
FEDERAL REGISTER

Vol. 79 Friday,

No. 197 October 10, 2014

Part II

# Department of Labor

Occupational Safety and Health Administration

29 CFR Parts 1910, 1915, 1917, et al.

Chemical Management and Permissible Exposure Limits (PELs); Proposed Rule

**DEPARTMENT OF LABOR**

**Occupational Safety and Health Administration**

**29 CFR Parts 1910, 1915, 1917, 1918, and 1926**

**[Docket No. OSHA 2012–0023]**

**RIN 1218–AC74**

## Chemical Management and Permissible Exposure Limits (PELs)

**AGENCY:** Occupational Safety and Health Administration (OSHA), DOL.

**ACTION:** Request for Information (RFI).

**SUMMARY:** OSHA is reviewing its overall approach to managing chemical exposures in the workplace and seeks stakeholder input about more effective and efficient approaches that addresses challenges found with the current regulatory approach. This review involves considering issues related to updating permissible exposure limits (PELs), as well as examining other strategies that could be implemented to address workplace conditions where workers are exposed to chemicals. The notice details the role of past court decisions on the Agency's current approach to chemical management for the purpose of informing stakeholders of the legal framework in which the Agency must operate. It then describes possible modifications of existing processes, along with potential new sources of data and alternative approaches the Agency may consider. The Agency is particularly interested in information about how it may take advantage of newer approaches, given its legal requirements. This RFI is concerned primarily with chemicals that cause adverse health effects from long-term occupational exposure, and is not related to activities being conducted under Executive Order 13650, Improving Chemical Facility Safety and Security.

**DATES:** Comments must be submitted by the following dates:

*Hard copy:* must be submitted (postmarked or sent) by April 8, 2015.

*Electronic transmission or facsimile:* must be submitted by April 8, 2015.

**ADDRESSES:** Comments may be submitted by any of the following methods:

*Electronically:* Submit comments electronically at: *www.regulations.gov,* which is the Federal eRulemaking Portal. Follow the instructions online for making electronic submissions.

*Fax:* Submissions no longer than 10-pages (including attachments) may be faxed to the OSHA Docket Office at (202) 693–1648.

*Mail, hand delivery, express mail, or messenger or courier service:* Copies must be submitted in triplicate (3) to the OSHA Docket Office, Docket No. OSHA–2012–0023, U.S. Department of Labor, Room N–2625, 200 Constitution Avenue NW., Washington, DC 20210. Deliveries (hand, express mail, messenger, and courier service) are accepted during the Department of Labor and Docket Office's normal business hours, 8:15 a.m. to 4:45 p.m. (E.T.).

*Instructions:* All submissions must include the Agency name and the OSHA docket number (*i.e.* OSHA–2012–0023). Submissions, including any personal information provided, are placed in the public docket without change and may be made available online at: *www.regulations.gov*. OSHA cautions against the inclusion of personally identifiable information (*e.g.,* social security number, birth dates).

If you submit scientific or technical studies or other results of scientific research, OSHA requests that you also provide the following information where it is available: (1) Identification of the funding source(s) and sponsoring organization(s) of the research; (2) the extent to which the research findings were reviewed by a potentially affected party prior to publication or submission to the docket, and identification of any such parties; and (3) the nature of any financial relationships (*e.g.,* consulting agreements, expert witness support, or research funding) between investigators who conducted the research and any organization(s) or entities having an interest in the rulemaking. If you are submitting comments or testimony on the Agency's scientific and technical analyses, OSHA requests that you disclose: (1) The nature of any financial relationships you may have with any organization(s) or entities having an interest in the rulemaking; and (2) the extent to which your comments or testimony were reviewed by an interested party prior to its submission. Disclosure of such information is intended to promote transparency and scientific integrity of data and technical information submitted to the record. This request is consistent with Executive Order 13563, issued on January 18, 2011, which instructs agencies to ensure the objectivity of any scientific and technological information used to support their regulatory actions. OSHA emphasizes that all material submitted to the rulemaking record will be considered by the Agency to develop the final rule and supporting analyses.

*Docket:* To read or download submissions or other material in the docket go to: *www.regulations.gov* or the OSHA Docket Office at the address above. All documents in the docket are listed in the index; however, some information (*e.g.* copyrighted materials) is not publicly available to read or download through the Web site. All submissions, including copyrighted material, are available for inspection and copying at the OSHA Docket Office.

**FOR FURTHER INFORMATION CONTACT:** *General information and press inquiries:* Mr. Frank Meilinger, Director, Office of Communications, U. S. Department of Labor, Room N–3647, 200 Constitution Avenue NW., Washington, DC 20210, telephone (202) 693–1999; email *meilinger.francis2@dol.gov*. *Technical information:* Ms. Lyn Penniman, Office of Physical Hazards, OSHA, Room N–3718, 200 Constitution Avenue NW., Washington, DC 20210, telephone (202) 693–1950; email *penniman.lyn@dol.gov*.

**SUPPLEMENTARY INFORMATION:**

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**List of Acronyms: Request for Information on Chemical Management and Permissible Exposure Limits**

ACGIH American Conference of Governmental Industrial Hygienists
ADI Allowable Daily Intake
AIHA American Industrial Hygiene Association
AISI American Iron and Steel Institute
ANSI American National Standards Institute
APHA American Public Health Association
ATSDR Agency for Toxic Substances Disease Registry
BAuA Federal Institute for Occupational Safety and Health (Germany)
BMD Benchmark Dose
BMDL Benchmark Dose Low
BMR Benchmark Response
CDR Chemical Data Reporting
CFD Computational Fluid Dynamics
COSHH Control of Substances Hazardous to Health (U.K.)
CrVI Hexavalent Chromium
CSTEE Scientific Committee on Toxicity, Ecotoxicity and the Environment (E.U.)
CT Control Technology
DfE Design for the Environment (EPA)
DHHS Department of Health and Human Services (U.S.)
DMEL Derived Minimal Effect Level
DNEL Derived No Effect Level
DOE Washington Department of Ecology
DOL Department of Labor (U.S.)
ECB European Chemicals Bureau (E.U.)
ECHA European Chemicals Agency (E.U.)
EPA Environmental Protection Agency (U.S.)
ES Exposure Scenario
EU European Union
FDA Food and Drug Administration (U.S.)
GAO Government Accountability Office (U.S.)
GHS Globally Harmonized System for the Classification and Labeling of Chemicals
HazCom 2012 Revised OSHA Hazard Communication Standard
HCS Hazard Communication Standard (OSHA)
HHE Health Hazard Evaluation (NIOSH)
HPV High Production Volume (EPA)
HPVIS High Production Volume Information System (EPA)
HSE Health and Safety Executive (U.K.)
HTS High Throughput Screening
IFA Federation of Institutions for Statutory Accident Insurance and Prevention (Germany)
IMIS Integrated Management Information System (OSHA)
IPCS World Health Organization International Programme on Chemical Safety
IRIS Integrated Risk Information System (EPA)
ISTAS Institute of Work, Environment, and Health (Spain)
ITC Interagency Testing Committee (EPA TSCA)
IUR Inventory Update Reporting
LETE Low-end Toxicity Exposure
LOAEL Lowest Observed Adverse Effect Level
LOD Limit of Detection
LTFE Lowest Technologically Feasible Exposure
MA DEP Massachusetts Department of Environmental Protection
MIBK Methyl isobutyl ketone
MOA Modes of Action
MOE Margin of Exposure
MRL Minimal Risk Level
NAICS North American Industry Classification System
NCGC National Institutes of Health Chemical Genomics Center
NIEHS National Institute of Environmental Health Sciences (U.S.)
NIOSH National Institute for Occupational Safety and Health (U.S.)
NIST National Institute of Standards and Technology (U.S.)
NMCSD Navy Medical Center San Diego
NOAEL No Observed Adverse Effect Level
NOES National Occupational Exposure Survey
NORA National Occupational Research Agenda (NIOSH)
NPRM Notice of Proposed Rulemaking (OSHA)
NRC National Research Council (U.S., private)
NTP National Toxicology Program (U.S.)
OECD Organization for Economic Cooperation and Development (multiple countries, private)
OEL Occupational Exposure Limit
OPPT Office of Pollution Prevention and Toxics (EPA)
OSHA Occupational Safety and Health Administration
OTA Massachusetts Office of Technical Assistance and Technology
PBT Persistent, Bioaccumulative and Toxic
PBZ Personal Breathing Zone
PCRARM (EPA) Presidential/Congressional Commission on Risk Assessment and Risk Management
PEL Permissible Exposure Limits
PMN Pre-manufacture Notification (EPA)
PNEC Predicted No Effect Concentration
POD Point of Departure
PPE Personal Protective Equipment
PPM Parts Per Million
QCAT Quick Chemical Assessment Tool (DOE)
QSAR Quantitative Structure-Activity Relationship
REACH Registration, Evaluation, Authorization and Restriction of Chemicals (E.U.)
REL Recommended Exposure Level
RfC Reference Concentration
RFI Request for Information
SAR Structural Activity Relation
SBREFA Small Business Regulatory Enforcement Fairness Act (U.S.)
SDS Safety Data Sheet
SEP Special Emphasis Program
SIC Standards Industrial Classification
SIDS Screening Information Data Set (OECD)
STEL Short-term Exposure Limit
TLV Threshold Value Limit (ACGIH)
TSCA Toxic Substances Control Act (EPA)
TTC Threshold of Toxicological Concern
TWA Time-weighted Average
vPvB Very Persistent and Very Bioaccumulative
WEEL Workplace Environmental Exposure Level (AIHA)

