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To: John Graham/OMB/EOP@EOP

cc:
Subject: FW: BNA News - Dennis' views on the 2003 Proposed Cancer Guidelin es for Childhood Exposure - April 25, 2003

I would suggest that OMB should give my comments serious consideration. The impact on the regulatory community could be substantial. About 30-50, 000 in DC read it on Monday.

All the best,

Dennis

> Friday, April 25, 2003
> Risk Assessment
>
> A VIEW ON THE 2003 PROPOSED CANCER GUIDELINES FOR CHILDHOOD EXPOSURE
> By Dennis J. Paustenbach
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> Risk Assessment
> Assessing Cancer Susceptibility from Early-Life Exposure
>
> There are, the author argues, more pressing environmental issues worthy of
> our attention that do not require the leaps of faith needed to embrace the
> Environmental Protection Agency's proposed guidelines for assessing cancer
> susceptibility from early-life exposure to carcinogens. Eliminating
> certain known hazards for children, improving education about lifestyle
> choices, and promulgating rules for some chemicals which have yet to be
> regulated almost certainly would be more likely to improve the well-being
> of children than applying EPA's broad recommendations to future risk
> assessments. Nonetheless, he says, as a society we have rightfully decided
> to focus on the various potential hazards to children. The author would
> not oppose many of the recommendations in this guidance, but says it would
> be inappropriate for society to think "science was telling us to do it."
>
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> engineering and science consulting firm headquartered in Menlo Park,
> Calif. He has 20 years of experience in risk assessment, environmental
> engineering, toxicology, and occupational health. He has worked on many
> high-profile projects, including the assessments of contaminated soils at
> Times Beach, Love Canal, and The Meadowlands, and the sediments in the
> Hudson River. He is the editor of a textbook, Human and Ecological Risk
> Assessment: Theory and Practice, and of the new scientific publication,
> "The Journal of Children's Health." The views expressed in this article
> are those of the author and do not represent an editorial position of BNA,
> which welcomes other points of view.

>
> On February 28, 2003 the Environmental Protection Agency issued the
> Supplemental Guidance for Assessing Cancer Susceptibility from Early-Life
> Exposure to Carcinogens [hereafter called guidance]. This has also been
> nicknames the "Cancer Guidelines for Children." Unlike many other
> guidelines, EPA states in the Preface that "this Supplemental Guidance
> will have no binding effect on EPA or any regulated entity." However, EPA
> noted it reserves the right to use the "approaches in Supplemental
> Guidance in developing a future risk assessment ... [if] the approaches
> from the Supplemental Guidance that were employed are suitable and
> appropriate." As a practical matter, it is quite likely that the final
> version of this guidance will have significant impact on future decisions
> by EPA and the courts.1
>
> Like so many regulatory policies, guidance or criteria this is a "good
> news/bad news" story. The good news is EPA apparently believes the United
> States has the financial resources to investigate more thoroughly whether
> low level exposure to carcinogens at an early age (e.g., neonate or young
> child) poses a larger cancer risk than for adults exposed to the same
> dose. Most risk assessors and/or toxicologists who have studied
> carcinogens for the past two decades have suspected the fetus or the very
> young child was more susceptible than the adult to a later cancer hazard
> from some genotoxic chemicals; but only if the dose were substantial. By
> substantial, it was meant at the doses used in cancer bioassays or,
> perhaps, at doses to which some people might be exposed in the workplace.
> In general, the toxicology community has assumed, based on various lines
> of reasoning and basic scientific principles, that the doses associated
> with current regulations contain a sufficient margin of safety to protect
> children.
>
> The bad news is there is a dearth of published information upon which to
> offer quantitative, or even qualitative, guidance. In short, there have
> not been any published studies specifically designed to answer the
> question which EPA and the scientific community would like to address. The
> guidance does a good job of piecing together the very limited information
> from various studies to suggest the young child probably is more
> susceptible to mutagens during periods of rapid organ development.
> However, there is very little acknowledgment by EPA in this draft guidance
> that the doses in the studies they rely upon were significantly, often a
> thousand fold, above any likely environmental dose.
>
> It should be noted that EPA is not intending this guidance to prevent
> childhood cancers but rather as a mechanism for reducing adult cancers due
> to early lifetime exposure. Also, the guidance only addresses exposure
> after birth and does not consider the possible risks associated with
> prenatal exposure through the mother.
>
>
> Background
>
> EPA correctly notes in its Supplemental Guidance that standard animal
> cancer bioassays generally begin dosing after the animals are six to eight
> weeks old, when many organs and systems are relatively mature, though
> substantial growth in body size continues thereafter. In the few review
> articles that compare the results of perinatal carcinogenesis testing to
> the standard cancer bioassay, the authors usually note that (1) the same

