NIOSH CIB 68: NIOSH Chemical Carcinogen Policy
NIOSH Responses to Peer Review Comments
December 15, 2016

Peer Reviewer	Reviewer Comment	NIOSH Response
1	**Classifying carcinogens** The proposed approach to identifying carcinogens (section 3) is clear and sound. I strongly support the proposal to draw from the work of the NTP, EPA and IARC. I agree that NIOSH should determine the GHS carcinogen classification of occupational carcinogens. I also agree that NIOSH should treat all carcinogens (GHS categories 1A, 1B and 2) the same, and assume that they are all capable of causing cancer in exposed workers. Looking ahead to future developments in toxicology, the policy should include reference to the possibility that additional authoritative sources of carcinogenicity evidence may be added to the list of sources for NIOSH's determinations. In particular, I believe that it will soon be acknowledged that judgments about carcinogenicity for new chemicals must be made on the basis of structure-activity and in vitro bioassay data alone. The only way that NIOSH will ever be able to approach a complete database of occupational carcinogens will be through assigning GHS classifications without animal or human evidence. While this is probably not currently feasible, I believe it will happen before long.	*NIOSH appreciates these supportive comments on the carcinogen classification strategy.* *In the final document, the section describing the NIOSH GHS classification process was removed to avoid confusion and to allow further development of that process. NIOSH appreciates that additional authoritative sources of carcinogenicity evidence may be available in the future. This policy does not prevent NIOSH from utilizing such information when it comes available for individual risk assessments. However, since we do not know what the structure of such future information will be, NIOSH has not addressed this issue in this policy.*

Peer Reviewer	Reviewer Comment	NIOSH Response
1	**Determining occupational relevance** I disagree with the draft policy's proposed approach to determining whether a carcinogen should be considered occupational. I propose that NIOSH take the position that all carcinogens are presumed to be relevant to some group of workers. If a member of the public wishes to contest this position for a particular chemical, the burden should be on that person to provide NIOSH with evidence demonstrating that the carcinogen should not be considered to be occupationally relevant. The policy should state that NIOSH will evaluate such evidence, and issue a judgment of whether or not to accept the position that the carcinogen will not increase the risk of cancer for any American worker. The default position should be that all carcinogens are occupationally relevant. There are very few, if any, known carcinogens for which no human (worker) exposure somewhere along the production, supply, use and disposal chain is possible. The other aspect of the determination of occupational relevance has to do with mechanism, and the possibility that a carcinogen acts by a mechanism which can't function in workers, because of the route of exposure for example. But mechanistic evidence for human carcinogens is rarely strong enough that NIOSH would confidently state that there is no chance that workers will be affected. The draft policy implies this on page 24, lines 11 -13, which state: "NIOSH would need compelling evidence to show that a …carcinogen…would not raise the risk of cancer in workers." I agree, and think that this situation is so unlikely that NIOSH is proposing an unnecessarily bureaucratic and resource-intensive process by suggesting that this determination needs to be made for every chemical singularly. A default assumption of occupational relevance is parsimonious and scientifically defensible. The flow chart in Figure 1 describing the carcinogen review process should not begin with the determination of whether occupational exposure is likely.	*This language was clarified to strengthen the presumption that all carcinogens are relevant to workers, although NIOSH intends to evaluate any compelling evidence indicating that a carcinogen might not pose an occupational hazard. NIOSH agrees that mechanistic evidence is rarely strong enough that it would indicate confidently that workers would not be affected. This language has been strengthened to indicate that any such determination would be rare. The bureaucratic burden should not be high because of the rarity of the situation.* *Figure 1 has been removed from this document based on reviewer input; it was found to be more confusing than helpful.*

Peer Reviewer	Reviewer Comment	NIOSH Response
	Occupational exposure should be a rebuttable presumption, as should the "occupational relevance" of the carcinogen data.	

Peer Reviewer	Reviewer Comment	NIOSH Response
1	**Recommended exposure levels** My strongest objection to the proposed draft policy is the plan to set RELs based on exposures likely to increase cancer risk for workers by 1 in 1,000 (10-3). This proposal errs in several important ways. First, I believe that NIOSH's statutory obligation to inform OSHA about safe exposures does not mean that NIOSH must choose a single "safe" exposure concentration to recommend. In the post-Benzene Supreme Court decision era, NIOSH can and should provide OSHA with the best available evidence about which exposure levels will likely result in excess cancer risks of 10-2, 10-3, 10-4, 10-5, and 10-6. These data would represent the most scientifically defensible evidence of "safe" exposures, as required under the OSHAct. Providing OSHA with the exposure-risk curve connecting these points would allow OSHA to pick a number for setting a PEL if it chose to do so. It would also place the responsibility for determining what risk was "acceptable" in OSHA's hands where it should appropriately lie. This is not a scientific judgment but a policy determination. NIOSH should determine the science and let OSHA set the policy. My second concern about section 5 of the draft policy is the proposal to use 1 in 1,000 as the risk level for setting RELs. Several other experts who have provided written and oral comments on the draft policy have made this point clearly: the Supreme Court did not say that 1 in 1,000 was the level of risk that OSHA should choose to set standards. The Court merely stated that this was the upper bound of the range in which this risk might lie. Were NIOSH to use 10-3 as the risk level upon which to base RELs, it would be validating a serious inequity by which workers would be legally exposed to much higher risks than the general public. This would be a major error, undermining NIOSH's role in protecting workers. It would also place NIOSH on the wrong side of history. The public is increasingly demanding safer products and materials, and more and more companies are finding it profitable to eliminate carcinogens from products because of this demand. The implication that NIOSH finds a 1 in 1,000 cancer risk to be acceptable sends the wrong	*NIOSH appreciates these comments on the risk levels. The discussion in this section of the document was revised to clarify that NIOSH provides a range of risk levels, which is our current and continuing practice. NIOSH responsibility goes beyond providing information to OSHA to provide useful information directly to employers on appropriate levels of protection. To that end, the policy has been revised to provide a Risk Management Level for Carcinogens (RML-CA) that will equate to a 1 in 10,000 risk level or the limit of quantification for the analytical method. This change in terminology from Recommended Exposure Limit acknowledges that there is no safe level for exposure to carcinogens and the RML-CA is a reasonable starting place for controlling exposures. NIOSH recommends that workplace exposures be kept below the RML-CA. The risk level that supports NIOSH recommendations (RML-CAs) has been amended to 1 in 10,000.*

Peer Reviewer	Reviewer Comment	NIOSH Response
	message about how the federal government views market-driven and voluntary trends towards safer products.	

Peer Reviewer	Reviewer Comment	NIOSH Response
2	A third problem that I see with the proposed methods for setting RELs has to do with analytical feasibility. The draft proposes a complex method for dealing with the problem that the exposure corresponding to a risk of 10-3 may not be measurable with current analytic methods. This gives rise to the proposal that sometimes the REL should be set as the level that can be measured, even if the resulting risk will be even higher than 10-3. NIOSH should never "recommend" (as in 'REL') that workers be exposed to a carcinogen at a level that will increase their risk by something greater than 1 in 1,000. Such a concentration should be more accurately labelled the TEL – Toxic Exposure Level. This entire problem (and the flow chart in Figure 2) is avoided if RELs are not set by NIOSH. Again, NIOSH should tell OSHA which risks are associated with which exposures, and then let OSHA decide what to do. The fourth problem that I see with the proposed approach to setting RELs is that it undermines the only scientifically-defensible approach to protecting workers from occupational cancer which is eliminating exposure completely. If this is the goal, then it follows that the only acceptable level that NIOSH should "recommend" would be zero. It is understood that this goal will not always be possible. But NIOSH undermines efforts to achieve this if it enshrines an unacceptably high risk in an REL. I believe that the NIOSH carcinogen policy should include recommendations similar to European Directive 2004/37/EC- Carcinogens or Mutagens at Work. Article 5 of this Directive on prevention and reduction of exposure contains a series of sound recommendations on what steps employers should follow to eliminate exposures whenever possible. When elimination is not possible, exposure reduction steps like enclosing processes and limiting the numbers of workers in the area are proposed.	*In response to this and other comments, NIOSH has revised its Chemical Carcinogen Policy. First, NIOSH emphasizes that there is no safe level of exposure to carcinogens and recommends the hierarchy of controls with substitution/elimination of hazardous chemicals at the top of the hierarchy. Second, NIOSH agrees that "recommending" an exposure limit for carcinogens may not adequately communicate NIOSH's concern for those exposures. To address this issue, NIOSH has changed its terminology so it will not be setting RELs for carcinogens. Instead, NIOSH will set Risk Management Limits for Carcinogens (RML-CA) which represent the starting place for controlling exposures. NIOSH will continue to encourage employers to control exposures to well below the RML-CA. Third, the RML-CAs will be set at a lifetime occupational cancer risk level of 1 in 10,000, when possible. This is below the 1 in 1000 level proposed in the public draft. In cases where the limit of quantification (LOQ) for the analytical method is higher than the concentration at a 1 in 10,000 risk level, NIOSH will set the RML-CA at the LOQ. NIOSH has determined that the ability to measure the chemical exposure is a critical component in a strategy to protect workers. NIOSH will communicate the risks at the RML-CA and also indicate the air concentration associated with* a *1 in 10,000 risk level, whenever possible.*