## I. Purpose

The purpose of this Request for Information (RFI) is to present background information and request comment on a number of technical issues related to aspects of OSHA's rulemaking process for chemical hazards in the workplace. In particular, the purpose of the RFI is to:

- Review OSHA's current approach to chemical regulation in its historical context;
- Describe and explore other possible approaches that may be relevant to future strategies to reduce and control exposure to chemicals in the workplace; and
- Inform the public and obtain public input on the best approaches for the

Agency to advance the development and implementation of approaches to reduce or eliminate harmful chemical exposures in the 21st century workplace.

By all estimates, the number of chemicals found in workplaces today far exceeds the number which OSHA regulates, and is growing rapidly. There is no single source recording all chemicals available in commerce. Through its Chemical Data Reporting Rule, EPA collects information on chemicals manufactured or imported at a single site at 25,000 pounds or greater; currently this number exceeds 7,674 chemicals (U.S. EPA, 2013a; *Ex. #1*)

The American Chemistry Council estimates that approximately 8,300 chemicals (or about 10 percent of the 87,000 chemicals in the TSCA inventory) are actually in commerce in significant amounts (Hogue, 2007; *Ex. #2*). By contrast the European Chemicals Agency database contains 10,203 unique substances (as of 9/12/2013) (ECHA, 2013; *Ex. #3*). Of these, OSHA has occupational exposure limits for only about 470 substances. Most of these are listed as simple limits and appear in tables (referred to as ''Z-tables'') in 29 CFR 1910.1000, *Air Contaminants,* Subpart Z, *Toxic and Hazardous Substances; Ex. #4.* Approximately 30 have been adopted by OSHA as a part of a comprehensive standard, and include a number of additional requirements such as regulated areas, air sampling, medical monitoring, and training However, with few exceptions, OSHA's permissible exposure limits, (PELs), which specify the amount of a particular chemical substance allowed in workplace air, have not been updated since they were established in 1971 under expedited procedures available in the short period after the OSH Act's adoption (see 29 CFR 1910.1000; *Ex. #4,* 1915.1000; *Ex. #5,* and 1926.55; *Ex. #6*). Yet, in many instances, scientific evidence has accumulated suggesting that the current limits are not sufficiently protective. Although OSHA has attempted to update its PELs, the Agency has not been successful, except through the promulgation of a relatively few substance-specific health standard rulemakings (e.g., benzene, cadmium, lead, and asbestos).

The most significant effort to update the PELs occurred in 1989 when OSHA tried to update many of its outdated PELs and to create new PELs for other substances in a single rulemaking covering general industry PELs. After public notice and comment, the Agency published a general industry rule that lowered PELs for 212 chemicals and added new PELs for 164 more (54 FR 2332; *Ex. #7*). Appendix B to this Request for Information contains the table of PELs from the 1989 Air Contaminants Final Rule. The table includes both the PELs originally adopted by OSHA in 1971 and the PELs established under the 1989 final rule. While the Agency presented analyses of the risks associated with these chemicals, as well as the analyses of the economic and technological feasibility of the proposed limits for these chemicals, these analyses were not as detailed as those OSHA would have prepared for individual rulemakings. The final rule was challenged by both industry and labor groups. The 1989 PEL update was vacated by the Eleventh Circuit Court of Appeals because it found that OSHA had not made sufficiently detailed findings that each new PEL would eliminate significant risk and would be feasible in each industry in which the chemical was used. (*AFL–CIO* v. *OSHA, 965 F.*2d 962 (11th Cir. 1992) (the *Air Contaminants* case; *Ex. #8*). This decision is discussed further below and in Appendix A.

Despite these challenges, health professionals and labor and industry groups have continued to support addressing PELs which may be outdated and or inconsistent with the best available current science. The 1989 Air Contaminants rulemaking effort was supported by the American Industrial Hygiene Association (AIHA), the American Conference of Governmental Industrial Hygienists (ACGIH), and the American Public Health Association (APHA), among many other professional organizations and associations representing both industry and labor. In an October 2012 survey, members of the AIHA identified updating OSHA PELs as their number one policy priority. The U.S. Chamber of Commerce, in a letter dated April 8, 2011 to then Deputy Secretary of Labor, Seth Harris, also supported updating OSHA's PELs.

Much has changed in the world since the OSH Act was signed in 1970. However, workers are essentially covered by the same PELs as they were forty years ago. And while OSHA has been given no new tools or increased resources to control workplace exposures, it has had to conduct increasingly complex analyses, which has effectively slowed the process. The purpose of this RFI is for OSHA to solicit information as to the best approach(es) for the Agency to help employers and employees devise and implement risk management strategies to reduce or eliminate chemical exposures in the 21st century workplace environment. This is likely to involve a multi-faceted plan that may include changing or improving OSHA policies and procedures regarding the derivation and implementation of PELs, as well as pursuing new strategies to improve chemical management in the workplace. The Agency is publishing this notice to inform the public of its consideration of these issues, as well as solicit public input that can be used to inform further deliberations, and the determination of an appropriate approach.

## II. Legal Requirements for OSHA Standards

In the past, OSHA has received many suggestions for updating its PELs, but these suggestions often do not take account of the requirements imposed by the OSH Act, and thus have been of limited value to OSHA. OSHA is providing an overview of its legal requirements for setting standards in order to help commenters responding to this RFI to provide suggestions that can satisfy these requirements. This section summarizes OSHA's legal requirements, which are discussed in greater detail in Appendix A. The next section provides an overview of OSHA's previous attempts to update the PELs.

Section 6(b) of the OSH Act (*Ex. #9*) provides OSHA with the authority to promulgate health standards. It specifies procedures that OSHA must use to promulgate, modify, or revoke its standards, including publishing the proposed rule in the **Federal Register**, providing interested persons an opportunity to comment, and holding a public hearing upon request. However, much of the labor and analysis that goes into the final rule starts before the publication of the proposal. Section 6(b)(5) of the Act specifies:

> The Secretary, in promulgating standards dealing with toxic materials or harmful physical agents under this subsection, shall set the standard which most adequately assures, to the extent feasible, on the basis of the best available evidence, that no employee will suffer material impairment of health or functional capacity even if such employee has regular exposure to the hazard dealt with by such standard for the period of his working life. Development of standards under this subsection shall be based upon research, demonstrations, experiments, and such other information as may be appropriate. In addition to the attainment of the highest degree of health and safety protection for the employee, other considerations shall be the latest available scientific data in the field, the feasibility of the standards, and experience gained under this and other health and safety laws. Whenever practicable, the standard promulgated shall be expressed in terms of objective criteria and of the performance desired.

In general, as this provision has been construed by the courts, any workplace

health standard adopted by OSHA must meet the following requirements:

(1) The standard must substantially reduce a significant risk of material harm.

(2) Compliance with the standard must be technically feasible. This means that the protective measures required by the standard currently exist, can be brought into existence with available technology, or can be created with technology that can reasonably be developed.

(3) Compliance with the standard must be economically feasible. This means that the standard will not threaten the industry's long term profitability or substantially alter its competitive structure.

(4) It must reduce risk of adverse health to workers to the extent feasible.

(5) The standard must be supported by substantial evidence in the record, consistent with prior agency practice or is supported by some justification for departing from that practice.

