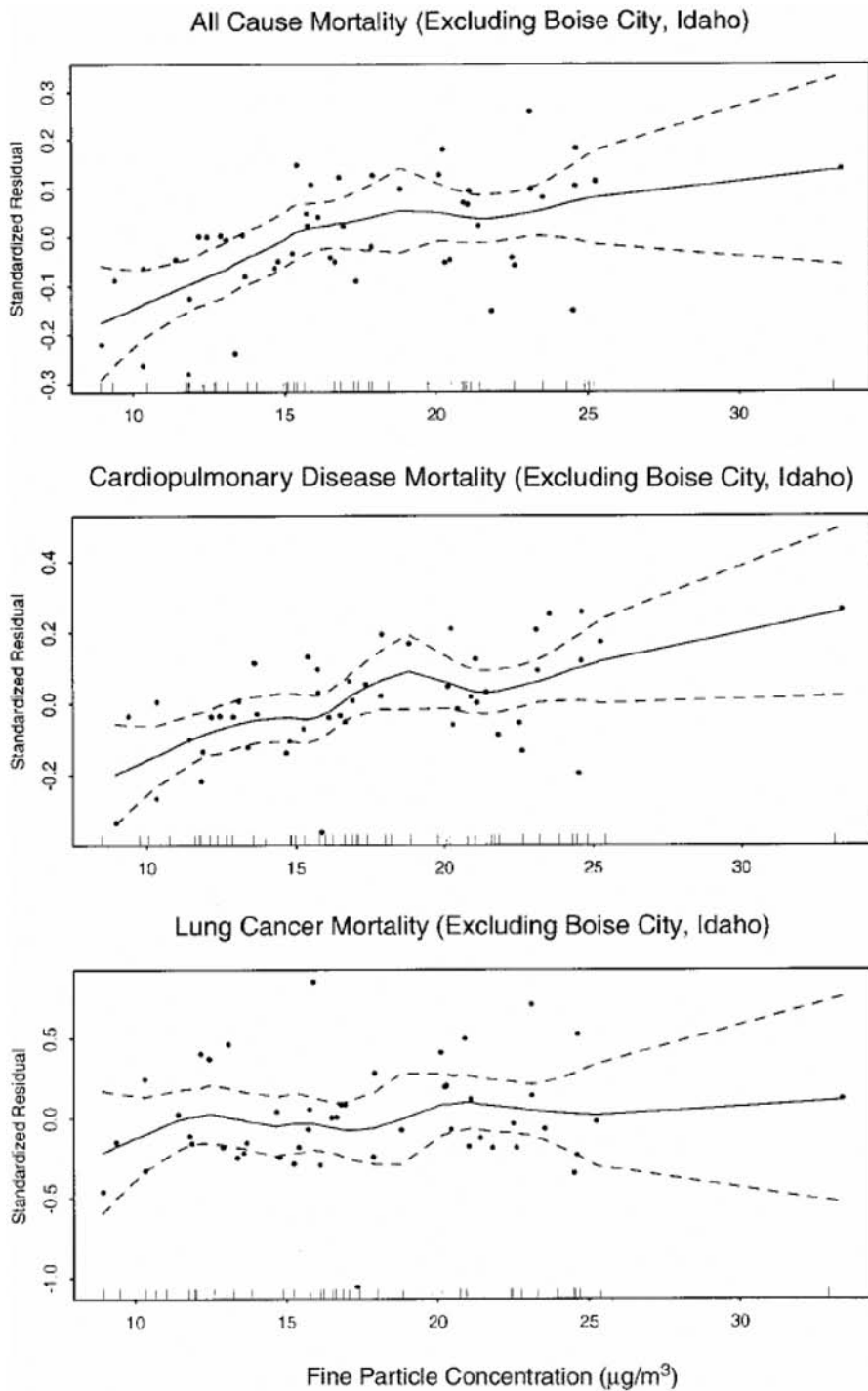

Fine Particle Concentration ($\mu g/m^3$)

FIGURE 2. Shape of the CR function using standardized residuals generated during analysis of data from the ACS cohort (Adapted from Krewski *et al.* 2000). Graphs copied from reanalysis of the original ACS data performed by Krewski *et al.* (2000).