Peer Reviewer	Reviewer Comment	NIOSH Response
1	**Impacts on innovation** I was disappointed that the draft policy did not include more guidance on how to eliminate carcinogens from workplaces. I believe that NIOSH should state clearly that carcinogens should be controlled to the lowest feasible level, and that the first priority should be placed on eliminating them. NIOSH should recommend a formal alternatives assessment process for all carcinogens. Such a process can help to avoid the problem of regrettable substitution – replacing carcinogens with chemicals that are merely less-well studied but not necessarily safer. It should recommend policies like those noted above in Article 5 of the European Union directive. The policy should state that if a carcinogen cannot be eliminated, then exposure should be limited to the lowest feasible level. Toxicology is undergoing rapid change through expansion of the number of in vitro tests, dramatic improvements in predictive structure-activity models, and innovations in rapid and inexpensive automation of testing methods. These developments are leading to exponential increases in the amounts of data on chemical toxicity. At present, it is not clear how these biomarker data should be used to identify new occupational carcinogens. But the NIOSH carcinogen policy should acknowledge the potential benefits of in vitro data by inviting researchers and stakeholders to propose new sources of data for identifying carcinogens. At a minimum, the policy should state that additional sources of data will be adopted when their accuracy has been determined.	*NIOSH has decided to separate guidance on managing carcinogens from the Chemical Carcinogen Policy document. This guidance would include issues such as substitution and elimination of chemical carcinogens, selection of alternatives and related issues.* *While NIOSH has not specified methods of using additional sources of data in its carcinogen classification policy, the NTP, IARC and EPA all have mechanisms in place to address such data. In addition, when NIOSH classifies a carcinogen, the GHS criteria will be used. This criteria also has guidance on how to consider newer sources of data during classification.*

Peer Reviewer	Reviewer Comment	NIOSH Response
2	**Reviewer Summary statement on the updates:** This reviewer applauds NIOSH for their recent update on their Carcinogen classification and policies for setting of health based target risk levels. It is an important document that is thoughtful and develops a "doable" approach for time and effort efficient approaches for carcinogen classification and setting of target risk levels for chemical hazards. It is to be commended as it does not "re-invent" the wheel but uses resources from current agencies to identify carcinogens and thus meets their goal to "enhance the efficiency of assessing risks across the federal government". By utilizing hazard assessments conducted by the US NTP, US EPA, and IARC, NIOSH is able to focus on determining occupationally relevant context for chemicals of interest. They will utilize the scientific expertise and review of these extensive national and international bodies to focus on identification of chemical carcinogens. They will then review the chemicals for occupational relevancy and context and by doing this they do not set up a duplicative review process for hazards. They have also directly addressed earlier identified limitation where the term "potential occupational carcinogen" was used (NIOSH, 1978b). This approach also allows NIOSH to fully utilize their position as a founding member of NTP, an active member nominating chemicals of interest and also their representation on the executive board to ensure that NTP includes chemicals of interest as occupational carcinogens. NIOSH has also suggested chemicals for consideration by IARC and they have directly benefited from IARC's frequent approach to review chemical classes and chemicals of relevance for common usage of direct relevance for occupational settings. (See excellent examples from IARC on Benzedrine dyes, Beryllium and Beryllium Compounds and Anramine production.) The agency is also to be applauded for setting risk based recommended exposure levels (RELs) in a more transparent manner directly clarifying	*NIOSH appreciates these supportive comments.*

Peer Reviewer	Reviewer Comment	NIOSH Response
	approaches for when standards would fall below limits of quantification (LOQs) as well as policies for those agents detectable at the REL.	

Peer Reviewer	Reviewer Comment	NIOSH Response
2	**Question 1: Are the proposed carcinogen policies consistent with the current scientific knowledge of toxicology, risk assessment, industrial hygiene, and occupational cancer? If not, provide specific information and references that should be considered.** The approaches for carcinogen policies are consistent with current scientific knowledge of toxicology, risk assessment, industrial hygiene and occupational cancer. They are strengthened by illustrating how scientific expertise from three independent groups (USEPA, NTP, and IARC) will be assimilated to form the basis for NIOSH policies. They will use both national and International expertise. The NIOSH document does discuss each group's approach for classification and identifies where there are differences in how animal or other supportive information (mechanistic) is utilized in their deliberations. This discussion provides important supportive information for how NIOSH will include this information and still link with the GHS classification scheme. Although the document acknowledges the context for classification and does directly show the relationship with how NIOSH will use this information for quantitative evaluation it does not directly state the key limitations overall in using classification versus characterization systems, i.e. the variations in how mode of action and human relevance and potency are included in the rankings and how potency is not usually discussed simultaneously within the weight and strength of evidence. This reviewer feels that the document should explicitly state this fact. It is significant and because potency is not included in these classification schemes, agents that are classified as GHS category 1B or even 2 could be more potent but less certain human carcinogens. This is a significant concept that cannot be ignored when policies are established and could help to explain when or if RELs are lower for agents classified as category 2 carcinogens versus category 1 carcinogens in the GHS categories. This reviewer was glad to see that the revisions addressed risk based approaches for setting levels and feel that potency is addressed in this section of the materials.	*NIOSH acknowledges and appreciates the support for using EPA, NTP, and IARC expertise for carcinogen classification. The classification step is only the first step in characterizing occupational hazards. Full explication of how potency and mode of action considerations impact the development of recommended exposure limits (RELs) is beyond the scope of this document. NIOSH conducts quantitative risk assessment when possible to provide quantitative, health-based support for RELs. Quantitative risk assessment includes consideration of mode of action and potency, uncertainty and variability and modeling strategies. Discussion of these points is beyond the scope of this policy. The text was amended to strengthen the discussion of risk assessment and to clarify that the policy covers only specific points in the hazard characterization process: carcinogen classification, risk level, and feasibility of the analytical method. Additional information about all the steps in NIOSH occupational risk assessment can be found in recent NIOSH documents, including the NIOSH Hexavalent Chromium Criteria Document and NIOSH Current Intelligence Bulletin on Titanium Dioxide.*

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	NIOSH has also proposed a risk basis for identifying RELs which are now health based and which are included in the assessments and not just " as low as reasonably achievable" (ALARA) approaches. This action also should be applauded. In addition, this reviewer feels it is clearly significant to explicitly state that if good occupational safety and health is practiced fewer chemicals will ever be identified in Category 1A and more identified as Category 1B and 2. Thus the approaches to describe how the agency will address agents in these categories is very important. Ultimately, the goal is to prevent sufficient evidence in humans, thus reducing Category 1A carcinogens and this could be stated as well. The document discusses both linear and non-linear approaches for calculating RELs however it will be good to see additional documentation in a short appendix to the document that provides more technical references to modeling approaches. As stated there are limited examples and applications of this type of data in deciding the approaches to use.	