> tumor sites are usually observed following either perinatal or adult
> exposure and (2) perinatal exposure in conjunction with adult exposure
> usually increases the incidence of tumors or reduces the latency period
> before tumors are observed. As noted previously, the extrapolation of this
> information from relatively high dose animal studies to infer that
> children, for example, are more susceptible to chemicals found in the air,
> water, food, or soil is not easily justified given the available
> information.
>
> In the Introduction, EPA correctly notes a number of possible reasons why
> young children could be more susceptible to the adverse effects of
> chemicals, but the guidance tends to talk more about evidence for the
> developmental hazard than evidence they are more susceptible to
> carcinogens. They list a few characteristics of early development, which
> if perturbed, might increase the cancer hazard including:
>
> * More frequent cell division during development, which can result in
> enhanced fixation of mutations due to the reduced time available for
> repair of DNA lesions. Also, clonal expansion of mutant cells gives a
> larger population of mutants.
> * Some embryonic cells, such as brain cells, lack key DNA repair
> enzymes.
> * Some components of the immune system are not fully functional during
> development.
> * Hormonal systems operate at different levels during different life
> stages.
> * Induction of developmental abnormalities can result in a
> predisposition to carcinogenic effects later in life.
>
> It should be noted, however, that the above list definitely describes why,
> following exposure to chemicals at some dose, the fetus or young child is
> vulnerable to developmental effects but the list is not nearly so
> compelling as evidence for an increased cancer hazard. Moreover, the
> guidance specifically states that the safety factors apply to children
> after birth, not fetuses, and the data on which these factors are based do
> not include prenatal exposure. To EPA's credit, it recognizes the
> available data only suggest the genotoxic carcinogens might be of concern
> and acknowledges a lot more information is needed.
>
>
> Mode Of Action
>
> As in the primary document, EPA's Draft Final Guidelines for Carcinogen
> Risk Assessment,2 a significant amount of discussion is directed at the
> importance of the mode of action through which a chemical produces its
> carcinogenic effect. For those scientists who have studied the mechanism
> of action of the various classes of chemical carcinogens or specific
> chemicals, this section deserves special attention, as it is in many ways
> the foundation upon which the guidance is based.
>
> Without going into a detailed discussion of whether there is sufficient
> evidence to indicate certain modes of action present a greater
> carcinogenic hazard for the young child compared with the adult, there are
> a few parts of the EPA discussion which probably would benefit from
> comments of substance from members of the scientific community. In
> particular, there seems to be some degree of reliance on the assumption

> that cancer risks are proportional to exposure duration. Although the
> assumption as applied in the guidance is acknowledged to be a bit weak, it
> is nonetheless later used as a basis for some of the quantitative
> recommendations. EPA noted that it had difficulty coming up with a good
> estimate of the daily dose when trying to apply information from animals
> studies not intended to assess risk to the young animals. This is because
> the young animals eat and drink larger quantities per body weight when
> they are young. This, regrettably, complicates the quantitative
> interpretation of most of the published studies.
>
> Not surprisingly, perhaps the best information for determining whether the
> neonate or child is at greater risk of developing cancer (per unit of
> dose) than adults is contained within the radiation literature. Again, EPA
> acknowledges very substantial differences between the toxicokinetics and
> toxicodynamics of mutagenic chemicals and ionizing radiation. However, due
> to a paucity of good studies on chemicals, they tend to rely on
> information from the A-bomb survivors for inferring an increased cancer
> risk to adults based on early-life exposure. Because of the reliance on
> the radiation literature, it is clear throughout the document that EPA
> would like to focus on the possible increased susceptibility of children
> to chemicals which are clearly genotoxic. Even though this is a prudent
> approach, it would have been useful for EPA to have spent more time
> discussing why exposure to relatively high doses of ionizing radiation is
> different from exposure to low doses of even fairly potent genotoxic
> chemical carcinogens.
>
>
>
> The Database
>
> Twenty three animal studies on sixteen chemicals are used to derive some
> level of qualitative and quantitative understanding of the increased
> susceptibility of the young child. The primary data sets relied upon by
> EPA derive from seven multiple dose studies of five mutagenic
> compounds--benzo[a]pyrene, benzidine, diethylnitrosamine, safrole, and
> vinyl chloride--and six multiple dose studies of six non-mutagenic
> carcinogens. EPA readily acknowledged that these studies were not designed
> to answer the questions being asked. Many more data sets investigating
> exposure of young animals to mutagens and carcinogens are available..
> However, in an attempt to use the data to answer the question at
> hand--does early life exposure increase carcinogenic risk--EPA chose to
> use only studies from the same laboratories, using the same species and
> strain of animal, the same route of exposure and similar doses.
>
> EPA attempts to adjust or normalize the doses from the studies of the five
> mutagens and six non-mutagens so that it can determine whether a
> consistent message surfaces from this data set. Because the studies do not
> have an accurate estimation of dose for the young animals, EPA uses time
> as a surrogate for dose. Since these studies were not intended for the
> purpose to which EPA would like them to apply, it is quite possible that
> no matter how much the data are scrutinized, no light will be shed on the
> central issue of the Supplemental Guidance: Are children genuinely more
> susceptible to low doses of chemical carcinogens?
>
> The rest of the discussion about the database is clear and relatively
> concise. In fact, this guidance document is as readable and understandable