147

J. Bukowski and others

olds, given that the plots of the residuals from the linear model are not flat and the plots for all-cause mortality and cardiopulmonary mortality show negative residuals below approximately 15 µg/m³ (Krewski *et al.* 2000; Pope *et al.* 2002).

CONCLUSIONS

Research in disciplines ranging from business to patient care has addressed the problem of "silos," whereby professionals in one discipline work within that restricted environment without tapping into the breadth of knowledge and experience in the wider universe of science, medicine, and engineering (Lunn 1997; Conway 1997). Such may be the case for QRA, with some risk assessors so highly focused on the theoretical world of hypothetical risk that they tend to lose sight of the practical realities of the world around them. In the hypothetical world, theories about extreme sensitivity and vulnerability make sense and support models that fail to demonstrate nonlinearity. But these theories break down under the pathophysiologic realities of human biology and medicine.

The extreme sensitivity argument is predicated on a population with extreme background vulnerability, so that even trivial exposures can be viewed as hazardous to their fragile state. In this paper, we offer several scientific arguments that bring this assumption into question:

1. The tightly regulated homeostasis of mammalian systems suggests that extreme sensitivity/variability is usually incompatible with life.
2. From a clinical standpoint, groups such as children and seniors are not inherently highly sensitive, and appear to have a range of susceptibility not greatly different from that of middle-aged adults.
3. Those with the highest background disease vulnerability would likely succumb to real-world competing risks that dwarf any hypothetical hazard from trace-chemical exposures.
4. The most highly vulnerable are often isolated from pollution, precluding impacts from such exposures.

All this argues for practical, real-world thresholds for most chemical exposures.

The recent regulatory trend has been to assume linearity in concentration-response unless proven otherwise. To this end, linear models are proposed and then rejected only if significant departures from linearity can be demonstrated. This violates the basics of hypothesis testing, in that failure to reject a model does not prove its appropriateness. Furthermore, the tests used to assess thresholds often have weak power and will frequently fail to reject even in the presence of nonlinear trends. Frequently, nonlinear/threshold models have a similar or better fit than their linear counterparts, especially for the typical situation in which the majority of

148

data are at the higher levels of exposure away from the threshold region.

The theoretical world of extreme vulnerability is inconsistent with the biology of mammalian systems and clinical medicine. Therefore, rather than pursuing ever-diminishing exposures in an effort to protect an ever-diminishing hypothetical population, resources would seem better directed toward the competing risks of greater magnitude and proven importance.

ACKNOWLEDGMENTS

REFERENCES

Abbey DE, Nishino N, McDonnell WF, Burchette RJ, Knutsen SF, Lawrence BW, and Yang JX. 1999. Long-term inhalable particles and other air pollutants related to mortality in nonsmokers. Am J Respir Crit Care Med 169:373-382.

Abrahamowicz M, Schopflocher T, Leffondre K, du Berger R, and Krewski D. 2003. Flexible modeling of exposure-response relationship between long-term average levels of particulate air pollution and mortality in the American Cancer Society study. J Toxicol Environ Health, Part A 10;66:1625-1654.

Albertini RJ, Sram RJ, Vacek PM, Lynch J, Wright M, Nicklas JA, Boogaard PJ, Henderson RF, Swenberg JA, Tates AD, and Ward JB Jr. 2001. Biomarkers for assessing occupational exposures to 1,3-butadiene. Chem Biol Interact 135-136:429-453.

Albertini RJ, Sram RJ, Vacek PM, Lynch J, Nicklas JA, van Sittert NJ, Boogaard PJ, Henderson RF, Swenberg JA, Tates AD, Ward JB Jr, Wright M, Ammenheuser MM, Binkova B, Blackwell W, de Zwart FA, Krako D, Krone J, Megens H, Musilová P, Rajská G, Ranasinghe A, Rosenblatt JI, Rössner P, Rubes J, Sullivan L, Upton P, and Zwinderman AH. 2003. Biomarkers in Czech workers exposed to 1,3-butadiene: A transitional epidemiologic study. HEI Research Report 116.