Peer Reviewer	Reviewer Comment	NIOSH Response
2	**Question 2: Is there additional scientific information related to the issues of the proposed NIOSH carcinogen policies that should be considered for inclusion? If so, provide information and specify references for consideration. Is there any discussion in the document that should be omitted?** Regarding Question 2 whether there is any discussion in the document that should be omitted; this author noted a strange "without context" statement referring to "hazard banding" in the initial short one page introduction (document page 9, line 32). This reviewer would suggest putting this into a future directions section at the end of the document with other items that NIOSH will be working on as the policies go forth. As it is currently placed it is undefined, without reference and appears to be an afterthought. This listing does not fit in with the other information and referencing and careful thinking in the overall document.	*The topic of hazard banding is not included in the final document. NIOSH has a separate published document on hazard banding and is developing a separate document on occupational exposure banding.*

Peer Reviewer	Reviewer Comment	NIOSH Response
2	**Question 3: Is the proposed carcinogen classification policy explained in a clear and transparent manner? Is the basis for the proposed policy adequately explained? If not, specify (section, page, and line number) where clarification is needed.** In general the document is directed, straight-forward and concise in its presentation. The document could provide additional information to discuss how information from new methods like biological activity in vitro and in silico evidence can be used to strengthen the classification of chemicals. A brief reference is made in the document in Section 3 however as this is a rapidly expanding area and much information is developing within USEPA assessments some further acknowledgement of this could be useful at this time. One of the challenges for occupational chemicals is that frequently decisions about substitute chemicals may need to be made prior to a time when fully developed databases are available. This is a challenge for making real time assessments. The document would benefit from a small but directed paragraph that acknowledges developing approaches for such types of evaluations. Would structure activity assessments be enough to trigger action and setting of a provisional REL? Would some decisions be made in the absence of a complete data set? Or in a situation where immediate action was needed? The document could give some indication how this might be handled. Similar sentences could be added to address the situation when related compounds are under consideration (see earlier comments on utility of the IARC monographs on their group or process related reviews) would the agency anticipate that decisions on a class of compounds might be made due to similarities. Please briefly indicate how NIOSH might use this type of information from an agency like IARC.	*NIOSH agrees that it is important to consider how additional information and methods, such as in vitro and in silico evidence, can be used to strengthen classification of chemicals. However, the classification portion of this document is directed at utilizing other authoritative organization classifications. To the extent that new methods are incorporated in those agencies' processes, NIOSH would directly consider them. While we appreciate the challenge of developing hazard characterizations on limited data, a full discussion of how such assessments would be made in an occupational setting is beyond the scope of this document. Much of the risk assessment community is struggling with this issue. NIOSH intends to consider these approaches on a case-by-case basis.*

Peer Reviewer	Reviewer Comment	NIOSH Response
2	**Question 4: Are there issues relevant to the classification of occupational carcinogens that have not been adequately addressed in this proposed policy? If so, provide information and specify references for consideration.** See above responses for Question 1 and 3.	*See responses above to comments about Questions 1 and 3.*

Peer Reviewer	Reviewer Comment	NIOSH Response
2	**Question 5: NIOSH adapted the OSHA Hazard Communication Table Relating Approximate Equivalences among IARC, NTP RoC, and GHS Carcinogenicity Classifications (Appendix F, Part D, OSHA Globally Harmonized System for Hazard Communication) to provide a simple, systematic method of determining GHS cancer hazard categories. However, NIOSH has further considered the GHS carcinogen categories 1B and 2 because NTP classification reasonably anticipated to be a human carcinogen and IARC classification 2B have criteria that overlap the two GHS categories. NIOSH has reviewed the criteria for GHS classification and has determined that chemicals classified by NTP as reasonably anticipated and chemicals classified as IARC 2B "that have sufficient evidence from animal data" meet the criteria for GHS Carcinogen Category 1B. Chemicals classified by NTP as reasonably anticipated and chemicals classified by IARC as 2b "that have limited evidence from animal data" meet the criteria for GHS Carcinogen Category 2. NIOSH is requesting comments on the validity of the NIOSH Correspondence table (Table 2) and its usefulness as a guide to determine GHS hazard categories.** This reviewer is supportive of this approach and this is illustrated in my comments above. This reviewer thought the information in Sections 3 and 4 provided the necessary background and context for the approach that they have chosen. The agency included good guidance that described the situation where a review of the chemical classifications would not agree and this reviewer was supportive of the considerations that NIOSH lists on page 24 lines 17-25 for review which include: differences in available data, differences in times of assessment and of course differences in use of mechanistic and mode of action information. NIOSH makes a clear statement that it will "..adopt the classification determined to be the most relevant to occupational exposures." This will be important criteria for application and evaluation. Has the agency evaluated the impact of these new approaches? For example	*NIOSH appreciates the supportive comments. NIOSH has clarified and reorganized the language regarding when NIOSH will use the classifications of EPA, IARC and NTP. With regard to the GHS categorization, NIOSH has removed that section from the document to avoid confusion and to allow further development. NIOSH has not developed a formal analysis of the impact of its approach on the number of carcinogens in each of the GHS categories. NIOSH will consider that during its development of the GHS categorization piece in the future.*

Peer Reviewer	Reviewer Comment	NIOSH Response
	has NIOSH determined the number of carcinogens in each of the GHS categories that they anticipate? Some indication of scale of impact could be good so a phased in approach could be considered.	

Peer Reviewer	Reviewer Comment	NIOSH Response
2	**Question 6: Is the proposed target risk level policy explained in a clear and transparent manner? Is the basis for the proposed policy adequately explained? If not, specify (section, page, and line number) where clarification is needed.** The NIOSH document presents a good summary of the historical basis for setting the target risk level for occupationally relevant carcinogens at 1 in a 1000 (based on the benzene trial precedence) however for this reviewer this discussion seems to focus on the legal rather than occupational health and safety considerations. Yes, as the document discusses in Section 5, in general other occupational health and safety actions have centered on levels in the range of 1 incident death in a 1000 for other occupational hazards such as construction. However, this reviewer noted that there was no discussion in this section on distribution of sensitivities of healthy workers. The document should explicitly state how the 1 in 1000 protection level might vary even among healthy workers. For occupationally relevant chemicals there is a significant literature on variation in healthy workers especially as workers can start younger and work longer that the time frame reflected in the referred to 45 year working lifetime. The document should at least acknowledge these facts and state that worker populations can be significantly variable and in taking central estimates that this does not reflect this variability. The document could go further and add an example or two for such occupational chemicals such as asbestos (age differences in susceptibility) or Beryllium (genetic variation). The more we know about genetic variability in populations we realize that workers can also have this range in variability for occupational settings and under conditions of primarily healthy working status. The document is silent in how such a genetic variability might be incorporated in NIOSH approaches yet this could be addressed by using the lower limit on REL estimates. Note that recent legislation that specifically does not allow anyone with a genetic predisposition to occupational chemical sensitivity to be excluded from the workplace suggest that some language is needed to recognize this consideration.	*NIOSH appreciates the issues of genetic susceptibility and the fact that some variability in the population may not be adequately accounted for, even with a 95% confidence interval. Lowering the RML-CA to correspond with a 1 in 10,000 excess cancer risk level will help to partially address this issue. In individual NIOSH documents, issues of genetic susceptibility and population variability are addressed more fully. This allows us to handle issues on a considered case-by-case basis.*

Peer Reviewer	Reviewer Comment	NIOSH Response
2	**Question 7: An analytical feasibility (AF) notation will be used to identify those RELs that are established to reflect the limitations of the sampling and analytical method (i.e., AF) and not the target risk level of 1 in 1,000. Is this notation adequately explained?** The notation for AF is explained adequately however please see the note below regarding use of AF designation.	*See response to Question 8 below.*
2	**Question 8: Is the proposed analytical feasibility and technical achievability policy explained in a clear and transparent manner? Is the basis for the proposed policy adequately explained? If not, specify (section, page and line number) where clarification is needed.** As stated above the document does explain how AF approaches and notation will be used. However, this reviewer does not fully agree with this scenario. Either standards are health based or they are not. If the standards do not meet the health basis then they should not be "best available technology" but rather "technology forcing". One could envision that for all those standards that are not health based then a more frequent review process or goal basis for reduction of exposures would be specified for implementation. Also a minimum requirement for analytical detection (LOQ) would be established with a health basis as the context. As proposed, there are no incentives to improve analytical detection and in fact in many cases a disincentive. One would imagine that a minimum acceptable health standard (risk) basis would be needed for the situations where current analytical methods do not allow for a REL setting on the 1 in 1000 risk level. Perhaps something like a minimum acceptable stand of quantitation of 1 in 100 should be set for limited time periods without an "open-ended" approach now proposed?	*NIOSH has determined that the risk management limit for carcinogens (RML-CA) should be set at a lifetime occupational cancer risk level of 1 in 10,000. However, when the limit of quantification (LOQ) of the analytical method is higher than the 1 in 10,000 risk level, the RML-CA will be based on the LOQ. NIOSH will provide the risk estimate at the LOQ when it is the basis of the RML-CA and also the 1 in 10,000 risk level in order to communicate risks consistently. NIOSH weighed the advantages of providing a purely health-based RML-CA with a value constrained by the LOQ, and has determined that measuring worker exposure is a critical component of developing a strategy to protect workers. Therefore, NIOSH will use the LOQ as the basis for the RML-CA when it is higher than the 1 in 10,000 risk level. However, NIOSH will simultaneously consider initiating research to develop new measurement methods.*