The significant risk, economic and technological feasibility, and substantial evidence requirements are of particular relevance in setting PELs, and are discussed further below.

*A. Significant Risk of a Material Impairment: The Benzene Case*

The significant risk requirement was first articulated in a plurality decision of the Supreme Court in *Industrial Union Department, AFL–CIO* v. *American Petroleum Institute,* 448 U.S. 607 (1980), commonly referred to as the *Benzene* case. The petitioners challenged OSHA's rule lowering the PEL for benzene from 10 ppm to 1 ppm. In support of the new PEL, OSHA found that benzene caused leukemia and that the evidence did not show that there was a safe threshold exposure level below which no excess leukemia would occur; OSHA chose the new PEL of 1 ppm as the lowest feasible exposure level. The *Benzene* Court rejected OSHA's approach, finding that the OSH Act only required that employers ensure that their workplaces are safe, that is, that their workers are not exposed to ''significant risk[s] of harm.'' 448 U.S. at 642 (*Ex. #10*). The Court also made it clear that it is OSHA's burden to establish that a significant risk is present at the current standard before lowering a PEL, stating that the burden of proof is normally on the proponent. Thus, the Court held, before promulgating a health standard, OSHA is required to make a ''threshold finding that a place of employment is unsafe—in the sense that significant risks are present and can be eliminated or lessened by a change in practices'' before it can adopt a new standard. Id.

Although the Court declined to establish a set test for determining whether a workplace is unsafe, it did state that a significant risk was one that a reasonable person would consider significant and ''take appropriate steps to decrease or eliminate.'' 448 U.S. at 655. For example, it said, a one in a 1,000 risk would satisfy the requirement. However, this example was merely an illustration, not a hard line rule. The Court made it clear that determining whether a risk was ''significant'' was not a ''mathematical straitjacket'' and did not require the Agency to calculate the exact probability of harm. Id. The 1 ppm PEL was vacated because OSHA had not made a significant risk finding at the 10 ppm level.

Following the *Benzene* case, OSHA has satisfied the significant risk requirement by estimating the risk to workers subject to a lifetime of exposure at various possible exposure levels. These estimates have typically been based on quantitative risk assessments in which OSHA, as a general policy, has considered an excess risk of one death per 1000 workers over a 45-year working lifetime as clearly representing a significant risk. However, the *Benzene* case does not require OSHA to use such a benchmark. In the past, OSHA has stated that a lower risk of death could be considered significant. *See, e.g.,* Preamble to Formaldehyde Standard, 52 FR 46168, 46234 (suggesting that risk approaching six in a million could be viewed as significant). (*Ex. #11*)

*B. Technological and Economic Feasibility*

Under section 6(b)(5) of the Act, a standard must protect against significant risk, ''to the extent feasible, and feasibility is understood to have both technological and economic aspects. A standard is technologically feasible if ''a typical firm will be able to develop and install engineering and work practice controls that can meet the PEL in most operations.'' *United Steelworkers* v. *Marshall,* 647 F.2d 1189, 1272 (D.C. Cir. 1981) (''*Lead I''; Ex. #12*). OSHA must show the existence of ''technology that is either already in use or has been conceived and is reasonably capable of experimental refinement and distribution within the standard's deadlines.'' Id. Where the Agency presents ''substantial evidence that companies acting vigorously and in good faith can develop the technology,'' the Agency is not bound to the technological status quo, and ''can require industry to meet PELs never attained anywhere.'' Id. at 1264–65.

Some courts have required OSHA to determine whether a standard is technologically feasible on an industry-by-industry basis, *Color Pigments Manufacturers Assoc.* v. *OSHA,* 16 F.3d 1157, 1162–63 (11th Cir. 1994; *Ex. #13*); AFL–CIO v. OSHA, 965, F.2d 962, 981–82 (11th Cir. 1992) (*Air Contaminants; Ex. #8*). However, another court has upheld technological feasibility findings based on the nature of an activity across many industries rather than on an industry-by-industry basis, *Public Citizen Health Research Group* v. *United States Department of Labor,* 557 F.3d 165,178–79 (3d Cir. 2009; *Ex. #14*).

With respect to economic feasibility, the courts have stated ''A standard is feasible if it does not threaten massive dislocation to . . . or imperil the existence of the industry.'' *Lead I,* 647 F.2d at 1265 *(Ex. #12).* In order to show this, OSHA should ''construct a reasonable estimate of compliance costs and demonstrate a reasonable likelihood that these costs will not threaten the existence or competitive structure of an industry.'' Id. at 1266. However, ''[T]he court probably cannot expect hard and precise estimates of costs. Nevertheless, the agency must of course provide a reasonable assessment of the likely range of costs of its standard, and the likely effects of those costs on the industry.'' Id.

While OSHA is not required to show that all companies within an industry will be able to bear the burden of compliance, at least one court has held that OSHA is required to show that the rule is economically feasible on an industry-by-industry basis. *Air Contaminants,* 965 F.2d at 982, 986. *(Ex. #8)*

*C. The Substantial Evidence Test*

The ''substantial evidence test'' is used by the courts to determine whether OSHA has reached its burden of proof for policy decisions and factual determinations. ''Substantial evidence'' is defined as ''such relevant evidence as a reasonable mind might accept as adequate to support a conclusion.'' *American Textile Mfrs. Inst., Inc.* v. *Donovan,* 452 U.S. 490, 522 (1981; *Ex. #15*) (quoting *Universal Camera Corp.* v. *NLRB,* 340 U.S. 474, 477 (1951); *Ex. #16*). The substantial evidence test does not require ''scientific certainty'' before promulgating a health standard (*AFL–CIO* v. *American Petroleum Institute,* 448 U.S. 607, 656 (1980); *Ex. 10*), but the test does require OSHA to ''identify relevant factual evidence, to explain the logic and the policies underlying any legislative choice, to state candidly any

assumptions on which it relies, and to present its reasons for rejecting significant contrary evidence and argument.'' *Lead I,* 647 F.2d. at 1207. (*Ex. #12*)

**III. History of OSHA's Efforts To Establish PELs**

The history of OSHA's PELs has three stages. First, OSHA adopted its current PELs in 1971, shortly after coming into existence. Second, OSHA attempted to update its PELs wholesale in 1989, but that effort was rejected by the Eleventh Circuit Court of Appeals in 1992. Third, OSHA has made subsequent, smaller efforts to update certain PELs, but those efforts have never come to fruition. This history is summarized below, and discussed in further detail in Appendix A.

*A. Adopting the PELs in 1971*

Under section 6(a), OSHA was permitted an initial two-year window after the passage of the OSH Act to adopt ''any national consensus standard and any established Federal standard'' 29 U.S.C 655(6)(a). OSHA used this authority in 1971 to establish PELs that were adopted from federal health standards originally set by the Department of Labor through the Walsh-Healy Act, in which approximately 400 occupational exposure limits were selected based on ACGIH's 1968 list of Threshold Limit Values (TLVs). In addition, about 25 additional exposure limits recommended by the American Standards Association (now called the American National Standards Institute) (ANSI), were adopted as national consensus standards.

These standards were intended to provide initial protections for workers from what the Congress deemed to be the most dangerous workplace threats. Congress found it was ''essential that such standards be constantly improved and replaced as new knowledge and techniques are developed.'' S. Rep. 91–1282 at 6. (*Ex. #17*) However, because OSHA has been unable to update the PELs, they remain frozen at the levels at which they were initially adopted. OSHA's PELs are also largely based on acute health effects and do not take into consideration newer research regarding chronic health effects occurring at lower occupational exposures.

*B. The 1989 PELs Update*

In 1989, OSHA published the *Air Contaminants* final rule, which remains the Agency's most significant attempt at updating the PELs (54 FR 2332). (*Ex. #7*) Unlike typical substance-specific rulemakings, where OSHA develops a comprehensive standard, the *Air Contaminants* final rule was only intended to update existing PELs or to add PELs for substances within established boundaries. After extensive review of all available sources of occupational exposure limits (OELs), OSHA selected the ACGIH's 1987–88 TLVs as the boundaries for identifying the substances that would be included in the proposed rule. OSHA proposed 212 more protective PELs and new PELs for 164 substances not previously regulated. In general, rather than performing a quantitative risk assessment for each chemical, the agency looked at whether studies showed excess effects of concern at concentrations lower than allowed under the existing standard. Where they did, OSHA made a significant risk finding and either set a PEL (where none existed previously) or lowered the existing PEL. These new PELs were based on Agency judgment, taking into account the existing studies and, as appropriate, safety factors. Safety factors (also called uncertainty factors) are applied to the lowest level an effect is seen or to a level where no effects are seen to derive a PEL.