Albertini RJ, Sram RJ, Vacek PM, Lynch J, Rossner P, Nicklas JA, McDonald JD, Boysen G, Georgieva N, and Swenberg JA. 2007. Molecular epidemiological studies in 1,3-butadiene exposed Czech workers: female-male comparisons. Chem Biol Interact 166:63-77.

Brauer M, Brumm J, Vedal S, and Petkau AJ. 2002. Exposure misclassification and threshold concentrations in time series analyses of air pollution health effects. Risk Anal 22:1183-1193.

Bukowski JA and Lewis RJ. 2004. Practical implications of nonlinear effects in risk-assessment harmonization. Dose-Response [formerly *Nonlinearity in Biology, Toxicology, and Medicine*] 2:3-10.

Burden R and Tomson C. 2005. Identification, management and referral of adults with chronic kidney disease: concise guidelines. Clin Med 5:635-642.

CalEPA (California Environmental Protection Agency). 2010. Cumulative Impacts: Building a Scientific Foundation. Public Review Draft, August 19, 2010.

Chan M, Patwardhan A, Ryan C, Chabdan S, Westgarth F, and Fry K. 2011. Evidence-based guidelines for the nutritional management of adult kidney transplant recipients. J Renal Nutrition 21:47-51.

Conway JB. 1997. Breaking down professional silos: the potential of integrated management. Radiol Manage 19:30-34.

Crawford M and Wilson R. 1996. Low-dose linearity: The rule or the exception? Human Ecol Risk Assess 2:305–330.

Dadd G, McMinn P, and Monterosso L. 2003. Protective isolation in hematopoietic stem cell transplants: A review of the literature and single institution experience. 2003. J Pediatric Oncol Nursing 20:293-300.

Daniel WW. 1991. Biostatistics: A foundation in the health sciences. Fifth Edition, New York: John Wiley & Sons.

149

J. Bukowski and others

Daniels M, Dominici F, and Zeger SL. 2004. The National Morbidity, Mortality, and Air Pollution Study, Part III: PM10 Concentration-Response Curves and Threshold for the 20 Largest US Cities. Research Report 94. Health Effects Institute, Boston, MA.

Dienstag JL and McHutchison JG. 2006. American Gastroenterological Association medical position statement on the management of hepatitis C. Gastroenterol 130:225-230.

Dockery DW, Pope CA, Xu X, Spengler JD, Ware JH, Fay ME, Ferris BG Jr, and Speizer FE. 1993. An association between air pollution and mortality in six U.S. cities. N Engl J Med 329:1753-1759.

Dominici F, McDermott A, Zeger SL, and Samet JM. 2003. Airborne particulate matter and mortality: timescale effects in four US Cities. Am J Epid 157:1055-1065.

Dourson M, Charnley G, and Scheuplein R. 2002. Differential sensitivity of children and adults to chemical toxicity. Reg Toxicol Pharmacol 35:448-467.

ECETOC (European Centre for Ecotoxicology and Toxicology of Chemicals). 2005. Trends in children's health and the role of chemicals: State of the science review. Tech. Report 96, June 2005.

EFSA (European Food Safety Authority). 2004. Scientific Panel on Food Additives, Flavourings, Processing Aids and Materials in Contact with Food. Opinion on Flavouring Group FGE.03 Acetals of branched- and straightchain aliphatic saturated primary alcohols and branched- and straight-chain saturated aldehydes, and an orthoester of formic acid, from chemical groups 1 and 2. Opinion expressed on 7 October 2004.

Federal Register /Vol. 71, No. 10 /Tuesday, January 17, 2006 / Proposed Rules (p 2635).

Federal Register /Wednesday, August 28, 2002 / Proposed Rules (p 55253-55254).

Fustinoni S, Soleo L, Warholm M, Begemann P, Rannug A, Neumann HG, Swenberg JA, Vimercati L, and Colombi A. 2002. Influence of metabolic genotypes on biomarkers of exposure to 1,3-butadiene in humans. Cancer Epidemiol Biomarkers Prev 11:1082-1090.

Geronimus AT. 1992. The weathering hypothesis and the health of African-American women and infants: Evidence and speculation. Ethn Dis 2:207-221.