> as any of the dozens of documents EPA has produced over the past 30 years.
> The thought process was relatively easy to follow. However, the handling
> of data from the various studies presented in the tables was not entirely
> transparent. Specifically, it was not always clear why certain data were
> presented from the studies and not others. In addition, the use of acute
> dosing studies, without appropriate complementary long-term studies, to
> try to understand the cancer hazard seemed to involve a lot of wishful
> thinking on the part of the agency. Also, there was not sufficient
> discussion of the importance of separating those chemicals requiring
> activation (metabolism) to form the reactive chemical species versus those
> that are direct acting carcinogens. This is important because, when
> compared to the adult, one of the genuine differences between the fetus,
> the newborn, and the developing child, is that certain metabolic enzymes
> are not fully functional. Thus, if metabolic activation of a chemical is
> required, the fetus or young child would be less susceptible to the
> carcinogenic hazard compared to later in life.
>
> One could take issue with the mathematical model used by EPA (i.e., the
> ratio of early exposure tumor incidence/ratio of adult exposure tumor
> incidence=risk adjustment factor) since it may mask two significant
> problems with the methodology. First, EPA is not sure of the dose to the
> young animals in the various studies. Second, one might expect earlier
> exposure would shift the latency curve to the left, thus resulting in an
> apparent increase in tumors. EPA would do well to reexamine this method.
>
> The database and results section closes with a discussion of "carcinogen
> with modes of action other than mutagenicity." It seems EPA simply had to
> concede not enough is known about the non-genotoxic chemicals at this time
> to conclude that they do or do not pose an increased cancer hazard to
> children at any dose. This was courageous and, given what is known, a
> valid position.
>
>
> Implementation Guidance for Assessing Cancer Risks from Early-Life
> Exposure
>
> This section is only about five pages in length, but EPA makes a number of
> recommendations that surely will stimulate discussion within the
> scientific community.
>
> In an attempt to give the Supplemental Guidance some substance, EPA offers
> some quantitative recommendations about estimating the cancer risk due to
> early life exposures. One must assume these recommendations were thought
> to be reasonable given the data presented in the animal studies and what
> was learned from the human experience with ionizing radiation. These
> recommendations, in fact, are useful for generating thoughtful discussion
> and for generating research hypotheses but are probably lacking sufficient
> foundation to warrant being the basis of EPA's future risk assessments of
> scenarios involving newborns or young children.
>
> The key recommendations within this section are almost certainly those
> listed in item 2a on page 34 of the Implementation Guidance section of the
> draft document:
>
> When the data indicate a mutagenic mode of action, the available
> science indicates that higher cancer risks typically result from a given