In order to determine whether the *Air Contaminants* rule was feasible, OSHA prepared the regulatory impact analysis. As part of the analysis, OSHA performed an industry survey as well as site visits. The survey was the largest survey ever conducted by OSHA and included responses from 5,700 firms in industries believed to use chemicals addressed in the scope of the *Air Contaminants* proposal. (*Ex. #18)* It was designed to focus on industry sectors that potentially had the highest compliance costs, identified through an analysis of existing exposure data at the four-digit SIC (Standards Industrial Classification) code level. OSHA analyzed the data collected to determine whether the updated PELs were both technologically and economically feasible for each industry sector covered.

For technological feasibility, OSHA found that ''in the overwhelming majority of situations where air contaminants [were] encountered by workers, compliance [could] be achieved by applying known engineering control methods, and work practice improvements.'' 54 FR at 2789; *Ex. #7.* For economic feasibility, OSHA assessed the economic impact of the standard on industry profits at the two-digit SIC code level, and found the economic impact not to be significant, and the new standard therefore economically feasible.

In the *Air Contaminants* final rule, OSHA summarized the health evidence for each individual substance, discussed over 2,000 studies, reviewed and addressed all major comments submitted to the record, and provided a rationale for each new PEL chosen. OSHA estimated that over 21 million employees were potentially exposed to hazardous substances in the workplace and over 4.5 million employees were exposed to levels above the applicable exposure limits. OSHA projected that the final rule would result in a potential reduction of over 55,000 lost workdays due to illnesses per year and that annual compliance with this final rule would prevent an average of 683 fatalities annually from exposures to hazardous substances.

*C. The 1989 PELs Update Is Vacated by the Court of Appeals*

The update to the *Air Contaminants* standard generally received widespread support from both industry and labor. However, there was dissatisfaction on the part of some industry representatives and union leaders, who brought petitions for review challenging the standard. For example, some industry petitioners argued that OSHA's use of generic findings, the inclusion of so many substances in one rulemaking, and the allegedly insufficient time provided for comment by interested parties created a record inadequate to support the new set of PELs. In contrast, the unions challenged the approach used by OSHA to promulgate the standard and argued that several PELs were not protective enough. The unions also asserted that OSHA's failure to include any ancillary provisions, such as exposure monitoring and medical surveillance, prevented employers from ensuring the exposure limits were not exceeded, and resulted in less-protective PELs.

Although only 23 of the 428 PELs were challenged, the court ultimately decided to vacate the entire rulemaking, finding that ''OSHA [had] not sufficiently explained or supported its threshold determination that exposure to these substances at previous levels posed a significant risk of these material health impairments or that the new standard eliminates or reduces that risk to the extent feasible.'' *Air Contaminants* 965 F.2d at 986–987; *Ex. #8*

With respect to significant risk, the court held that OSHA had failed to ''explain why the studies mandated a particular PEL chosen.'' Id. at 976. Specifically, the court stated that OSHA failed to quantify the risk from individual substances and merely provided conclusory statements that the new PEL would reduce a significant risk

of material health effects.'' Id. at 975. Further, the court rejected OSHA's argument that it had relied on safety factors in setting the new PELs, stating that OSHA had not adequately supported their use. The court observed that ''the difference between the level shown by the evidence and the final PEL is sometimes substantial.'' Id. at 978. It said that OSHA had not indicated ''how the existing evidence for individual substances was inadequate to show the extent of risk for these factors'' and that the agency had ''failed to explain the method by which its safety factors were determined.'' Id. ''OSHA may use assumptions but only to the extent that those assumptions have some basis in reputable scientific evidence,'' the court concluded. Id. at 978–79.

The *Eleventh Circuit* court also rejected OSHA's technological feasibility findings. The Agency had made these findings mainly at the two-digit SIC level, but also at the three- and four- digit level where appropriate given the processes involved. The court rejected this approach, finding that OSHA failed to make industry-specific findings or identify the specific technologies capable of meeting the proposed limit in industry-specific operations. Id. at 981. While OSHA had identified primary air contaminant control methods: Engineering controls, administrative controls and work practices and personal protective equipment, the agency, ''only provided a general description of how the generic engineering controls might be used in the given sector.'' Id. Though noting that OSHA need only provide evidence sufficient to justify a ''general presumption of feasibility,'' the court held that this ''does not grant OSHA license to make overbroad generalities as to feasibility or to group large categories of industries together without some explanation of why findings for the group adequately represents the different industries in that group.'' Id. at 981–82.

The court rejected OSHA's economic feasibility findings for similar reasons. As discussed above, OSHA supported its economic feasibility findings for the 1989 Air Contaminants rule based primarily on the results of a survey of over 5700 businesses, summarizing the projected cost of compliance at the two-digit SIC industry sector level. The court held that OSHA was required to show that the rule was economically feasible on an industry-by industry basis, and that OSHA had not shown that its analyses at the two-digit SIC industry sector level were appropriate to meet this burden. Id. at 982. ''[A]verage estimates of cost can be extremely misleading in assessing the impact of particular standards on individual industries'' the court said, and ''analyzing the economic impact for an entire sector could conceal particular industries laboring under special disabilities and likely to fail as a result of enforcement.'' Id. While OSHA might ''find and explain that certain impacts and standards do apply to entire sectors of an industry'' if ''coupled with a showing that there are no disproportionately affected industries within the group,'' OSHA had not explained why its use of such a ''broad grouping was appropriate.'' Id. at 982 n.28, 983.

*D. Revising OSHA's PELs in the Wake of the Eleventh Circuit Decision*

In the wake of the Eleventh Circuit's decision, OSHA has generally pursued a conservative course in satisfying its judicially imposed analytical burdens. The set of resulting analytical approaches OSHA has engaged in is highly resource-intensive and has constrained OSHA's ability to prioritize its regulatory efforts based on risk of harm to workers. In 1995, OSHA made its first attempt following the *Air Contaminants* ruling to update a smaller number of PELs using a more rigorous analysis of risk, workplace exposures, and technological and economic feasibility. (*Ex. #20)* OSHA and the National Institute for Occupational Safety and Health (NIOSH) conducted preliminary research on health risks associated with exposure and extent of occupational exposure. Sixty priority substances were identified for further examination and twenty of the sixty substances were selected to form a priority list. Early in 1996, the Agency announced its plans for a stakeholder meeting, and identified the twenty priority substances, as well as several risk-related discussion topics. (*Ex. #21)* During the meeting, almost all stakeholders from industry and labor agreed that the PELs needed to be updated; however, not one group completely supported OSHA's suggested approach. Overall, many of the stakeholders did not support the development of a list of priority chemicals targeted for potential regulation and felt there was a lack of transparency in the process for selecting the initial chemicals.

In response to stakeholder input and OSHA's research, the agency selected seven of the 20 substances discussed at the stakeholder meeting for detailed analysis of risks and feasibility. The chemicals selected were: (i) Glutaraldehyde, (ii) carbon disulfide, (iii) hydrazine, (iv) perchloroethylene, (v) manganese, (vi) trimellitic anhydride, and (vii) chloroprene. Quantitative risk assessments were performed in-house, and research (including site visits) was undertaken to collect detailed data on uses, worker exposures, exposure control technology effectiveness, and economic characteristics of affected industries.

The research and analysis were carried out over several years, after which OSHA decided not to proceed with rulemaking. (*Ex. #22)* This decision was influenced by findings that (i) prevalence and intensity of worker exposures for some of the substances (*e.g.,* carbon disulfide and hydrazine) had declined substantially since the 1989 rule was promulgated; (ii) industry had voluntarily implemented controls to reduce the exposure to safe levels; and (iii) for others, substantial Agency resources would have been required to fully assess technological and economic impacts.

In 1997, OSHA held another meeting with industry and labor on the proposed PEL development process. Although the project did not result in a rulemaking to revise the PELs, OSHA gained valuable experience in developing useful approaches for quantifying non-cancer health risks through collaboration with external reviewers in scientific peer reviews of its risk analyses. OSHA is now examining ways to better address chemical exposures given current resource constraints and regulatory limitations.