Peer Reviewer	Reviewer Comment	NIOSH Response
3	**(1) Are the proposed carcinogen policies consistent with the current scientific knowledge of toxicology, risk assessment, industrial hygiene, and occupational cancer? If not, provide specific information and references that should be considered.** In my opinion, the proposed policies are entirely consistent with the current state of our knowledge and understanding in these disciplines.	*NIOSH appreciates this support of this policy.*
3	**(2) Is there additional scientific information related to the issues of the proposed NIOSH carcinogen policies that should be considered for inclusion? If so, provide information and specify references for consideration. Is there any discussion in the document that should be omitted?** NIOSH has identified the sources of scientific information that will be relied upon for its hazard assessments. The proposed strategy of evaluating the occupational relevance of these classifications is a prudent, and efficient approach to fulfilling NIOSH's mandate to protect workers. There will always be uncertainty surrounding the classifications of NTP, IARC and EPA, but NIOSH is clearly capable of considering the scientific basis of these classifications as it evaluates their occupational relevance.	*NIOSH appreciates this support of this policy.*
3	**(3) Is the proposed carcinogen classification policy explained in a clear and transparent manner? Is the basis for the proposed policy adequately explained? If not, specify (section, page, and line number) where clarification is needed.** The policy is in my view clearly explained, as is the basis for the policy.	*NIOSH appreciates this support of this policy.*

Peer Reviewer	Reviewer Comment	NIOSH Response
3	**(4) Are there issues relevant to the classification of occupational carcinogens that have not been adequately addressed in this proposed policy? If so, provide information and specify references for consideration.** I found the discussion of the carcinogen classifications to be clear and thoughtfully explained. The use of the two examples (benzene and heptachlor) was an effective way to illustrate the implementation of this policy.	*NIOSH appreciates this support of this policy.*
3	**(5) NIOSH adapted the OSHA Hazard Communication Table Relating Approximate Equivalences among IARC, NTP RoC, and GHS Carcinogenicity Classifications (Appendix F, Part D, OSHA Globally Harmonized System for Hazard Communication) to provide a simple, systematic method of determining GHS cancer hazard categories. However, NIOSH has further considered the GHS carcinogen categories 1B and 2 because NTP classification reasonably anticipated to be a human carcinogen and IARC classification 2B have criteria that overlap the two GHS categories. NIOSH has reviewed the criteria for GHS classification and has determined that chemicals classified by NTP as reasonably anticipated and chemicals classified as IARC 2B ''that have sufficient evidence from animal data'' meet the criteria for GHS Carcinogen Category 1B. Chemicals classified by NTP as reasonably anticipated and chemicals classified by IARC as 2B ''that have limited evidence from animal data'' meet the criteria for GHS Carcinogen Category 2. NIOSH is requesting comments on the validity of the NIOSH Correspondence table (Table 2) and its usefulness as a guide to determine GHS hazard categories.** The approach depicted in the NIOSH Correspondence table (Table 2) is a rational and useful approach to guide these determinations. It is well-founded and will be very helpful in NIOSH's REL development process.	*The NIOSH GHS Carcinogen Classification process was removed from this document to avoid confusion and to allow further development. NIOSH will use the GHS criteria for carcinogenicity when developing a new chemical carcinogen classification.*

Peer Reviewer	Reviewer Comment	NIOSH Response
3	**(6) Is the proposed target risk level policy explained in a clear and transparent manner? Is the basis for the proposed policy adequately explained? If not, specify (section, page, and line number) where clarification is needed.** The proposed target risk level policy is explained but not well justified. What is the rationale, for example, for basing RELs set using epidemiologic data on the maximum likelihood estimate, or central estimate of the dose producing a 1 in 1,000 lifetime excess risk when RELs based on experimental animal data use the 95% lower confidence limit estimate of the dose producing a 1 in 1,000 lifetime excess risk? Then under the new policy, NIOSH will project both a central estimate and 95% lower confidence limit, and the REL will typically be based on the 95% lower confidence limit. What will be the practical effect of this approach? And in the case of epidemiologic data, is it likely that the dose-response data will support reliable estimates of the 95% lower confidence limit? How will that determination be made? By comparison with the earlier sections of the document, this discussion seems underdeveloped, it should be revisited. My previous comment does not speak directly to the choice of the 1 in 1,000 risk level, as I know NIOSH has already received many comments on this point (for example from the December 16 public meeting). I would simply echo the points others have raised, and ask whether setting a level at which risk is deemed to be significant (1 in 1,000) as the target for a policy to protect workers from cancer is good public health practice.	*Due to the large variability in many epidemiology studies (in exposure assessment as well as ascertainment of health effects), sometimes the central estimate is a more reasonable summary of the risk estimates. However, ideally, we would like to project both a central estimate and confidence limits for both animal and human data. The discussion in this section was amended to provide some clarification, but a full discussion of all the potential issues is beyond the scope of this document. A full discussion of all decision points and how the data are used and represented can be found in individual NIOSH criteria documents. With regard to the 1 in 1000 risk level, in the final document this has been revised in response to comments to a 1 in 10,000 excess cancer risk.*

Peer Reviewer	Reviewer Comment	NIOSH Response
3	**(7) An analytical feasibility (AF) notation will be used to identify those RELs that are established to reflect the limitations of the sampling and analytical method (i.e., AF) and not the target risk level of 1 in 1,000. Is this notation adequately explained?** The notation is adequately explained but the concept is flawed, my reasons for this observation are explained in question (8) below.	See response to question 8 comment below.

Peer Reviewer	Reviewer Comment	NIOSH Response
3	**(8) Is the proposed analytical feasibility and technical achievability policy explained in a clear and transparent manner? Is the basis for the proposed policy adequately explained? If not, specify (section, page, and line number) where clarification is needed.** The goal of addressing the misperception that all RELs are based solely on quantitative risk assessment of the health effects of chemical exposure is worthwhile. I think the correct approach, however, would be to actually base the RELs on health effects, and on the issue of analytical feasibility, include notations and explanations about the inadequacies of the measurement methods, but not make these limitations the determinants of the levels at which the RELs are set. The policy wanders into dangerous waters by stipulating that NIOSH will evaluate all existing analytical methods for the chemical and determine whether a method exists that is partially or fully validated. First, what will this validation include, a review of the literature? A set of laboratory and field trials? Second, what criteria will NIOSH apply to this validation, this needs to be specified. Then if a method does not exist, NIOSH will recommend research to develop a reliable method. To whom will that recommendation be made? Will NIOSH itself undertake a methods development and validation effort? Then in cases where an analytical method already exists, but the limit of quantitation is higher than the health-based target risk level, NIOSH will set the REL at the limit of quantitation of the sampling and analytical method. Research will be considered to improve the sensitivity and accuracy of the method. Research will be considered? So could a REL be set at a level that is clearly not health-protective and stay there while someone considers doing research on a measurement method? Clearly this approach is deeply flawed and needs to be reconsidered. The approach to considering feasibility of engineering controls is more rational, as Section 6.4.2 states that when lacking exposure	*The language has been clarified to specify that it will assess NIOSH and OSHA methods to determine whether a method exists that is partially or fully validated. NIOSH analytical methods and validation procedures can be found in the NIOSH Manual of Analytical Methods [http://www.cdc.gov/niosh/nmam/]. It has also been clarified that if there is no analytical method, it will consider initiating research to develop a method. NIOSH currently has a robust effort developing and validating analytical methods for measuring workplace exposures. NIOSH weighed the advantages of providing a purely health-based RML-CA with a value constrained by the LOQ, and has determined that measuring worker exposure is a critical component of a strategy to protect workers. Therefore, NIOSH will use the LOQ as the basis for the RML-CA when it is higher than the 1 in 10,000 risk level. However, NIOSH will simultaneously consider initiating research to develop new measurement methods.*

Peer Reviewer	Reviewer Comment	NIOSH Response
	measurement/control data, the absence of such data will be explained when the REL is set and NIOSH will recommend that research be conducted to determine the efficacy of existing engineering controls. This a much more sound and protective approach than that proposed for setting RELs based upon analytical feasibility. NIOSH should set the RELs based upon protection against health effects, then include notations, and recommendations to address inadequacies in measurement and control methods.	

Peer Reviewer	Reviewer Comment	NIOSH Response
4	**(1) Are the proposed carcinogen policies consistent with the current scientific knowledge of toxicology, risk assessment, industrial hygiene, and occupational cancer? If not, provide specific information and references that should be considered.** The proposed carcinogen policies achieve consistency with the current state of scientific knowledge by explicitly relying on the scientific authority of the NTP's Report on Carcinogens (RoC) process, the US EPA's carcinogen risk assessment guidelines, and the evaluation principles laid out by the International Agency for Research on Cancer (IARC). Although not the only relevant sources (additional insights are available from various publications on risk assessment methods by the National Academies, and from the State of California's Air Toxics Hot Spots: Technical Support Document for Cancer Potencies), these clearly lay out the current scientific position on the key issues, especially for cancer hazard identification. The additional reliance on the Globally Harmonized System for Hazard Communication (GHS) criteria is understandable from an organizational and practical standpoint, but this system needs to be recognized as a secondary authority only: as is to be expected from the bargaining product of a committee system representing diverse and in some cases incompatible interests this fall some way short of the scientific leadership provided by RoC, US EPA and IARC. The incorporation of insights on industrial hygiene and occupational exposure situations is consistent with the latest scientific knowledge, which is to be expected since NIOSH is itself one of the most respected authorities in this area.	*NIOSH appreciates the supportive comments on the NIOSH use of NTP, EPA and IARC assessments. The document was amended to remove the GHS read-across section in order to avoid confusion and for further development. The GHS carcinogen classification criteria are to be used by NIOSH when evaluating the carcinogenicity of a chemical substance independently. These criteria are similar in scope and effect to the NTP, IARC, and EPA criteria.*

Peer Reviewer	Reviewer Comment	NIOSH Response
4	**(2) Is there additional scientific information related to the issues of the proposed NIOSH carcinogen policies that should be considered for inclusion? If so, provide information and specify references for consideration. Is there any discussion in the document that should be omitted?** The treatment of hazard identification for carcinogens is thoroughly considered and explained, with primary reference to RoC, US EPA and IARC. However, when discussion turns to target risk levels the availability of cancer potency information (risk-specific intake levels or slope factors) for calculating this risk is assumed, but there is no recommendation or discussion of how these risk determinants are to be determined or obtained. This is a clear weakness in the current description of the target risk policy. There is an extensive scientific literature on this topic, but for the purposes of this policy statement this requirement could be addressed by referencing the dose-response analysis sections of US EPA's carcinogen risk assessment guidelines. (RoC and IARC deal primarily with hazard identification, and do not address dose-response assessment methodology directly). NIOSH may wish to suggest suitable sources for cancer potency information: US EPA's IRIS program and the EU's REACH program being obvious sources, but other US agencies (ATSDR, FDA, etc.) and State programs (California for example) may have values not available elsewhere. Given that occupational carcinogens may be relatively novel substances not much encountered outside certain workplaces it is necessary to provide at least some general guidance on how to derive potency estimates *ab initio*.	*NIOSH agrees that this policy does not address methods for calculating risk levels; it is not intended to. The text was amended to clarify that the intent of this policy is to address only three facets of carcinogen characterization: carcinogen classification, risk level and the feasibility of the analytical method.* *While it would be useful to have a full discussion of exposure-response modeling, that discussion is beyond the scope of this document. Examples of how NIOSH has conducted its exposure-response modeling can be found in recent policy documents such as the NIOSH Hexavalent Chromium Criteria Document and NIOSH Current Intelligence Bulletin on Titanium Dioxide.*

Peer Reviewer	Reviewer Comment	NIOSH Response
4	**(3) Is the proposed carcinogen classification policy explained in a clear and transparent manner? Is the basis for the proposed policy adequately explained? If not, specify (section, page, and line number) where clarification is needed.** For the most part the document is well written and explains both the basis and content of the carcinogen classification policy clearly. A few minor page and line level comments are provided below.	*Page and line level comments are addressed separately below.*
4	Page 23, line 19 et seq. The criteria for workplace relevance emphasizes the importance of inhalation and skin contact as routes of exposure to workplace hazards, in contrast to oral or other routes. However, in evaluating the significance of possibly oral route-specific carcinogenic effects, it should be noted that inhalation of particulates results in deposition of these particles in the lung, followed by their clearance via the mucociliary escalator and swallowing, resulting in a substantial portion of the dose eventually creating an exposure by the oral route.	*NIOSH recognizes that inhaling particles can result in exposure through the GI tract. However, the intent of this text is to clarify that the major occupational concerns are for inhalation and dermal exposures rather than chemical contaminants in drinking water or food. While oral exposure may be an important route of exposure for a specific substance, the primary exposure concerns for NIOSH assessments are inhalation and skin contact. For an individual substance being assessed, NIOSH considers all routes of exposure.*
4	Page 31, lines 7-23 In the discussion of linear and sublinear vs. threshold models, it is worth also clarifying that many of the biochemical mechanisms (e.g. receptor binding, Hill-type co-operative enzyme kinetics) proposed to contribute to the appearance of a threshold in fact show dose response characteristics which may be sub-linear in some concentration ranges but are nevertheless continuous functions with a non-zero slope at low doses rather than exhibiting a true threshold. As a general rule, all such continuous functions approach linearity at sufficiently low doses, although of course the slope at theses doses may be higher or lower than that observed at higher doses.	*NIOSH concurs with this comment. The discussion on modeling and on non-linear dose-response has been clarified.*

Peer Reviewer	Reviewer Comment	NIOSH Response
4	**(4) Are there issues relevant to the classification of occupational carcinogens that have not been adequately addressed in this proposed policy? If so, provide information and specify references for consideration.** The description of carcinogen classification given in the report follows and explains the procedures used by RoC, US EPA, IARC and GHS thoroughly and adequately with regard to the evaluation and interpretation of animal and human carcinogenicity data. However, the narrative gives insufficient attention to the importance of supporting data such as genetic toxicity, mechanistic information and structure-activity comparisons. This may partly be the result of deficiencies in the GHS analysis, but in any case should be corrected. US EPA and, especially, IARC provide thorough analysis of the proper role of these types of data in carcinogen classification. The National Academies have also repeatedly emphasized the importance of including mechanistic information (where available) in both hazard identification and dose-response analysis. These authorities have made it clear that this type of information is not a minor add-on which is only considered in resolving ambiguities in the bioassay data, or can be ignored if perceived as inconvenient to a desired conclusion. Rather, it is an important and fundamental part of the overall data on the carcinogenicity of the compound of interest, and needs to be carefully considered and its implications taken account of in all cases.	*NIOSH appreciates the importance of supporting data such as genetic toxicity, mechanistic data and structure-activity comparisons. However, the intent of this section of the policy is to streamline carcinogen classification by adopting IARC, NTP, or EPA classifications. To the extent that these organizations use that information, it will be directly incorporated in the NIOSH classification. When NIOSH classifies chemical carcinogens it intends to make use of all available data in its classification and also in its risk assessment. Language has been clarified in the text.*

Peer Reviewer	Reviewer Comment	NIOSH Response
4	**(5) NIOSH adapted the OSHA Hazard Communication Table Relating Approximate Equivalences among IARC, NTP RoC, and GHS Carcinogenicity Classifications (Appendix F, Part D, OSHA Globally Harmonized System for Hazard Communication) to provide a simple, systematic method of determining GHS cancer hazard categories. However, NIOSH has further considered the GHS carcinogen categories 1B and 2 because NTP classification reasonably anticipated to be a human carcinogen and IARC classification 2B have criteria that overlap the two GHS categories. NIOSH has reviewed the criteria for GHS classification and has determined that chemicals classified by NTP as reasonably anticipated and chemicals classified as IARC 2B ''that have sufficient evidence from animal data'' meet the criteria for GHS Carcinogen Category 1B. Chemicals classified by NTP as reasonably anticipated and chemicals classified by IARC as 2B ''that have limited evidence from animal data'' meet the criteria for GHS Carcinogen Category 2. NIOSH is requesting comments on the validity of the NIOSH Correspondence table (Table 2) and its usefulness as a guide to determine GHS hazard categories.** The apparent disconnect between the RoC reasonably anticipated and IARC 2B classifications on the one hand, and the GHS 1B and 2 on the other, is basically an artifact of the insufficient consideration of additional data types (genotoxicity, mechanism, structure etc.) in the GHS scheme. At least in the formal narrative the GHS evaluation relies more exclusively on the carcinogenicity data which, as noted above, is an insufficient representation of the current scientific understanding of carcinogenicity. However, the GHS decision tree does, as noted by NIOSH, allow for consideration of these additional types of data where available, although at least as represented in this NIOSH policy this seems to be left rather up to the discretion of the analyst. In practice this divergence is likely to affect only a relatively small number of cases overall, but these could be important for NIOSH since, as noted previously, occupational carcinogens may be relatively novel substances with carcinogenicity databases of smaller size and possibly lower	*The GHS Carcinogen Classification cross-walk procedure was removed from the final document to avoid confusion and to allow further development. NIOSH will use the GHS criteria for carcinogenicity when developing a new chemical carcinogen classification. NIOSH particularly appreciates this reviewer's perspective on the difference between IARC 2B and GHS 1B and 2 and will consider this during the development of the GHS Carcinogen Classification process piece in the future.*

Peer Reviewer	Reviewer Comment	NIOSH Response
	overall quality than more widespread and therefore more extensively studied chemicals. In any event, NIOSH should be considering the additional data types in these cases in reaching a final classification. NIOSH should rely on the consideration of these data by IARC and/or RoC when generating GHS classifications, rather than taking the option of either considering or ignoring this evidence as appears to be proposed in the draft NIOSH policy. Thus an IARC 2B should be considered a GHS 1B, including cases where additional evidence is used to support less than perfect carcinogenicity data. In cases where IARC and RoC have not provided an evaluation, NIOSH can undertake the analysis independently, and will reach similarly scientifically sound conclusions if the IARC guidance (in particular) is followed.	

Peer Reviewer	Reviewer Comment	NIOSH Response
4	(**6) Is the proposed target risk level policy explained in a clear and transparent manner? Is the basis for the proposed policy adequately explained? If not, specify (section, page, and line number) where clarification is needed.** For the most part the policy is clearly described, although as noted previously there is currently no direction for determination of slope factors or other measures of carcinogenic potency. However, both the policy itself and its alleged basis have some logical flaws which need to be addressed. The actual basis appears in fact to be mainly historical, citing a 1980 Supreme Court decision on benzene and subsequent use of the 1 in 1000 target risk level for many years. This can be seen as an explanation for its continued use, but hardly a justification. The policy does acknowledge that this is a minimum level of protection, but do not offer any real procedure or incentive to improve on this very lax standard for public health protection. Moreover, the discussion (page 32, lines 15-30) misrepresents the general interpretation of carcinogenic risk levels by federal regulators and others. It is stated that "for chemical exposures to large populations, the risk level of concern is 1 in 10,000 (10-6). This is simply not true: the de minimis risk level for carcinogenic exposures is universally taken as 1 in 106, and any increment above this is seen as an undesirable increment in risk. Programs typically recognize that this level of risk cannot always be achieved at reasonable cost and without other potentially undesirable consequences however, so actual regulatory actions may tolerate somewhat higher risks attributable to an identifiable cause before demanding remedial action. This range of discretion is usually considered to extend up to 10-5 or 10-4 depending on the situation. But virtually all such programs regard a risk of 10-4 as the upper limit of what is tolerable, not the threshold for concern. This level is normally seen by Superfund and other regulators as the trigger to "send in the cavalry" and shut down or dig up the offending situation. That NIOSH continues to use a historical standard ten times less health	*The risk level supporting the Risk Management Limit for Carcinogens (RML-CA) has been revised to 1 in 10,000 excess cancer risk in response to this and other peer review and public comments. The RML-CA is a level at which control strategies should be undertaken to reduce exposures below this level.*

Peer Reviewer	Reviewer Comment	NIOSH Response
	protective than that generally accepted control level seems undesirable. It is recognized that occupational health standards are generally expected to be less stringent than those applied to the general population. For non-cancer effects, it is commonly recognized that variation in sensitivity among the general population is greater than among workers, who are typically younger, healthier and often less diverse in gender and ethnicity. This may be seen as reducing the necessary uncertainty factor used in REL development to allow for human intraspecies variability. Workers also typically self-select to some extent when minor health impacts are perceptible, since those more sensitive to an adverse impact of the working environment may choose to leave and get a different job. However it is not clear that these contributors to the well-known "healthy worker effect" necessarily apply to sensitivity to carcinogens. (The healthy worker effect may well select workers to have a lower incidence of cancers from non-work related causes, but this is not the same as changing the sensitivity to the occupational carcinogen). Due to the long lead time and stochastic nature of cancer incidence it is unlikely that any substantial self-selection can occur. Similarly, since the underlying basis of individual sensitivity to carcinogenesis is largely unknown it cannot be assumed that the lesser diversity of the workforce has any protective effect either. NIOSH should consider these objections to its current proposal and present discussion of them to support its final selection of a target risk level for development of RELs for carcinogens.	

Peer Reviewer	Reviewer Comment	NIOSH Response
4	**(7) An analytical feasibility (AF) notation will be used to identify those RELs that are established to reflect the limitations of the sampling and analytical method (i.e., AF) and not the target risk level of 1 in 1,000. Is this notation adequately explained?** This notation is clearly explained in the policy. In quoting from the NIOSH REL policy (page 34, lines 21-22) it appears that NIOSH will, in cases where the AF restriction needs to be applied, identify both the health-protective target level (which for a carcinogen would be based on the chosen maximum acceptable risk standard) and the final AF qualified REL. This is important for transparency and general understanding of the REL derivation in such cases. In situations where the divergence between these figures is large it also highlights the urgency of analytical method development.	*NIOSH has determined that the risk management limit for carcinogens (RML-CA) should be set at a lifetime occupational cancer risk level of 1 in 10,000. However, when the limit of quantification (LOQ) of the analytical method is higher than the 1 in 10,000 risk level, the RML-CA will be based on the LOQ. NIOSH will provide the risk estimate at the LOQ when it is the basis of the RML-CA and also the 1 in 10,000 risk level in order to communicate risks consistently. NIOSH weighed the advantages of providing a purely health-based RML-CA with a value constrained by the LOQ, and has determined that measuring worker exposure is a critical piece in developing a strategy to protect workers. NIOSH will use the LOQ as the basis for the RML-CA when it is higher than the 1 in 10,000 risk level. NIOSH will also simultaneously consider initiating research to develop new analytical measurement methods.*

Peer Reviewer	Reviewer Comment	NIOSH Response
4	**(8) Is the proposed analytical feasibility and technical achievability policy explained in a clear and transparent manner? Is the basis for the proposed policy adequately explained? If not, specify (section, page, and line number) where clarification is needed.** The basis for using the analytical feasibility limitation is clearly explained, including the flow chart figure on page 37 which is helpful in clarifying the process. This is obviously an inevitable constraint on setting useable RELs for both carcinogens and non-carcinogens. The basis for identifying engineering achievability (section 6.4.2 beginning line 28, page 35) is not so clearly explained. It would appear that RELs will no longer be modified to allow for achievability (page 36, line 2), but this statement could be made clearer and more definitively. It appears that any feasibility assessment will be handled in supporting documentation for the REL. This is necessarily going to be case-specific in terms of the detailed implementation, but there is a lack of even general principles in this section of the carcinogen policy. As in the case noted above for AF RELs it is important for transparency and general understanding that both health-goals and any target levels reflecting engineering constraints be separately identified in any determination of required control measures and exposure limits.	*NIOSH established a 1 in 10,000 as the risk level corresponding to the maximum worker exposure concentration that risk management efforts should control to. NIOSH will disassociate this risk level with the terminology, "recommended exposure limit" (REL), and will instead use the terminology "risk management limit for carcinogens" (RML-CA). In this case, 1 in 10,000 is the risk level corresponding to the concentration at which NIOSH will set the RML-CA, but this value should only be considered a starting point for continually reducing exposures in order to lower the remaining risk. NIOSH has established the terminology RML-CA instead of REL to bring the language used for NIOSH recommendations consistent with the recognition that there is no safe exposure concentration for carcinogens. If the RML-CA cannot be accurately measured at the 1 in 1000 risk level the RML-CA will be set at the limit of quantitation (LOQ) of the analytical method. NIOSH will not consider the capability of controlling exposures (i.e., engineering achievability) in setting the RML-CA. However, NIOSH will continue to evaluate available information on existing engineering controls and make that information available when publishing RML-CAs.*

Peer Reviewer	Reviewer Comment	NIOSH Response
5	IARC is now evaluating potential carcinogens in the context of specific tumors in humans, rather than just giving an overall assessment without this. Would be good for NIOSH to do the same.	*In its risk assessments on individual chemicals, NIOSH does evaluate carcinogens with regard to specific tumors and that information would be included in NIOSH assessments. However, NIOSH intended this policy to provide a basis for classifying the carcinogenicity of a chemical, rather than providing further information on the specific tumors in humans, therefore, the text was not amended for this comment.*
5	One thing that is lacking through-out is an appreciation for the role the biomarkers have played and will continue to play in evaluating the carcinogenic potential of workplace agents in workers. On page 23, only human studies evaluating cancer as an endpoint are mentioned. High quality human studies of relevant, intermediate endpoint biomarkers (e.g., cytogenetics, hematotoxicity, etc.) have been used by IARC in its evaluation of carcinogenic potential for many years and in some instances have made the difference between how a chemical was classified. NIOSH should be using these studies conducted in humans (in addition to studies conducted in animals) when considering carcinogenic potential as well. This is particularly the case when epidemiological studies (also, these should be defined more clearly....is it meant to refer only to studies of cancer as an endpoint, or to all studies conducted in humans?) of cancer are equivocal. In this instance, the next type of evidence that should be reviewed are epidemiological studies of biomarker endpoints (sometimes referred to as molecular epidemiology studies) in workers. Finally, molecular epidemiology studies are particularly important when a new compound has been introduced into the workplace and not enough time has occurred for cancer to have arisen. Indeed, NIOSH is conducting such studies of workers exposed to man-made nanoparticles for this very purpose.	*NIOSH appreciates this information about additional data, such as biomarker data and molecular epidemiology studies, that may be useful for chemical assessments. For many carcinogens, NIOSH will adopt IARC, NTP or EPA classifications. To the extent that these organizations use these data in their assessments, such as IARC as indicated in the comment, that information will be incorporated into the NIOSH classification. When NIOSH classifies and assesses chemical carcinogens, it intends to assess all available data. This language has been clarified in the text.*
5	Overall, nicely written and a very effective update.	*NIOSH appreciates this support of this policy.*

Peer Reviewer	Reviewer Comment	NIOSH Response
6	One serious risk communication problem with that discussion was immediately apparent from its title: “Target Risk Level for Carcinogen RELs.” An ordinary citizen confronting the term “target risk level” for the first time and trying to understand what it means would deduce that a target risk level must be the optimum level of risk – and would instantly judge that the target risk level for occupational chemical exposures ought to be zero. What NIOSH is trying to identify isn’t a target risk level; it’s an acceptable risk level.	*NIOSH agrees that the "Target Risk Level" terminology could be potentially confusing and has removed that language from the document. The language now refers to risk levels at the Risk Management Limit for Carcinogens (RML-CA).*

Peer Reviewer	Reviewer Comment	NIOSH Response
6	Similarly, much depends on whether "REL" means "recommended exposure level" or "recommended exposure limit." The former sounds like the optimum amount of exposure to a risky substance (wouldn't that be zero again?), whereas the latter is presumably the maximum amount of exposure NIOSH thinks regulators should tolerate. The document itself defines "REL" as "recommended exposure limit." But it uses the full phrase only occasionally; usually it just says "REL." And Google shows plenty of other sources (including dictionaries of acronyms) that define REL as recommended exposure level. The intermingled use of REL and "target risk level" throughout Section 5, not just in its title, could easily leave the impression that NIOSH is comfortable with some target (goal) other than trying to minimize chemical exposures and their associated risk. I realize that these terms have a regulatory history, and are probably not ambiguous to readers familiar with that history. And I realize that NIOSH anticipates few if any lay readers. But if risk communication is nonetheless worth some attention, I would recommend abandoning the concept of a "target risk level." I'd be much happier with "target maximum risk level," inelegant though that is. And I would recommend emphasizing that a REL isn't a recommended level of exposure, it's a recommended limit on exposure, a recommended maximum. In a nutshell, NIOSH is trying to figure out how much risk it thinks employers should be permitted to impose on their employees, so that it can calculate how much exposure to specifed substances it thinks should be permitted, based on much risk it thinks is associated with that amount of exposure. NIOSH should say precisely that, clearly and often throughout the document.	*The NIOSH REL has always signified "recommended exposure limit" to the occupational safety and health community but agrees this may not be clear to lay readers. NIOSH has attempted to further clarify the issue by stating more clearly and strongly that no exposure to a carcinogen is safe and changing the limit for carcinogens to a Risk Management Limit for Carcinogens (RML-CA) to emphasize that exposures should be controlled below that level and not to imply that it is a recommended exposure.*

Peer Reviewer	Reviewer Comment	NIOSH Response
6	It follows for me that NIOSH should explain in some detail why it thinks it ought to produce such recommendations. As the Introduction to Section 5 notes, "[h]istorically, NIOSH did not typically issue quantitative RELs for carcinogens; instead, the Institute recommended that carcinogen exposures be reduced to the lowest feasible level." I understand why you would need to decide how much occupational risk ought to be acceptable before you can decide how much occupational exposure to some substance ought to be acceptable. But I consider it a well-established principle of epistemology and the social studies of science that risk acceptability is not a scientific judgment; it is a trans-scientific value judgment. Regulators have no choice but to make that value judgment. But since NIOSH is not a regulator, why must it do so as well?	*NIOSH has determined that to be useful for employers, the recommendations for controlling workplace chemical exposures must have a numerical value. Otherwise, "as low as feasible" can be construed as "as low as can be technologically achieved" or "as low as an employer can afford"; neither of these is tied to health risks in any way. A numerical value tied to a specified risk level allows employers to make informed decisions about worker protection.*
6	As a science-based agency, NIOSH should arguably confine itself to advising all participants in the values debate about the exposure-risk (dose-response) relationship for various substances. "Here's what we think we know so far about how much exposure entails how much risk. Here is our best estimate. Here are our 95% confidence limits. If you know that employees have X amount of exposure to this substance, we think the likeliest amount of cancer risk employees are bearing as a result is Y, and we're 95% sure they're not bearing more risk than Z. Alternatively, if you want to be 95% sure not to impose more risk than Z on employees, you have to keep their exposure below X." These are scientific claims, based on data and modeling. They can usefully inform a values debate over how much exposure is acceptable to specific substances under specific circumstances. NIOSH proposes to go beyond informing that debate; it wants to recommend what the outcome of the debate should be, based on the scientific evidence alone. My initial reaction is that it shouldn't do so. At the very least, it should explain why it has chosen to do so.	*This is an interesting perspective on separating the policy from the science in setting a risk level. NIOSH has carefully considered this issue and while it is important to be clear about the science, such as how much risk is associated with varying exposures, it is also important to give employers guidance on an appropriate level of protection. We agree that this falls under policy considerations rather than science. NIOSH will provide both the risks associated with varying levels of exposure (with measures of uncertainty and variability where appropriate) and to provide a single Risk Management Limit for Carcinogens that is set at an exposure limit associated with 1 in 10,000 excess risk of cancer from working lifetime exposure or the analytical method limit of quantitation, whichever is higher. This recognizes that for practical purposes, employers need a numerical value to*

Peer Reviewer	Reviewer Comment	NIOSH Response
		serve as a starting place for reducing exposures and that it is important that the substance be measureable in the workplace. NIOSH has amended the text in the document to clarify its reasoning.

Peer Reviewer	Reviewer Comment	NIOSH Response
6	Only then does it make sense for NIOSH to go to explain why the "target maximum risk level" it has chosen is one-in-a-thousand. At first glance, NIOSH seems to be relying here on the Supreme Court's benzene decision. As Section 5 explains, the Supreme Court said that "a reasonable person might well consider" one-in-a-thousand to be a "significant" risk, whereas one-in-a-billion "clearly could not be considered significant." So, Section 5 sensibly concludes, "the threshold for a 'significant' risk must lie within this interval." This is a (legal) rationale for not setting the recommended maximum risk any higher than one-in-a-thousand. But it is not a rationale for setting it at one-in-a-thousand, rather than choosing a more conservative (lower) maximum risk. NIOSH's rationale for sticking to one-in-a-thousand appears to be twofold: (a) Various fatality risks higher than one-in-a-thousand appear to be tolerated, in venues other than occupational carcinogen risk; and (b) NIOSH has sometimes used one-in-a-thousand before. I doubt readers whose personal values preferences are more conservative would find either point compelling.	*NIOSH received many comments from peer and public reviewers regarding the 1 in 1000 risk level published in its draft document and found merit in them. In response, NIOSH has revised its Risk Management Limit for Carcinogens so that exposure to a carcinogen would not increase excess cancer risk by more than 1 in 10,000.*

Peer Reviewer	Reviewer Comment	NIOSH Response
6	It's worth mentioning that NIOSH's choice of one-in-a-thousand is more conservative than it will sound to readers who miss the point that the REL will "typically" be the exposure associated with a 95% lower confidence limit, not a central best estimate. I don't like "typically" here; it sounds like a loophole. But leaving that aside, you're not proposing to recommend that regulators allow a level of exposure that will probably add a one-in-a-thousand cancer fatality risk for a worker who works with that substance at that level of exposure for 45 years. You're proposing to recommend to regulators that they keep the level of exposure to that substance sufficiently low that a worker could work with that substance at that level for 45 years and still be 95% sure of increasing his or her cancer fatality risk by less than one-in-a-thousand. Assuming that roughly one-third of us die from some kind of cancer (that number sticks in my mind), this would mean a worker would be 95% sure his/her cancer fatality risk would go up from 333-in-a-thousand to less than 334-in-a-thousand. And even this is your recommended worst case. If I am reading the document correctly, you seem to be saying that regulators should set even lower standards where they can do so cost-effectively – but that regardless of cost-effectiveness they should not permit employers to expose their employees to any chemical to an extent that has more than a 5% chance of imposing a lifetime cancer risk greater than one-in-a-thousand.	*NIOSH appreciates this perspective regarding the communication of the risk. The issue in this case is about the excess risk of cancer attributable to exposure to the carcinogen of interest rather than the overall cancer risk. The goal is to reduce the attributable risk of cancer from workplace exposure to a carcinogen as low as possible. In the draft document, NIOSH had proposed keeping exposures below the 95% confidence limit for 1 in 1000 excess cancer risk. In the final document, NIOSH has changed that value to 1 in 10,000, in response to peer review and public comments. There was also an attempt to improve the risk communication as suggested.*

Peer Reviewer	Reviewer Comment	NIOSH Response
6	Of course there are other ways your proposed standard is less conservative than it might seem. For example, each chemical is apparently to be assessed independently, without regard to their combined (and possibly synergistic) effects. I would urge you to do a better job of explaining the ways in which your proposed one-in-a-thousand standard is more protective of employee health than it might seem (as well as the ways in which it is less protective than it might seem). But more fundamentally, I would urge you to do a better job of explaining why you picked one-in-a-thousand rather than a more protective number. (The benzene decision, as you interpret it, wouldn't have let you pick a less protective number. Thus you picked the least protective number you could; you need to admit that and explain why.) And more fundamentally still, I would urge you to do a better job of explaining why you picked any number at all, trying to preempt a values debate with a science-based answer. At the very least, I think the document should acknowledge that there is and ought to be such a values debate.	*The NIOSH RML-CA process does consider each chemical separately and a worker may be exposed to many chemicals and chemical mixtures in their working life. This is another reason it is important to reduce the attributable excess risk to 1 in 10,000. NIOSH has amended the text in the document to better explain the reasoning for the RML-CA risk level and the strengths and limitations of selecting a risk level.*

Peer Reviewer	Reviewer Comment	NIOSH Response
6	What should a thoughtful citizen pondering the proposed NIOSH policy keep in mind? Here's a partial list of values-related points that NIOSH might productively include in the document: • Nothing is risk-free, and how safe is safe enough is fundamentally a values question, not a scientific question. Different people have different answers to that question, and any policy risk-related proposal will seem excessively protective to some and insufficiently protective to others. • Moreover, most people's judgment of how safe is safe enough varies with the situation. Among the documented sources of this variability are these: o Many people believe that occupational risks are acceptable at a higher level than risks to bystanders. o Many people believe that voluntary risks are acceptable at a higher level than coerced risks. o Many people believe that risks that offer commensurate benefits to the risk-bearer are acceptable at a higher level than risks that confer no such benefits. o Many people believe that risks that are especially dreaded, such as cancer risks, are acceptable at a lower level than risks that are less dreaded. o Many people believe that the cost of reducing a risk and the availability of alternatives should be considered in deciding what level of risk is acceptable. • Science can usefully inform this values debate with information about how much risk various situations entail. The extent to which this scientific evidence should influence or even preempt the values debate is itself a values debate. But everyone agrees that the scientific evidence is at least relevant.	*NIOSH appreciates the values debate that goes into determinations of "safe" levels for various applications. NIOSH will provide a clear description of the underlying science, but also a policy decision on an appropriate exposure concentration for the Risk Management Limit for Carcinogens. This concentration corresponds to an excess cancer risk level of 1 in 10,000. NIOSH has carefully considered this risk level and believes that this risk level incorporates values and concerns expressed by peer reviewers and stakeholders and provides a practical level at which risk management efforts should begin.*

Peer Reviewer	Reviewer Comment	NIOSH Response
6	And here are some points about the science itself that NIOSH might productively include: • The science of assessing cancer risk from chemical exposures is much stronger than it was in past decades, and continues to improve. • Nonetheless, it has many weaknesses. Human epidemiology can identify only the largest impacts. So we rely heavily on data from animal toxicology, and then on modeling to extrapolate to humans. To oversimplify unfairly: We measure the impact on small groups of rodents of large doses of one substance at a time over a short period of time, and then we try to deduce the impact on large groups of human beings of small doses of many substances at once over a long period of time. • The science is especially weak in assessing the cumulative and possibly synergistic effects of multiple chemicals, and in assessing the risk to especially vulnerable individuals. • The weakness of the science in carcinogen risk assessment justifies considerable tentativeness, humility, and skepticism in applying its findings. • It also justifies considerable conservativeness. In various ways we put our thumb on the scales, overestimating the risk in order to be fairly confident we are not underestimating it. For example, we typically pay more attention to the lower 95% confidence limit of a risk estimate than we do to the estimate itself; that is, we rely less on our best guess of what the risk actually is than on a risk estimate we think will be too high 95% of the time, and too low only 5% of the time.	*NIOSH appreciates these issues that impact the science of risk assessment. In each of its criteria documents, NIOSH attempts to carefully explain the strengths and limitations of the underlying science. In uncertain situation, NIOSH tends to err on the side of worker protection, as suggested by this reviewer. While we appreciate the complexity of cumulative risk assessment, it is beyond the scope of this carcinogen policy document to address this issue.*