> exposure occurring early in life when compared with the same amount of
> exposure during adulthood. Consequently, in the absence of early-life
> studies on a specific agent under consideration, U.S. EPA generally
> should:
>
> Use linear extrapolation to lower doses. This choice is based on
> mode-of-action data indicating that mutagens can give risk to cancers with
> an apparently low-dose-linear response.
>
> Adjust risk estimates that pertain to childhood exposure. This
> choice is proposed because risk estimates based on a lifetime-average
> daily dose do not consider the potential for higher cancer risks form
> early life exposure. The following adjustments represent a practical
> approach that reflects the results of the preceding analysis, which found
> that cancer risks generally were higher from early-life exposure than from
> similar exposure durations in life:
>
> * For exposures before two years of age, a ten-fold adjustment.
> * For exposures between two and 15 years of age, a three-fold
> adjustment
> * For exposures after 15 years of age, no adjustment.
>
> These adjustments reflect the potential for early-life exposure to
> make a greater contribution to cancers appearing later in life; any
> differences in early life also should be accounted for.
>
> Other general recommendations are offered and although one can support
> many of them and take issue with others, they do not have the potential
> impact on health risk assessment of the above-mentioned recommendations.
>
>
> One View of the Guidelines
>
> It was only a matter of time before the environmental revolution, which
> began nearly 40 years ago, would have the luxury of having a serious
> debate about whether standards or guidelines initially established to
> protect both adults and children were truly adequate, since they were
> based on testing of mature animals or human studies of exposed adults.
> Many of the genuinely significant and obvious, public health hazards
> associated with the presence of industrial chemicals in our environment
> have been identified and regulated. To a large extent, the concentrations
> to which the vast majority of Americans are now exposed are quite small.
> It has been inferred that, therefore, the possible risks to the typical
> America must also be quite small.
>
> However, as EPA points out, an argument can be made that it is logical to
> infer children may well be at some greater risk of harm to some agents
> simply because they inhale and ingest larger quantities per body weight
> than adults, and because cell turnover is great during the periods of
> development; thus increasing the risk of mutations if there is exposure to
> a genotoxic agent. Indeed, this is true, if the doses which may result
> even from compliance with current environmental regulations do not have an
> appreciable margin of safety built into them. The scientific community
> does not have solid information to indicate the majority of current
> regulations do not have an adequate margin of safety to protect children.
> On the other hand, it is probably not possible to demonstrate complete

> safety one way or the other using either animal or epidemiology studies.
>
> This brings up a point worth mentioning. Ever since the passage of the
> Food Quality Protection Act of 1996, many people have suggested current
> exposure limits of all types (i.e., air, food, water, soil) were not
> intended originally to protect children or adults who were first exposed
> as children. This is not the case. Going back to the work of Dr. Arnold
> Lehman, children were considered by the FDA in the 1950s when tolerances
> were established using the safety factor approach. Children were also
> considered in the first Carcinogenic Risk Assessment Guidelines
> promulgated by EPA in 1976. One is hard pressed to find many examples
> where this approach has not been adequate to protect our children.
> However, as noted previously, it is equally difficult to show there is a
> large margin of safety inherent in these criteria.
>
> This particular Supplemental Guideline is, in all likelihood,
> representative of the next generation of guidelines to be issued in the
> United States and Western Europe. The goal is to keep the pressure on
> society to be vigilant about how it uses chemicals and releases them into
> the environment. To apply this pressure is, de facto, the duty of EPA.
> Twenty years ago, issuance of these kinds of guidance documents or
> assessments of particular agents was termed "science forcing." That is,
> EPA or other agencies announced it was going to issue strict regulations
> in light of the possible hazards to workers or society unless the
> regulated community would conduct the scientific research convincing them
> that the risk was, in fact, negligible. Regrettably, this approach has not
> been used frequently over the past decade.
>
> Some might claim, as EPA has indicated, that because this guidance is not
> binding, it will have only modest impact on how risk assessments are
> conducted in the coming years. This is probably naive. History is quite
> clear that even draft EPA guidelines take on a life of their own--both
> here and in other countries. Further, EPA headquarters has only limited
> control over what the agency's regional offices do with its draft or final
> guidelines. For those who might not believe this, one need only look at
> the decision by EPA Region V to rely on EPA's Draft Dioxin Reassessment as
> part of its justification for not accepting a rather important risk
> assessment submitted by Dow Chemical for its Midland site (even though
> reliance on draft documents is discouraged by EPA headquarters).
>
> Because of the increasing expectations of citizens for cleaner air, water,
> food, soil and sediments EPA has a mandate to be absolutely certain
> current guidelines are amply protective. This is the rub: The science on
> the increased susceptibility of children compared to adults is simply not
> available, and it may not be obtainable, to answer these questions. For
> this reason, adoption of the Precautionary Principle has significant
> appeal to some citizens and many nongovernmental organizations. Many may
> believe that it is regrettable, but for multiple reasons, legal and
> otherwise, EPA is not yet able to implement the Precautionary Principle.
> However, EPA is able to conduct analyses like those presented in the
> so-called "Children's Cancer Guidelines" and use them to suggest
> quantitative changes are needed in how the country conducts risk
> assessments. Whether this guidance meets the expectation of the new Data
> Quality Act is unclear.3
>
> When faced with the very sparse data upon which the recommendations are

> based, to the extent that EPA is in fact embracing the Precautionary
> Principle, it should say so. Perhaps, EPA would be better off to simply
> state that "in light of the concern about this possible hazard, we
> recommend that the following approach be implemented beginning one to five
> years from the date of issuance unless certain data gaps are filled.."
> Accordingly, it would be useful if the agency, based on its efforts to
> develop these guidelines, identified the areas of research that could
> potentially satisfy its concerns and negate the need for promulgating the
> recommendations in these guidelines. Perhaps the regulated community and
> academia then would rise to the occasion and help to inform future
> decisions about the possible risks associated with childhood exposures.
>
> Applying the "science forcing" approach is likely a more useful approach
> to achieving what the citizens expect of EPA without going through the
> process of trying to make the available data support a position for which
> the data are inadequate. Virtually all companies and scientists find it
> difficult not to support reducing the concentrations of chemicals in our
> environment, and it is especially difficult not to support efforts that
> might ultimately be of some benefit to our children. If EPA believes some
> action is needed, it would be more appropriate to simply say it is
> embracing the Precautionary Principle as the justification for its
> recommendations rather than try to rely on the available data.
>
> This is not to say that I embrace or reject the Precautionary Principle.
> For one thing, there are many different proposed approaches for
> implementing the principle. The advantage of the approach is that it is
> simple. Some variations of the principle, including those which require
> corporations to arbitrarily reduce emissions of specific contaminants by
> 50 percent every 5 years, have certain benefits over traditional
> approaches to dealing with chemicals. This approach has proven to be
> effective, for example, in the Scandinavian countries where it was applied
> to the emissions of dioxins. However, one of the biggest shortcomings is
> that the approach is expensive and a poor tool for prioritizing the
> hazards posed by the 2,000 or more chemicals used frequently in industry.
> In short, the hazard is that the nation might spend a great deal of money
> controlling trivial hazards at the expense of not dealing with those that
> are significant.
>
> EPA has probably done the best job that it can with what is known about
> the possible increased susceptibility of children but it is not sufficient
> to warrant the quantitative recommendations offered by EPA. If adopted,
> the costs of dealing with the more strict cleanup and emissions limits
> could be quite substantial. For example, already some prognosticators have
> used these guidelines to support requests to "reopen" Records of Decisions
> at Superfund sites across the nation. They allege "new evidence has been
> presented in these guidelines" and that one can infer these sites were not
> cleaned to standards which will protect children.
>
> There are, in my view, many other more pressing environmental issues
> worthy of our attention which don't require the leaps of faith that are
> needed to embrace these proposed guidelines. Eliminating certain known
> health hazards for children, improving the public education about
> lifestyle choices and promulgating rules for some chemicals in our
> environment which have yet to be regulated would almost certainly be more
> likely to improve the well being of children than applying these broad
> recommendations to future risk assessments. Nonetheless, as a society we

> have rightfully decided to focus on the potential hazard to children posed
> by chemicals in our environment, and I would not be opposed to supporting
> many of the recommendations in this Supplemental Guidance but it would be
> inappropriate for society to think that the "science was telling us to do
> it."
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> 1 "Draft Guidance on Cancer Assessments Called Major Step to Improve
> Analyses" (42 DEN A-9, 03/4/03).
> 2 The draft guidelines are available at
> http://www.epa.gov/ncea/raf/cancer2003.htm on the World Wide Web.
> 3 "EPA Guidelines for Information Quality Include Procedures for
> 'Influential' Data" (193 DEN A-1, 10/4/02) and "Drive Under Way to Enact
> Legislation On Data Quality, Access at State Level" (29 DEN A-14,
> 02/12/03).
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