For readers who are interested in a more detailed account of the legislation and court decisions that shaped OSHA's current regulatory framework, Appendix A to this Request for Information, *History, Legal Background and Significant Court Decisions,* provides additional information. Readers may want to consult Appendix A as they frame responses to the questions posed in this Request for Information.

## IV. Reconsideration of Current Rulemaking Processes

As reviewed in Section II (Legal Requirements for OSHA Standards) and Section III (History of OSHA's Efforts to Establish PELs), OSHA has to use the best available evidence to make findings of significant risk, substantial reductions in risk, and technological and economic feasibility under the Act. This section reviews how interpretation of 6(b)(5) and subsequent case law has resulted in the methods it uses when developing risk, technical feasibility, and economic findings as well as the evidence OSHA has used in the past to make these findings (*i.e.,* OSHA's use of

formal risk assessment modeling to evaluate significant risk, and the Agency's use of worker exposure data and exposure control effectiveness data to evaluate technical feasibility and costs of compliance).

This section also reviews developments in science and technology and how these new advancements may improve the scientific basis for making findings of significant risk, technical feasibility, and economic feasibility. As an example, the National Academies of Science has released extensive reviews of advances in science, toxicology, and risk and exposure assessment and evaluated how the Federal government can potentially utilize these advancements in its decision-making processes (NRC, 2012; *Ex. #23,* NRC, 2009; *Ex. #24,* NRC, 2007; *Ex. #25*). While new technologies will advance the public's understanding in these critical areas, the Agency has obligations under the OSH Act to make certain findings under 6(b)(5), as discussed above in Section III. How OSHA might utilize these new developments to meet the Agency's evidentiary burden will be discussed in this section.

*A. Considerations for Risk Assessment Methods*

1. Current Quantitative Risk Assessment Methods Typically Used by OSHA To Support 6(b) Single Substance Rulemaking

As discussed in Section III, the Supreme Court requires OSHA to determine that a significant risk exists before adopting an occupational safety and health standard. While the Court did not stipulate a means to distinguish significant from insignificant risks, it broadly described the range of risks OSHA might determine to be significant:

> It is the Agency's responsibility to determine in the first instance what it considers to be a ''significant'' risk. Some risks are plainly acceptable and others are plainly unacceptable. If, for example, the odds are one in a billion that a person will die from cancer by taking a drink of chlorinated water, the risk clearly could not be considered significant. On the other hand, if the odds are one in a thousand that regular inhalation of gasoline vapors that are 2 percent benzene will be fatal, a reasonable person might well consider the risk significant and take the appropriate steps to decrease or eliminate it. (*Benzene,* 448 U.S. at 655). (*Ex. #10*),

OSHA has interpreted the Court's example to mean that a 1 in 1000 risk of serious illness is significant, and has used this measure to guide its significance of risk determinations. For example, OSHA's risk assessment for hexavalent chromium estimated that a 45-year occupational exposure at the PEL of 5μg/m$^3$ would lead to more than 10 lung cancer cases per 1000 workers exposed. Because this risk exceeds the value of one case of lung cancer per 1000 exposed workers, OSHA found it to be significant. The significance of risk determinations of other rules since the *Benzene* decision have typically followed a similar logic.

Over the three decades since the *Benzene* decision, OSHA has gradually built up a highly rigorous approach to derive quantitative estimates of risk such as those found in the hexavalent chromium preamble. First, the Agency reviews the available exposure-response data for a chemical of interest. It evaluates the available data sets and identifies those best suited for quantitative analysis. Using the best available data, the Agency then conducts extensive statistical analyses to develop an exposure-response model that is able to extrapolate probability of disease at exposures below the observed data. Once the model is developed, OSHA conducts further analyses to evaluate the sensitivity of the model to error and uncertainties in the modeling inputs and approach. The exposure-response model is used to generate estimates of risk associated with a working lifetime of occupational exposure to the chemical of interest over a range of PEL options that often include exposure levels below those considered to be technologically feasible. The entire risk assessment has always been subject to peer review, from choice of data set(s) through generation of lifetime risk estimates.When the proposed rule is released for comment, it receives additional scrutiny from the scientific community, stakeholders, and the general public. The Agency uses the feedback of the peer review panel and public comment at the time of proposal to further test and develop the risk analysis.

This model-based approach to risk assessment has a number of important advantages. The quantitative risk estimates can be easily compared with the level of 1 in 1000 that the Court cited as an example of significant risk. Sometimes, the best available data come from worker or animal populations with exposure levels far above the technologically feasible levels for which OSHA must evaluate risk, and a risk model is used to extrapolate from high to low exposures. When large, high-quality exposure-response data sets are available, a rigorous quantitative analysis can yield robust and fairly precise risk estimates to inform public understanding and debate about the health benefits of a new or revised regulation. However, there are also drawbacks to the model-based approach, and there are situations where a modeling analysis may not be necessary or appropriate for OSHA to make the significance of risk determination to support a new or revised regulation. Model-based risk analyses tend to require a great deal of Agency time and resources.

In some cases, the model-based approach is essential to OSHA's significant risk determination, because it is not evident prior to a modeling analysis whether there is significant risk at current and technologically-feasible exposures. In other cases, however, it may be evident from the scientific literature or other readily available evidence that risk at the existing PEL is clearly significant and that it can be substantially reduced by a more stringent regulation without the need for quantitative estimates extrapolated from an exposure-response model. In addition to reducing significant risk of harm, the OSH Act also directs the Agency to determine that health standards for toxic chemicals are feasible. At times, it is evident without extensive analysis that the most stringent PEL feasible can only reduce, not eliminate, significant risk. In such cases, the value of a model-based quantitative risk assessment may not warrant the Agency time and resources that model-based risk assessment requires.

In situations described above where the PEL may be set at the lowest feasible level, OSHA believes that it can establish significant risk more efficiently instead of relying on probabilistic estimates from dose-response modeling as described above. OSHA is exploring a number of more flexible, scientifically accepted approaches that may streamline the risk assessment process and increase the capacity to address a greater number of chemicals.

Question IV.A.1: OSHA seeks input on the risk assessment process described above. When is a model-based analysis necessary or appropriate to determine significance of risk and to select a new or revised PEL? When should simpler approaches be employed? Are there specific approaches OSHA should consider using when a model-based analysis is not required? To the extent possible, please provide detailed explanation and examples of situations when a model-based risk analysis is or is not necessary to determine significance of risk and to develop a new standard.

2. Proposed Tiered Approach to Risk Assessment in Support of Updating PELs for Chemical Substances

a. General Description and Rationale of Tiered Approach

OSHA is considering a tiered process to exposure-response assessment that may enable the agency to more efficiently make the significant risk findings needed to establish acceptable PELs for larger numbers of workplace chemicals. The approach involves three stages: dose-response analysis in the observed range, margin of exposure determination, and exposure-response extrapolation (if needed). The process overlaps with the risk-based methodologies employed by EPA IRIS, NIOSH, the Agency for Toxic Substances Disease Registry (ATSDR), the European Union Registration, Evaluation, Authorization, and Restriction of Chemicals (REACH) program, and other organizations that recommend chemical toxicity values or exposure levels protective of human health. The first step is dose-response analysis in the observed range. During this step, OSHA analyzes exposures (or doses) and adverse outcomes from human studies or animal bioassays, particularly at the lower end of the exposure range. This involves the derivation of a ''low-end toxicity exposure'' (LETE), which is discussed further in section IV.A.2.c. below.

The second step is margin of exposure determination, where LETEs are compared with the range of possible exposure limits that OSHA believes to be feasible for the new or proposed standard. Typically, there is a close and ongoing dialogue between those OSHA technical staff and management responsible for the risk assessment and their counterparts responsible for the feasibility analyses as the separate determinations are being simultaneously developed. Feasibility analyses, in particular, can take years of research, including site visits and industry surveys. In many of OSHA's rulemakings, the lowest feasible PEL can only reduce, not eliminate, significant risk. Thus, OSHA sets many PELs at the lowest feasible level, and not at a level of occupational exposure considered to be without significant risk. This significant risk orientation differs from other Federal Agencies, such as EPA and ATSDR that set environmental exposure levels determined to be health protective without consideration of feasibility.