Gibbons RJ, Abrams J, Chatterjee K Daley J, Deedwania PC, Douglas JS, Ferguson TB Jr, Fihn SD, Fraker TD Jr, Gardin JM, O'Rourke RA, Pasternak RC, Williams SV, Gibbons RJ, Alpert JS, Antman EM, Hiratzka LF, Fuster V, Faxon DP, Gregoratos G, Jacobs AK, and Smith SC Jr. 2003. Acc/AHA 2002 Guideline update for the management of patients with chronic stable angina—Summary article. Circulation 107:149-158.

Graham I, Atar D, Borch-Johnsen K, Boysen G, Burell G, Cifkova R, Dallongeville J, De Backer G, Ebrahim S, Gjelsvik B, Herrmann-Lingen C, Hoes A, Humphries S, Knapton M, Perk J, Priori SG, Pyorala K, Reiner Z, Ruilope L, Sans-Menendez S, Scholte op Reimer W, Weissberg P, Wood D, Yarnell J, Zamorano JL, Walma E, Fitzgerald T, Cooney MT, and Dudina A. 2007. European guidelines on cardiovascular disease prevention in clinical practice: executive summary. Euro Heart J 28:2375-2414.

Grundy SM, Cleeman JI, Daniels SR Donato KA, Eckel RH, Franklin BA, Gordon DJ, Krauss RM, Savage PJ, Smith Jr SC, Spertus JA, and Costa F. 2005. Diagnosis and management of the metabolic syndrome, an American Heart Association/National Heart, Lung, and Blood Institute scientific statement. Cardiol Rev 13:322-327.

Guerra IC and Shearer WT. 1986. Environmental control in management of immunodeficient patients: experience with "David." Clin Immunol Immunopathol 40:128-135

Harrell FE. 2010. Regression Modeling Strategies. New York:Springer-Verlag.

Hogg RJ, Furth S, Lemley KV, Portman R, Schwartz GJ, Coresh J, Balk E, Lau J, Levin A, and Kausz AT. 2003. National Kidney Foundation's kidney disease outcomes quality initiative clinical practice guidelines for chronic kidney disease in children and adolescents: Evaluation, classification, and stratification. Pediatrics 111:1416-1422.

IOM (Institutes of Medicine). 1999. Towards environmental justice: Research, education, and health policy needs. Washington DC: National Academies Press.

Jessup M, Abraham WT, Casey DE, Feldman AM, Francis GS, Ganiats TG, Konstam MA, Mancini DM, Rahko PS, and Silver MA. 2009. Focused update: ACCF/AHA Guidelines for the diagnosis and management of heart failure in adults. Circulation 119:1977-2016.

Johansson I and Ingelman-Sundberg M. 2011. Genetic polymorphism and toxicology—with emphasis on cytochrome P\$450. Toxicol Sci 120:1-13.

Kelsall JE, Samet JM, Zeger SL, and Xu J. 1997. Air pollution and mortality in Philadelphia, 1974–1988. Am J Epidemiol 146:750–762.

Sensitivity and risk assessment thresholds

Krewski D, Burnett RT, Goldberg MS, Hoover K, Siemiatycki J, Jerrett M, Abrahamowicz M, and White WH. 2000. Part II: Sensitivity Analysis. In: Reanalysis of the Harvard Six Cities Study and the American Cancer Society Study of Particulate Air Pollution and Mortality. A Special Report of the Institute's Particle Epidemiology Reanalysis Project. Health Effects Institute, Cambridge, MA.

Kroes R, Galli CL, Munro I, Schilter B, Tran L-A, Walker R, and Wurtzen G. 2000. Threshold of toxicological concern for chemical substances present in the diet: a practical tool for assessing the need for toxicity testing. Food Chem Toxicol 38:255–312.

Kroes R, Renwick AG, Cheeseman M, Kleiner J, Mangelsdorf I, Piersma A, Schilter B, Schlatter J, van Schothorst F, Vos JG, and Würtzen G. 2004. Structure-based thresholds of toxicological concern (TTC): Guidance for application to substances present at low levels in the diet. Food Chem Toxicol 42:65–83.

Kroes R, Kleiner J, and Renwick A. 2005. The Threshold of Toxicological Concern Concept in Risk Assessment. Toxicol Sci 86(2):226–230.

Kruger WH, Bohlius J, Cornely OA, Einsele H, Hebart H, Massenkeil G, Schuttrumpf GS, Ullmann AJ, Waldschmidt DT, and Wolf H. 2005. Antimicrobial prophylaxis in allogenic bone marrow transplantation. Guidelines of the Infectious Diseases Working Party (AGIHO) of the German Society of Haematology and Oncology. Annals Oncol 1381-1390.

Lee H, Park W, Yang JH, and You KS. 2010. Management of hepatitis B virus infection. Gastroenterol Nurs 33:120-126.

Li X-R and Li X-B. 2008. Common Fallacies in Applying Hypothesis Testing.

Proceedings of the 11th International Conference on Information Fusion, Cologne, Germany, 2008 IEEE Catalog Number CFP08FUS, pp 1085-1092

Lipfert FW, Perry HM, Miller JP, Baty JD, Wyzga RE, and Carmody SE. 2000. The Washington University-EPRI Veterans' cohort mortality study: preliminary results. Inhal Toxicol 12(Suppl 4):41-73.

Lunn T. 1997. Breaking down silos and building teamwork. Hosp Mater Manage 19:9-15.

Mant J, Al-Mohammad A, Swain S, and Laramee P. 2011. Management of chronic heart failure in adults: Synopsis of the National Institute for Health and Clinical Excellence guideline. Ann Intern Med 155:252-259.

Mar T F, Norris GA, Koenig JQ, and Larson T V. 2000. Associations between air pollution and mortality in Phoenix, 1995-1997. Environ Health Perspect 108:347-353.

Moolgavkar SH. 2003a. Air pollution and daily deaths and hospital admissions in Los Angeles and Cook Counties. Special Report, Revised Analyses of Time-Series Studies of Air Pollution and Health, Health Effects Institute, Boston, MA.

Moolgavkar SH. 2003b. Air pollution and daily mortality in two US counties:season-specific analyses and exposure-response relationships. Inhal Toxicol 15:877-907.

Morello-Frosch R and Shenassa ED. 2006. The environmental "riskscape" and social inequality: Implications for explaining maternal and child health disparities. Environ Health Perspect 114:1150-1153.

Murray CJ and Lipfert FW. 2010. Revisiting a population-dynamic model of air pollution and daily mortality of the elderly in Philadelphia. J Air Waste Manage Assoc 60(5):4728-4734.

Murray CJ and Nelson CR. 2000. State-space modeling of the relationship between air quality and mortality. J Air Waste Manage Assoc 50(7):1075e-1080e.

NRC (National Research Council). 1983. Risk Assessment in the Federal Government: Managing the Process. Washington, DC: National Academy Press.

NRC (National Research Council). 2009. Science and decisions: Advancing risk assessment. Committee on Improving Risk Analysis Approaches Used by the U.S. EPA. Washington, DC: National Academies Press.

Nicolich MJ and Gamble JF. 2011. What is the minimum risk that can be estimated from an epidemiology Study? In: Anca Maria Moldoveanu (ed.), Advanced Topics in Environmental Health and Air Pollution Case Studies, pp 3-26. InTech, Croatia. Available at http://www.intechopen.com/articles/show/title/what-is-the-minimum-risk-that-can-be-estimated-from-an-epidemiology-study-, accessed 1 Oct 2011.

Nicolich MJ and Gamble JF. 1999. Evidence of a threshold effect for TSP in the Philadelphia data set. J Environ Med 1:279-290.

J. Bukowski and others

Novo S, Balbarini A, Belch JJ, Bonura F, Clement DL, Diamantopoulos E, Fareed J, Norgren L, Poredos P, and Rotzocil K. 2008. The metabolic syndrome: definition, diagnosis and management. Int Angiol 27:220-231.

OAQPS (Office of Air Quality Planning and Standards). 2003. Review of the National Ambient Air Quality Standards for Particulate Matter: Policy Assessment of Scientific and Technical Information; OAQPS Staff Paper-First Draft. U.S. EPA; Office of Air Quality Planning and Standards, Research Triangle Park, NC 27711.

OAQPS (Office of Air Quality Planning and Standards). 2005. Review of the National Ambient Air Quality Standards for Particulate Matter: Policy Assessment of Scientific and Technical Information; OAQPS Staff Paper-Second Draft. U.S. EPA; Office of Air Quality Planning and Standards, Research Triangle Park, NC 27711.

O'Donnell DE, Hernandez P, Kaplan A, Aaron S, Bourbeau J, Marciniuk D, Balter M, Ford G, Gervais A, Lacasse Y, Maltais F, Road J, Rocker G, Sin D, Sinuff T, and Voduc N. 2008. Canadian Thoracic Society recommendations for management of chronic obstructive pulmonary disease – 2008 update – highlights for primary care. Can Respi J 15(suppl. A):1A-8A.

Ogden AK, Steuber CP, Mahoney DH, and Fernbach DJ. 1990. Bone marrow transplantation in childhood leukemia using reverse isolation techniques. Med Pediatric Oncol 18:1-5.

O'Shea SH, Schwartz J, Kosyk O, Ross PK, Ha MJ, Wright FA, and Rusyn I. 2011. *In Vitro* screening for population variability in chemical toxicity. Toxicol Sci 119:398-407.

Physician's Desk Reference, 57th Edition. 2003. Montvale, NJ: Thomson PDR.

Physician's Desk Reference, 65th Edition. 2010. Montvale, NJ: PDR Network.

Pope CAI, Schwartz J, and Ransom MR. 1992. Daily mortality and PM10 pollution in Utah valley. Arch Env Health 47:211-217.

Pope CA, Burnett RT, Thun MJ, Calle EE, Krewski D, Ito K, and Thurston GD. 2002. Lung cancer, cardiopulmonary mortality, and long-term exposure to fine particulate pollution. JAMA 287(9):1132-1141.

Qaseem A, Snow V, Shekelle P Sherif K, Wilt TJ, Weinberger S, and Owens DK. 2007. Diagnosis and management of stable chronic obstructive pulmonary disease: A clinical practice guideline from the American College of Physicians. Ann Intern Med 147: 633-638.

Renwick AG. 1998. Toxicokinetics in infants and children in relation to the ADI and TDI. Food Addit Contam 15:17-35.

Renwick AG and Lazarus NR. 1998. Human variability and noncancer risk assessment – An analysis of the default uncertainty factor. Regul Toxicol Pharmacol 27:3-20.

Rhomberg LR, Goodman JE, Haber LT, Dourson M, Andersen ME, Klaunig JE, Meek B, Price PS, McClellan RO, and Cohen SM. 2011. Linear low-dose extrapolation for noncancer health effects is the exception, not the rule. Crit Rev Toxicol 41:1-19.

Roberts S. 2011a. What are distributed lag models of particulate matter air pollution estimating when there are populations of frail individuals? Environ International 37(3):586-591.

Roberts S. 2011b. Can mortality displacement mask thresholds in the concentration-response relation between particulate matter air pollution and mortality? Atmos Environ 45:4728e-4734e.

Roberts S. 2004. Biologically plausible particulate air pollution mortality concentration-response functions. Environ Health Perspect 112:309-313.

Robins JM and Greenland S. 1986. The role of model selection in causal inference from nonexperimental data. Am J Epidemiol 123(3):392-402.

Samet JM, Zeger SL, and Berhane K. 1995. Particulate Air Pollution and Daily Mortality: Replication and Validation of Selected Studies. *Phase I Report*, Health Effects Institute, Boston, MA.

Samet JM, Dominici F, Curriero FC, Coursac I, and Zeger SL. 2000. Fine particulate air pollution and mortality in 20 U.S. cities, 1987-1994. N Engl J Med 343(24):1742-1749.

Schwartz J and Zanobetti Z. 2000. Using meta-smoothing to estimate dose-response trends across multiple studies, with application to air pollution and daily death. Epidemiology 11(6):666e-672e.

Schwartz, J. 1993. Air pollution and daily mortality in Birmingham, Alabama. Am J Epidemiol. 137:1136-147.

Sehulster L and Chinn RYW. 2003. Guidelines for environmental infection control in health-care facilities. Recommendations of CDC and the Healthcare Infection Control Practices Advisory Committee (HICPAC) U.S. Department of Health and Human Services Centers for Disease Control and Prevention (CDC) Atlanta, GA.

Sensitivity and risk assessment thresholds

Slikker W, Andersen ME, Bogdanffy MS, Bus JS, Cohen SD, Conolly, RB, David RM, Doerrer NG, Dorman DC, Gaylor DW, Hattis D, Rogers JM, Woodrow SR, Swenberg JA, and Wallace K. 2004. Dose-dependent transitions in mechanisms of toxicity. Toxico Appl Pharmacol 201:203-225.

Smith RJ, Davis JM, and Speckman P. 1997. Assessing the human health risk of atmospheric particles. ASA Proceeding Environmental Statisticians.

Smith RL, Davis JM, and Speckman P. 1999. Human health effects of environmental pollution in the atmosphere. In: Barnett, V., Stein, A., Turkman (eds.), Statistics in the Environment 4: Statistical Aspects of Health and the Environment. John Wiley and Sons Ltd, Chichester, United Kingdom, pp. 91-115.

Smith RL, Davis JM, Sacks J, Speckman P, and Styer P. 2000a. Regression models for air pollution and daily mortality: analysis of data from Birmingham, Alabama. Econometrics 11:719-743.

Smith RL, Spitzner D, Kim Y. and Fuentes M. 2000b. Threshold dependence of mortality effects for fine and coarse particles in Phoenix, Arizona. J Air Waste Manag Assoc 50(8):1367-1379.

Smith RL, Xu B, and Switzer P. 2009. Reassessing the relationship between ozone and short-term mortality in U.S. urban communities. Inhal Toxicol 21(Suppl 2):37-61.

Stylianou M and Nicolich MJ. 2009. Cumulative effects and threshold levels in air pollution mortality: data analysis of nine large US cities using the NMMAPS dataset. Environ Pollut 157(8-9):2216-2223.

Taylor SL, Gendel SM, Houben GE, and Julien E. 2009. The key events dose-response framework: A foundation for examining variability in elicitation thresholds for food allergens. Crit Rev Food Sci Nutrit 49:729-739.

USEPA. (U.S. Environmental Protection Agency). 2011. Integrated Risk Information System (IRIS). Washington, DC, http://www.epa.gov/iris/intro.htm, accessed on 12/14/2011.

USEPA. (U.S. Environmental Protection Agency). 2009. Integrated Science Assessment for Particulate Matter (Final Report). Washington, DC, EPA/600/R-08/139F.

Weinbaum CM, Williams I, Mast EE, Wang SA, Finelli L, Wasley A, Neitzel SM, and Ward JW. 2008. Recommendations for the identification and public health management of persons with chronic hepatitis B virus infection. MMWR 57:1-20.

Wejstal R, Alaeus A, Fischler B, Reichard O, Uhnoo I, and Weiland O. 2003. Chronic hepatitis C: Updated Swedish consensus. Scand J Infect Dis 35:445-451.

White RH, Cote I, Zeise L, Fox M, Dominici F, Burke TA, White PD, Hattis DB, and Samet JM. 2009. State-of-the-Science Workshop Report: Issues and approaches in low dose–response extrapolation for environmental health risk assessment. Environ Health Perspect 117:283-287. Available at: http://www.ehponline.org/members/2008/ 11502/11502.pdf. Accessed on 3 December 2010.

Yokoe D, Casper C, Dubberke E, Lee G, Muñoz P, Palmore T, Sepkowitz K, Young J-A, and Donnelly JP. 2009. Safe living guidelines after hematopoietic cell transplantation. Bone Marrow Transplant 44:509-519.

Zanobetti A, Wand MP, Schwartz J, and Ryan LM. 2000. Generalized additive distributed lag models: quantifying mortality displacement. Biostatistics1(3):279-292.

Zeger SL, Dominici F, and Samet J. 1999. Harvesting-resistant estimates of air pollution effects on mortality. Epidemiology 10(2):171e-175e.

Zhou SF, Yang LP, Zhou ZW, Liu YH, and Chan E. 2009. Insights into the substrate specificity, inhibitors, regulation, and polymorphisms and the clinical impact of human cytochrome P450 1A2. AAPS J 11:481-492.