OSHA is considering using a margin of exposure (MOE) approach to compare the LETE with the range of feasible exposure limits. If the MOE indicates the range of feasible exposures is in close proximity to the exposures where toxicity is observed (*i.e.,* a low MOE) then it may not be necessary to extrapolate exposure-response below the observed range in order to establish significant risk. In this situation, OSHA would set the PEL at the exposure level it determines to be feasible and the dose-response analysis in the observed range should be sufficient to support Agency significant risk findings. The PEL is set at the lowest feasible level, with the understanding that significant risk of adverse health outcomes remains at the new PEL. In the traditional risk assessment approach described previously, OSHA uses quantitative exposure-response modeling to estimate risks below the range of observed exposure, without regard to whether such exposures are considered to be technologically feasible. If the lowest technologically feasible workplace exposures are determined to be far below the LETE (*i.e.,* a high MOE), an exposure-response model would be needed to determine significant risk at exposures below the observed range and to set the appropriate PEL.

If there is a high MOE, then the Agency would move onto the final stage of the tiered approach, which is exposure-response extrapolation, where the dose-response relationship is extrapolated outside the observed range. Many regulatory agencies, such as EPA, choose to extrapolate outside the observed range for non-cancer health outcomes by applying a series of extrapolation factors, also called uncertainty factors, to an observed low-end toxicity value, referred to as a *point of departure* (POD). The POD is very similar to the LETE described above. The distinction between these toxicity values is discussed later in the subsection. The extrapolation factors are further explained below.

In many instances, EPA does not use the extrapolation factor approach for cancer effects. Rather, EPA uses dose-response modeling in the observed range and a linear extrapolation below the observed range to derive a unit risk (*i.e.,* risk per unit of exposure). As described previously, OSHA also uses dose-response modeling to extrapolate risk below the observed range for carcinogens as was done for hexavalent chromium (71 FR 10174–10221; *Ex. #26*) and methylene chloride (62 FR 1516–1560; *Ex. #27*). There is a reasonable body of scientific evidence that genotoxic carcinogens, and perhaps other carcinogenic modes of action, display linear, non-threshold behavior at very low dose levels. OSHA also uses dose-response modeling to extrapolate risk below the observed range for carcinogens. As mentioned earlier, the Agency develops appropriate exposure-response models (linear or non-linear) that best fit the existing data and are consistent with available information on mode of action. The models can be used to extrapolate risk associated with a working lifetime at occupational exposures below the observed range.

In some situations, the LETE is further adjusted to calculate worker equivalent exposures and to account for how the chemical is absorbed, distributed, and metabolized, and interacts with target tissues in the body. These features and other important issues related to the tiered approach to exposure-response assessment are discussed below. OSHA believes that there are a number of potential advantages to using a tiered risk assessment framework including opportunities to rely more heavily on peer-reviewed risk assessments already prepared by other Federal agencies.

b. Hazard Identification and Dose-Response Analysis in the Observed Range

Hazard identification is the first step in the Federal risk assessment framework as laid out by the National Research Council's 'red book' in 1983 (NRC, 1983; *Ex. #28*). In conducting a hazard identification, OSHA evaluates individual study quality and determines the weight of evidence from epidemiological, experimental, and supporting data. Study quality favors strong methodology, characterization of exposure during critical periods, adequate sample size/statistical power, and relevance to the workplace population. OSHA gives weight to both positive and negative studies according to study quality when the Agency evaluates the association between chemical agent and an adverse health effect. OSHA determines causality based on criteria developed by Bradford Hill (Hill, 1965; *Ex. #29,* Rothman & Greenland, 1998; *Ex. #30*). In its review of the available evidence, OSHA assesses the chemical's modes of action (MOA) and the key molecular, biological, pathological, and clinical endpoints that contribute to the health effects of concern.

The Mode of Action (MOA) is a sequence of key events and processes starting with the interaction of the agent with a molecular or cellular target(s) and proceeding through operational and anatomical changes that result in an adverse health effect(s) of concern. The key events are empirically measurable molecular or pathological endpoints and outcomes in experimental systems. These represent necessary precursor

steps or biologically-based markers along the progression to frank illness and injury.

MOA informs selection of appropriate toxicity-related endpoints and models for dose-response analysis. OSHA then conducts a dose-response analysis for critical health effects determined to be associated with a chemical, provided there are suitable data available. Dose-response analysis requires quantitative measures of both exposure and toxicity-related endpoints. OSHA gives preference to studies with relevant occupational routes that display a well-defined dose-related change in response with adequate power to detect effects at the exposure levels of interest. The Agency generally prefers high quality epidemiologic studies for dose-response analysis over experimental animal models, provided there is adequate exposure information and confounding factors are appropriately controlled. OSHA may only adopt standards for exposure to ''toxic materials and harmful physical agents'' that causes ''material impairment of health and loss of functional capacity even if such employee has regular exposure to the hazard dealt with by such standard for the period of his working life.'' OSH Act § 6(b)(5) (*Ex. #9*) Therefore, its dose-response analysis considers those biological endpoints and health outcomes that can lead to adverse physiological or clinical harm caused by continued exposure over a working lifetime. This includes key molecular and cellular biomarkers established as necessary precursor events along a critical disease pathway. It is important that the toxicity-related endpoints observed in experimental animals selected for dose-response analysis have relevance to humans and are not unique to the test species.

In the past, OSHA, for the most part, has undertaken an independent evaluation of the evidence in its identification of hazards and selection of critical studies and toxicity-related endpoints for dose-response analysis. However, other Federal agencies use the same risk assessment framework with similar hazard identification and dose-response selection procedures. EPA, ATSDR, NIOSH and others have active risk assessment programs and have recently evaluated many chemicals of interest to OSHA. These assessments undergo scientific peer review and are subject to public comment. The Agency is considering ways to reduce the time and resources needed to independently evaluate the available study data by placing greater reliance on the efforts of other credible scientific organizations. Although some organizations use their study evaluations to support non-occupational risk assessments, OSHA believes that, in most cases, these evaluations can be adapted to the occupational context.

Question IV.A.2: If there is no OSHA PEL for a particular substance used in your facility, does your company/firm develop and/or use internal occupational exposure limits (OELs)? If so, what is the basis and process for establishing the OEL? Do you use an authoritative source, or do you conduct a risk assessment? If so, what sources and risk assessment approaches are applied? What criteria do facilities/firms consider when deciding which authoritative source to use? For example, is rigorous scientific peer review of the OEL an important factor? Is transparency of how the OEL was developed important?

Question IV.A.3: OSHA is considering greater reliance on peer-reviewed toxicological evaluations by other Federal agencies, such as NIOSH, EPA, ATSDR, NIEHS and NTP for hazard identification and dose-response analysis in the observed range. What advantages and disadvantages would result from this approach and could it be used in support of the PEL update process?

c. Derivation of Low-End Toxicity Exposure (LETE)

An important aspect of the dose-response analysis is the determination of exposures that can result in adverse outcomes of interest. For most studies, response rates ranging from 1 to 10 percent represent the low end of the observed range. Epidemiologic studies generally are larger and can show a lower observed response rate than animal studies, which typically have fewer test subjects. EPA, ATSDR and EU REACH also derive an estimated dose at the low end of the observed range (*i.e.,* LETE) as part of their dose-response assessments. This dose is referred to as the POD ('point of departure') because it is used as a starting point for low dose extrapolation or the application of uncertainty factors as described above to derive toxicity values. EPA, ATSDR and EU REACH use the POD/extrapolation factor approach to determine Reference Concentrations (RfC), Minimal Risk Levels (MRL) and Derived No Effect Levels (DNELs), respectively. OSHA believes the LETE is an exposure where studies may have demonstrated significant risk. However, OSHA does not intend to use the LETE as the point of extrapolation for determining a ''safe'' exposure level in the manner used by the aforementioned agencies. OSHA may use the LETE in calculating an MOE to evaluate the need for low dose extrapolation as described in the next section.

Traditionally, either the Lowest Observed Adverse Effect Level (LOAEL) or No Observed Adverse Effect Levels (NOAEL) has served as easily obtainable LETE descriptors. More recently, the Benchmark Dose (BMD) methodology has increasingly been applied to derive an LETE. The BMD approach uses a standard set of empirical models to determine the dose associated with a pre-selected benchmark response (BMR) level. An example is the dose associated with a 10 percent incidence (*i.e.,* $BMD_{10}$) and the statistical lower confidence limit (*i.e.,* $BMDL_{10}$). Selection of an appropriate BMR considers biologic as well as statistical factors and a lower BMR is typically applied for clinically serious outcomes (*e.g.,* lung or heart disease) than for less serious adverse effects (*e.g.,* preclinical loss of neurological or pulmonary function). In some cases, more sophisticated models can be used in the LETE determination, based on physiologically-based toxicokinetics, toxicodynamics, or dosimetry models that relate the administered dose to a more toxicologically relevant dose metric at a biological target site, if sufficient data is available and the models are appropriately validated. This is discussed further below.

Question IV.A.4: OSHA is considering using the Point of Departure (POD) (*e.g.,* BMD, LOAEL, NOAEL), commonly employed by other authoritative organizations for carrying out non-cancer risk assessments as a suitable descriptor of the Low End Toxicity Exposure (LETE) level that represents a significant risk of harm. Is this an appropriate application of the POD by OSHA? Are there other exposure values that OSHA should consider for its LETE?

In many situations, the LETE must be adjusted to represent a typical worker exposure. The most common adjustments are to correct for the standard occupational exposure conditions of eight hours a day/five days a week and/or respiratory volume during work activity. OSHA and NIOSH have used a standard ventilation rate of 10 $m^3$ of air per 8-hour work shift for a typical worker undergoing light physical work activity.

Allometric scaling (*i.e.,* $BW^{3/4}$) is recommended by some Federal authorities when scaling animal doses to human equivalents to account for toxicokinetic differences in rates of absorption, metabolism, and excretion when more specific data is lacking. Allometric scaling refers to scaling

physiological rates and quantities to mass or volume of one animal species to another animal species. The relationship is generally dependent on body weight (BW), often in the form of $y=BW^{\alpha}$ where y is the physiological measure and $\alpha$ is the scaling component. Many physiological and biochemical processes (such as heart rate, basal metabolic rate, and respiration rate have been found to have a scaling component of 0.75.

Allometric scaling is most applicable when the toxicologically relevant dose is a parent compound or stable metabolite whose absorption rate and clearance from the target site is controlled primarily by first order processes. Allometric scaling is less well suited for portal-of-entry effects or when toxicity is a consequence of a highly reactive compound or metabolite. Portal of entry refers to the tissue or organ of first contact between the biological system and the agent. This is nasal, respiratory tract and pulmonary tissues for inhalation; skin for dermal contact, and mouth and digestive tract for oral exposure.

In the case of respiratory tract effects from inhalation, EPA recommends adjusting inhalation doses based on generic dosimetry modeling that depends on the form of the chemical (*e.g.,* particle of gas) and site of toxicity (*e.g.,* portal of entry or systemic) (EPA, 1994; *Ex. #31*). For example, the human equivalent for a reactive gas that exerts its toxic effect on the respiratory tract is scaled based on animal to human differences in ventilation rate and regional surface area of the respiratory tract. On the other hand, the dosimetry model adjustment for an insoluble gas that exerts its effect in a tissue remote from the lung is scaled by species differences in the blood: gas partition coefficient. The generic dosimetry models can accommodate specific chemical data, if available. The models are only intended to account for human-to-animal differences in bioavailability and further allometric or extrapolation factors may be needed to account for species differences in metabolic activation and toxicodynamics (*i.e.,* target site sensitivity to an equivalent delivered dose).

Question IV.A.5: Several methodologies have been utilized to adjust critical study exposures to a worker equivalent under representative occupational exposure conditions including standard ventilation rates, allometric scaling, and toxicokinetic modeling. What are reasonable and acceptable methods to determine worker equivalent exposure concentrations, especially from studies in animals or other experimental systems?

The worker-adjusted LETE that is derived from dose-response analysis in the observed range should be regarded as a chemical exposure level that leads to significant risk of harm. In most cases, the LETE is expected to elicit a toxic response in 1 to 10 percent of the worker population. This approximates an excess risk of 10 to 100 cases of impairment per 1000 exposed workers over a duration that is typically less than a 45-year working life. This degree of risk would exceed the 1 per 1000 probability that OSHA historically regards as a clearly significant risk.

d. Margin of Exposure (MOE) as a Decision Tool for Low Dose Extrapolation

As discussed previously, OSHA's statutory and legal obligations dictate that PELs be set at the level that eliminates significant risk, if feasible, or if not, at the lowest feasible level. Therefore, Agency risk assessments are directed at determining significant risk at these feasible exposures. Because of the feasibility constraints, low dose extrapolation is not always needed to make the required risk findings. The OSHA significant risk orientation differs from other Federal Agencies, such as EPA and ATSDR. The risk-based EPA RfCs and ATSDR MRLs are intended as environmental exposure levels determined to be health protective without consideration of feasibility. NIOSH also develops workplace exposure limits. These recommended exposure limits (RELs) are based on risk evaluations using human or animal health effects data. The exposure levels that can be achieved by engineering controls and measured by analytical techniques are considered in the development of RELs, but the recommended levels are often below what OSHA regards as technologically feasible.

A MOE approach can assist in determining the need to extrapolate risk below the observed range. The appropriate MOE for use as a decision tool for low dose extrapolation is the LETE divided by an estimate of the lowest technologically feasible exposure (LTFE). A large MOE (*i.e.,* LETE/LTFE ratio) means the LTFE is considerably below exposures observed to cause adverse outcomes along a critical toxicity pathway. This situation would require low-dose risk extrapolation to determine whether technologically feasible exposures lead to significant risk. A small MOE means the LTFE estimate is reasonably close to the observed toxic exposures indicating the LTFE likely leads to significant risk of harm. In this situation, OSHA would set the PEL at the exposure level it determines to be feasible and the dose-response analysis in the observed range should be sufficient to support Agency significant risk findings.

There are several factors that OSHA would need to consider in order to find that the MOE is adequate to avoid low-dose risk extrapolation. These include the nature of the adverse outcome, the magnitude of the effect, the methodological designs and experimental models of the selected studies, the exposure metric associated with the outcome, and the exposure period over which the outcome was studied. OSHA may regard a larger MOE as acceptable to avoid the need for low-dose extrapolation for serious clinical effects than a less serious subclinical outcome. A larger MOE may also be found acceptable for irreversible health outcomes that continue to progress with continued exposure and respond poorly to treatment than reversible health outcomes that do not progress with further exposure. Health outcomes that relate to cumulative exposures would tolerate higher MOEs than similar outcomes unrelated to cumulative exposure, especially in short-term studies. In some instances, an adverse outcome observed in experimental animals would tolerate higher MOEs than the same response in a human study that more closely resembles the occupational situation.

Other Federal agencies apply the MOE approach as part of the risk assessment process. EPA has included MOE calculations in risk characterizations of environmental exposure scenarios to assist in risk management decisions (EPA, 2005; *Ex. #32*). The EU has also applied a very similar Margin of Safety analysis to characterize results of risk assessment conclusions (ECB, 2003; *Ex. #33*). In its report on the appropriate uses of risk assessment and risk management in federal regulatory programs, the Presidential Commission on Risk Assessment and Risk Management recommended MOE as an approach that provides a common metric for comparing health risks across different toxicities and public health programs (PCRARM, 1997; *Ex. #34*).

Question IV.A.6: OSHA is considering a Margin of Exposure approach that compares the LETE with the Lowest Technologically Feasible Exposure (LTFE) as a decision tool for low dose extrapolation. Is this a reasonable means of determining if further low dose extrapolation methods are needed to meet agency significant risk findings?

What other approaches should be considered?

e. Extrapolation Below the Observed Range

The last step in the tiered approach is extrapolation of risk below the observed range. This low-dose extrapolation would only be needed if the MOE is sufficiently high to warrant further dose-response analysis. This situation occurs when technologically feasible exposures are far below the LETE and quantitative estimates of risk could be highly informative in the determination of significant risk. As described in subsection A.1, OSHA has historically used probabilistic risk modeling to quantitatively estimate risks at exposure levels below the observed range. Depending on the nature of the exposure-response data, the Agency has relied on a wide range of different models that have included linear relative risk (*e.g.,* hexavalent chromium/lung cancer), logistic regression (*e.g.,* cadmium/kidney dysfunction), and physiologically-based pharmacokinetic (*e.g.,* methylene chloride/cancer) approaches.

Probabilistic risk models can require considerable time and resources to construct, parameterize, and statistically verify against appropriate study data, especially for a large number of chemical substances. As mentioned previously, several government authorities responsible for managing the risk to human populations posed by hazardous chemicals commonly use the computationally less complex uncertainty factor approach to extrapolate dose-response below the observed range. The uncertainty factors account for variability in response within the human population, uncertainty with regard to the differences between experimental animals and humans, and uncertainty associated with various other data inferences made in the assessment. For each of these considerations, a numerical value is assigned and the point of departure is divided by the product of all applied uncertainty factors. The result is an exposure level considered to be without appreciable risk. OSHA attempted to apply uncertainty factors in the 1989 Air Contaminants Rule to ensure that new PELs were set at levels that were sufficiently below exposures observed to cause health effects. The Eleventh Circuit ruled that OSHA had failed to show how uncertainty factors addressed the extent of risk posed by individual substances and that similarly, OSHA failed to explain the method it used to derive the safety factors. *Air Contaminants* 965 F.2d at 978.( *Ex. #8)* Since the court ruling, the uncertainty factor approach has undergone considerable refinement. The scientific considerations for applying individual factors have been carefully articulated by EPA and other scientific authorities in various guidance materials (EPA, 2002; *Ex. #35,* IPCS, 2005; *Ex. #36,* ECHA, 2012a; *Ex. #37*). For some factors under certain circumstances, it is being proposed that standard 'default' values can be replaced with 'data-driven' values (EPA, 2011; *Ex. #38*). However, the type and magnitude of the uncertainty factor employed for any individual substance still requires a degree of scientific judgment. The methodology does not provide quantitative exposure-specific estimates of risk, such as one in a thousand, that can readily be compared to the significant risk probabilities discussed in the *Benzene* decision.

The National Research Council's *Science and Decisions* report recently advocated a dose-response framework that provides quantitative risk estimates by applying distributions instead of 'single value' factors (NRC, 2009; *Ex. #24*). The critical extrapolation factors, such as species differences in toxic response at equivalent target doses and inter-individual variability in the human population are defined by lognormal distribution with an estimated standard deviation. This allows the human equivalent LETE to be derived in terms of a median and statistical lower confidence bound. The distributional nature of the analysis facilitates extrapolation in terms of a probabilistic projection of average and upper bound risk at specific exposures, such as X number of individuals projected to develop disease out of 1000 workers exposed to Z level of a toxic substance within some confidence level Y. The NRC report describes several different conceptual models with case examples and extrapolation factor distribution calculations (NRC, 2009; *Ex. #24*).

Question IV.A.7: Can the uncertainty factor methodology for extrapolating below the observed range for non-cancer effects be successfully adapted by OSHA to streamline its risk assessment process for the purpose of setting updated PELs? Why or why not? Are there advantages and disadvantages to applying extrapolation factor distributions rather than single uncertainty factor values? Please explain your reasoning.

3. Chemical Grouping for Risk Assessment

OSHA is also considering the use of one or more chemical grouping approaches to expedite the risk assessment process. In certain cases, it may be appropriate to extrapolate data about one chemical across a group or category of similar chemicals. These approaches are discussed below.

a. Background on Chemical Grouping

The term 'grouping' or 'chemical grouping' describes the general approach to assessing more than one chemical at the same time. It can include formation of a chemical category or identification of a chemical analogue (OECD, 2007; *Ex. #39*). Chemical categories or analogues can be based on the structural relationship between the chemicals being grouped.

Structure-activity relationships (SAR) are relationships between a compound's chemical structure and physicochemical properties and its biological effects (*e.g.,* cancer) on living systems. Structurally diverse chemicals can sometimes be grouped for risk analysis based on a common mechanism/mode of action or metabolic activation pathway (*i.e.,* mechanism/mode of action clustering). Endpoint information for one chemical is used to predict the same endpoint for another chemical, which is considered to be ''similar'' in some way (usually on the basis of structural similarity and similar properties and/or activities).

A chemical category is a group of chemicals whose physical-chemical, human health, environmental, toxicological, and/or environmental fate properties are likely to be similar or follow a regular pattern as a result of structural similarity, structural relationship, or other characteristic(s). A chemical category is selected based on the hypothesis that the properties of a series of chemicals with common features will show coherent trends in their physical-chemical properties, and more importantly, in their toxicological effects (OECD, 2007; *Ex. #39*).

The use of a category approach means that it is possible to identify chemical properties which are common to at least some members of the category. This approach provides a basis for establishing trends in properties across that category and extends the measured data (*e.g.,* toxicological endpoint) to similar untested chemicals.

In the category approach, not every chemical in a group needs to have exposure-response data in order to be evaluated. Rather, the overall data for the category as a whole must prove adequate to support a risk assessment.

The overall data set must allow for an assessment of risk for the compounds and adverse outcomes that lack adequate study. Chemicals may be grouped for risk assessment based on the following:

- Common functional group (*e.g.,* aldehyde, epoxide, ester, specific metal ion);
- Common constituents or chemical classes, similar carbon range numbers;
- Incremental and constant change across the category (*e.g.,* a chain-length category);
- The likelihood of common precursors and/or breakdown products, via physical or biological processes, which result in structurally similar chemicals (*e.g.,* the metabolic pathway approach of examining related chemicals such as acid/ester/salt).

Within a chemical category, data gaps may be filled by read-across, trend analysis and Quantitative Structure-Activity Relationships (QSARs) and threshold of toxicological concern. In some cases, an effect can be present for some but not all members of the category. An example is the glycol ethers, where the lower carbon chain length members of the category indicate reproductive toxicity but the higher carbon chain length members of the category do not. In other cases, the category may show a consistent trend where the resulting potencies lead to different classifications (OECD, 2007; *Ex. #39*).

b. Methods of Gap Analysis and Filling

As a result of grouping chemicals based on similarities determined when employing the various techniques as described above, data gap filling in a chemical category can be carried out by applying one or more of the following procedures: read-across, trend analysis, quantitative (Q)SARs and threshold of toxicological concern (TTC).

i. Read-Across Method

The read-across approach uses endpoint information for one chemical (the source chemical) to predict the same endpoint for another chemical (the target chemical), which is considered to be ''similar'' in some way (usually on the basis of structural similarity or on the basis of the same mode or mechanisms of action). Read-across methods have been used to assess physicochemical properties and toxicity in a qualitative or quantitative manner. The main application for qualitative read-across is in hazard identification.

ii. Trend Analysis

Chemical category members are often related by a trend (*e.g.,* increasing, decreasing or constant) for any specific endpoint. The relationship of the categorical trend could be molecular mass, carbon chain length, or to some other physicochemical property.

The observation of a trend (increasing, decreasing or constant) in the experimental data for a given endpoint across chemicals can be used as the basis for interpolation and possibly also extrapolation to fill data gaps for chemicals with little to no data. Interpolation is the estimation of a value for a member using measured values from other members on ''both sides'' of that member within the defined category spectrum, whereas extrapolation refers to the estimation of a value for a member that is near or at the category boundary using measured values from internal category members (OECD, 2007; *Ex. #39*).

iii. QSAR

A Quantitative Structure-Activity Relationship (QSAR) is a quantitative relationship between a numerical measure of chemical structure, and/or a physicochemical property, and an effect/activity. QSARs use mathematical calculations to make predictions of effects/activities that are either on a continuous scale or on a categorical scale. ''Quantitative'' refers to the nature of the relationship between structurally related chemicals, not the endpoint being predicted. Most often QSARs have been used for determining aquatic toxicity or genotoxicity but can be used for evaluating other endpoints as well (OECD, 2007; *Ex. #39*).

Question IV.A.8: Are QSAR, read-across, and trend analysis acceptable methods for developing risk assessments for a category of chemicals with similar structural alerts (chemical groupings known to be associated with a particular type of toxic effect, *e.g.,* mutagenicity) or other toxicologically-relevant physiochemical attributes? Why or why not? Are there other suitable approaches?

iv. Threshold of Toxicological Concern (TTC)

The Threshold of Toxicological Concern (TTC) refers to the establishment of an exposure level for a group of chemicals below which there would be no appreciable risk to human health. The original concept proposed that a low level of exposure with a negligible risk can be identified for many chemicals, including those of unknown toxicity, based on knowledge of their chemical structures. The TTC approach is a form of risk characterization in which uncertainties arising from the use of data on other compounds are balanced against the low level of exposure. The approach was initially developed by the FDA for migration of chemicals from consumer packaging into food products and used a single threshold value of 1.5μg/day (referred to as the threshold of regulation).

The TTC principle extends the concept used in setting acceptable daily allowable intakes (ADIs) by proposing that a de minimis value can be identified for chemicals with little to no toxicity data utilizing information from structurally related chemicals with known toxicities.

A decision tree can be developed to apply the TTC principle for risk assessment decisions: