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# Proposed HTFOELs for Chronic Exposures – Nitrile-Class COPCs and 2,4-Dimethylpyridine

**May 2018**

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U.S. DEPARTMENT OF ENERGY

Prepared for the U.S. Department of Energy
under Contract DE-AC05-76RL01830

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# Proposed $_{HTF}$OELs for Chronic Exposures – Nitrile-Class COPCs and 2,4-Dimethylpyridine

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# Executive Summary

Chemicals of Potential Concern (COPC) related to Hanford Tank Farm (HTF) operations have been re-evaluated based on updated regulatory information that would impact existing Occupational Exposure Limits (OEL, termed $_{HTF}$OEL). A new focus on identifying regulatory information that may help understand acute health effects of COPCs is underway that led to a specific focus on the nitrile class COPCs in the present report. In the process of re-evaluating the 61 current COPCs, a difference in acute and chronic regulatory values for acetonitrile was identified. This justified re-evaluation to understand this unexpected difference. Specifically, the acute exposure guideline level (Acute Exposure Guideline Level -1; 13 parts per million [ppm]) for management of emergency situations developed by the U.S. Environmental Protection Agency for acetonitrile was lower than chronic OELs reported by the Occupational Safety and Health Administration and the American Conference of Governmental Industrial Hygienists (ACGIH) (20 ppm). The technical basis for this difference was a change in the weight-of-evidence used in updated risk assessments by the ACGIH. Based on this finding, the most comprehensive risk assessment for acetonitrile reported by the ACGIH is proposed for continued application. No changes were identified in regulatory information for surrogate nitriles used to develop $_{HTF}$OELs or additional nitrile-class COPCs with defined regulatory values. Therefore, existing $_{HTF}$OELs for nitrile-class COPCs are proposed for continued application. The compound 2,4-dimethylpyridine also was re-evaluated here to complete the COPC update.

# Acronyms and Abbreviations

| | |
|---|---|
| ACGIH | American Conference of Governmental Industrial Hygienists |
| AEGL | Acute Exposure Guideline Level |
| COPC | Chemicals of Potential Concern |
| DOE | U.S. Department of Energy |
| EPA | Environmental Protection Agency |
| HTF | Hanford Tank Farm |
| $_{HTF}$OEL | Hanford Tank Farm Occupational Exposure Limit |
| $LD_{50}$ | median lethal dose |
| NIOSH | National Institute of Occupational Safety and Health |
| OEL | Occupational Exposure Limits |
| OSHA | Occupational Safety and Health Administration |
| PNNL | Pacific Northwest National Laboratory |
| ppm | parts per million |
| REL | Recommended Exposure Limit |
| TEEL | Temporary Emergency Exposure Limit |
| TLV–TWA | Threshold Limit Value–Time-Weighted Average |

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# 1.0 Introduction

In 2016, current Chemicals of Potential Concern (COPC) related to Hanford Tank Farm (HTF) operations were evaluated for new regulatory information that would warrant updating Occupational Exposure Limits (OEL). The OELs used to guide safe HTF operations are termed $_{HTF}$OELs and were originally documented in an earlier Pacific Northwest National Laboratory (PNNL) technical report (PNNL-15736, Poet and Timchalk 2006). During the process of updating $_{HTF}$OELs, acute exposure guideline levels (AEGLs) used for emergency management by the U.S. Environmental Protection Agency (EPA) were identified for acetonitrile that were lower than chronic regulatory values reported by the American Conference of Governmental Industrial Hygienists (ACGIH). This discovery justified closer examination of the technical basis for the acetonitrile assessments reported by EPA and ACGIH. The primary mechanism of toxicity induced by nitriles is related to the metabolic generation of cyanide. Understanding the technical basis for the acute and chronic acetonitrile assessments was necessary to determine whether the difference was simply a change in weight-of-evidence, or whether a change in mode-of-action was apparent that may warrant consideration in the development of $_{HTF}$OELs for other nitrile-class COPCs. It is noted that priority for establishing $_{HTF}$OELs is given to values reported by ACGIH and the Occupational Safety and Health Administration (OSHA), due to contractual obligations (U.S. Department of Energy [DOE]) and legal authority (OSHA).

For some nitrile-class COPCs, the chronic $_{HTF}$OEL is based on the use of a surrogate chemical because no regulatory information on the specified nitrile COPC could be identified. The lack of human toxicity data for many chemicals has driven a need for computational efforts to exploit structure-activity relationships, a means by which the effect of a toxic chemical on an animal, a human, or the environment can be related to its molecular structure, to address this data gap in risk assessment (Wang et al. 2012). In the case of $_{HTF}$OELs based on surrogates, if regulatory information on the surrogate chemical has not changed from the values reported in PNNL-15736, continued use of the surrogate-based $_{HTF}$OEL for HTF operations is proposed. In cases in which regulatory information on surrogates had changed relative to values reported in PNNL-15736, uncertainty factors used in PNNL-15736 were reviewed and either modified (with justification) or directly applied to the new surrogate regulatory guidelines to update the $_{HTF}$OEL.

# 2.0 Definitions of Key Terms used in Chronic $_{HTF}$OEL Evaluations

## 2.1 Threshold Limit Values

Technical information on Threshold Limit Values (TLV) was taken directly from ACGIH documents that provide information on TLVs and Basic Exposure Indices (ACGIH 2016). TLVs refer to airborne concentrations of chemical substances and represent conditions under which it is believed that nearly all workers may be repeatedly exposed, day-after-day, over a working lifetime, without experiencing adverse health effects. Because the information available for a specified chemical substance varies over time, TLVs should be regularly updated. Chemical substances with equivalent TLVs (i.e., the same numerical values) cannot be assumed to have similar toxicological effects or similar biologic potency. TLVs do not represent a fine line between a healthy versus an unhealthy work environment or the point at which material impairment of health will occur.

TLVs will not adequately protect all workers. Some individuals may experience discomfort or even more serious adverse health effects when exposed to a chemical substance at the TLV or even at concentrations below the TLV. There are many possible reasons for increased susceptibility to a chemical substance, including age, gender, ethnicity, genetic factors (predisposition), lifestyle choices (e.g., diet, smoking, abuse of alcohol and other drugs, etc.), medications, and pre-existing medical conditions (e.g., aggravation of asthma or cardiovascular disease). Some individuals may become more responsive to one or more chemical substances following previous exposures (e.g., sensitized workers). Susceptibility to the effects of chemical substances may be altered during different periods of fetal development and throughout an individual's reproductive lifetime. Some changes in susceptibility may also occur at different work levels (e.g., light versus heavy work) or during exercise periods when increased cardiopulmonary demand is experienced. In addition, variations in temperature (e.g., extreme heat or cold) and relative humidity may alter an individual's response to a toxicant. The documentation for any given TLV should be periodically reviewed and updated, keeping in mind that other factors may modify biological responses.

## 2.2 Threshold Limit Value–Time-Weighted Average

The Threshold Limit Value–Time-Weighted Average (TLV–TWA) typically represents the TWA concentration for a conventional 8-hour workday and a 40-hour workweek, during which it is believed nearly all workers may be repeatedly exposed, day-after-day, for a working lifetime without adverse effects. However, as discussed above, different regulatory agencies may report TLV–TWA information based on different work shift schedules. Established guidelines exist for calculating adjustments that account for differences in exposure due to changes in work shift times. For cases in which National Institute of Occupational Safety and Health (NIOSH) OELs were identified as regulatory guidelines, the documented 10-hour TLV–TWA is applied directly to the 8-hour time period reported for implementation as a chronic $_{HTF}$OEL. It is noted that the typical "in-farm" time for HTF workers is less than 8 hours; therefore, TLV values listed for chronic exposures are conservative. It is possible that future efforts could examine the merit of exposure standard adjustments proposed by the Australian Institute of Occupational Hygienists (AIOH 2016). These suggested standard adjustments consider differences between ceiling standards, mild irritants, standards set by technological feasibility or good hygiene practices, acute toxicants, cumulative toxicants, and both acute plus cumulative toxicants.

## 2.3 Threshold Limit Value–Ceiling

TLV−Ceiling represents the concentration of a chemical substance that should not be exceeded during any part of the working exposure. If instantaneous measurements are not available, sampling should be conducted for the minimum period of time sufficient to detect exposures at or above the ceiling value. Regulatory agencies such as ACGIH believe that TLVs based on physical irritation should be considered no less binding than those based on physical impairment. There is increasing evidence that physical irritation may initiate, promote, or accelerate adverse health effects through interaction with other chemical or biologic agents or through other mechanisms.

## 2.4 Occupational Exposure Limit

An OEL is an upper limit on the acceptable concentration of airborne hazardous substances in the workplace for a particular material or class of materials. OELs are generally set by competent national authorities and enforced by legislation to protect occupational safety and health.

## 2.5 Temporary Emergency Exposure Limit

A Temporary Emergency Exposure Limit (TEEL) is a chemical exposure guideline to use in emergency planning developed by DOE when additional chemical exposure guidelines (i.e., AEGL or Emergency Response Planning Guidelines) are not available.

# 3.0 Assessment Description

In this report, we provide relevant background on historical efforts to establish $_{HTF}$OELs and current efforts to update $_{HTF}$OELs based on new regulatory information where applicable. Chapter 4 summarizes the initial recommended chronic $_{HTF}$OELs to Washington River Protection Solutions. The recommended chronic $_{HTF}$OELs (TLV–TWA or ceiling values) for nitrile-class COPCs and 2,4-dimethylpyridine are presented in Chapter 4 in Table 2. The COPC data set consists of nine chemicals. Discussions of the rationale and justifications for the recommended $_{HTF}$OELs follow Table 2 and are presented in the same order as listed in the table.

## 3.1 Historical Perspective on $_{HTF}$OELs for Nitriles

Nitriles are readily absorbed from the lung and gastrointestinal tract, resulting in systemic toxicity. Most of the systemic toxicity of aliphatic nitriles is mediated through hepatic and extrahepatic cytochrome P450 catalyzed oxidation of the carbon alpha to the cyano-group producing a cyanohydrin and an aldehyde. The metabolically liberated cyanide then is conjugated with thiosulfate to form thiocyanate and is excreted in the urine. The metabolic release of cyanide is the major mechanism by which nitriles induce toxicity. Cyanide interrupts cellular respiration by blocking the terminal step of electron transfer from cytochrome c oxidase to oxygen. Tissue concentrations of oxygen then rise, resulting in increased tissue oxygen tension and a decreased unloading of oxyhemoglobin. As a consequence, oxidative metabolism may slow to a point where it cannot meet metabolic demands. This is particularly critical in the brain stem nuclei where lack of an energy source results in central respiratory arrest and death. Cyanide also stimulates chemoreceptors of the carotid and aortic bodies to produce a brief period of hyperpnea. Cardiac irregularities may occur, but death results from respiratory arrest (Smith 1995).

The toxicity of nitriles is significantly influenced by the carbon side chain length (Figure 1; Tanii and Hashimoto 1984a). This was determined by a comparison of the $LD_{50}$[1] concentrations of nitriles with carbon side chain lengths ranging from 1 to 8. Short carbon side chains (2 to 4) were among the most potent nitriles, while longer carbon side chain lengths were associated with significant decreases in nitrile toxic potential. In PNNL-15736, $_{HTF}$OELs were developed for saturated alkyl nitriles with two to nine carbon alkyl side chains, and unsaturated alkenes with three to four carbon side chains. The $LD_{50}$ values determined by Tanii and Hashimoto (1984a) (Figure 1) formed the basis for the current $_{HTF}$OELs for nitriles that lacked regulatory information. For alkyl nitriles, propanenitrile (NIOSH Recommended Exposure Limit [REL], 6 parts per million [ppm]), and butanenitrile (NIOSH REL, 8 ppm) were identified as potent nitrile family members (two to three carbon side chain lengths), and propanenitrile was selected as a surrogate because it had the most robust toxicology data and was characterized by the most conservative regulatory value (NIOSH REL, 6 ppm). Nitrile-class COPCs with carbon side chains longer than three were then conservatively set at 6 ppm.

[1] Median lethal dose, $LD_{50}$ (abbreviation for lethal dose, 50%), is a measure of the lethal dose of a toxin, radiation, or pathogen. The value of $LD_{50}$ for a substance is the dose required to kill half the members of a tested population after a specified test duration. $LD_{50}$ values are frequently used as a general indicator of a substance's acute toxicity. A lower $LD_{50}$ is indicative of increased toxicity.

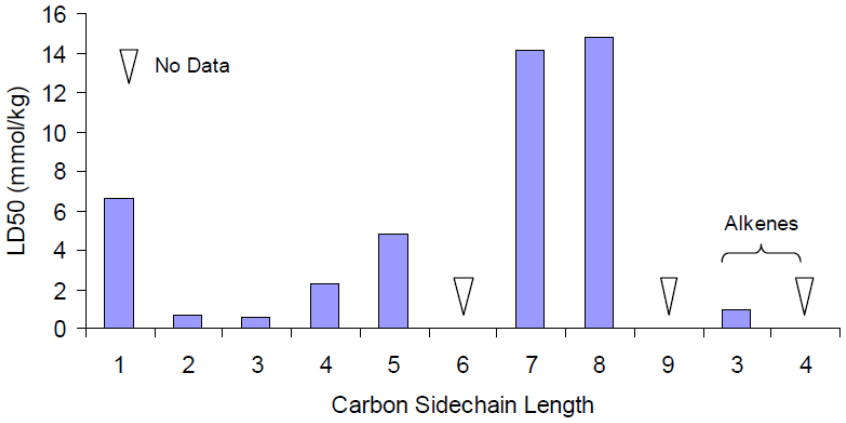


**Figure 1**. Comparison of Mice $LD_{50}$ Values Based on Nitrile Carbon Sidechain Length (Tanii and Hashimoto 1984a)

The approach used in PNNL-15736 was consistent with EPA efforts to develop risk assessments for nitrile-class chemicals. The EPA Office of Pollution Prevention and Toxics had accepted a proposal from Eastman Kodak Co. and Solutia, Inc. to group alkyl nitriles with up to three carbons (C–3) for the purposes of addressing data gaps. Upon adoption of this approach, nitriles with longer side chains also were considered within this family. A decision to combine the alkyl and alkene nitriles as a family for risk assessment also was made. This decision was driven by the comparable available data, the similarity of the compounds, and the common active group (C≡N) and mechanism of action (metabolically released cyanide; CN–). Tanii and Hashimoto (1984a, 1984b) found cyanide metabolism in all the tested members of the nitrile family, which supported the decision to combine the alkyl and alkene nitriles as a family for risk assessment. Similar to alkyl nitriles, several alkene nitriles did not have any available regulatory information and surrogate alkene nitriles were selected to develop $_{HTF}$OELs. NIOSH had recommended RELs for acrylonitrile (OSHA Permissible Exposure Limit [PEL], 2 ppm; NIOSH REL, 1 ppm) and methacrylonitrile (NIOSH REL, 1 ppm), which were structurally similar to alkene nitrile COPCs (2,-4-pentadienenitrile and 2-methylene butanenitrile). Toxicity data reported by Tanii and Hashimoto (1984a) indicated $LD_{50}$ values for the alkene nitriles that were comparable to alkyl nitriles with similar carbon side chain lengths (Table 1). Therefore, methacrylonitrile was selected as a surrogate for alkene nitrile-class COPCs using the most conservative regulatory value (NIOSH REL, 1 ppm) and an uncertainty factor of 3× was applied due to lack of toxicity data. Based on this approach, an $_{HTF}$OEL of 1 ppm was proposed for 3-butenenitrile, for which toxicity data were available, and 0.3 ppm for 2,-4-pentadienenitrile and for 2-methylene butanenitrile, for which no toxicity data were available.

**Table 1**. Acute or Subchronic $LD_{50}$ Values and OELs for Alkene Nitriles

| Nitrile | C# | Species | $LD_{50}$[a] (mmol/kg) | Exposure Limit/Agency |
|---|---|---|---|---|
| Acrylonitrile | 2 | Mouse | 0.73 | 2 ppm/OSHA PEL |
| Methacrylonitrile | 3 | Mouse | 0.26 | 1 ppm/NIOSH REL |
| 3-Butenenitrile | 3 | Mouse | 1.0 | 1 ppm/NIOSH REL |

[a] All $LD_{50}$ values are from Tanii and Hashimoto (1984a).

## 3.2 Acetonitrile Risk Assessment Technical Basis Reported by EPA and ACGIH

During the process of updating $_{HTF}$OELs, acute emergency management values for acetonitrile reported by EPA (AEGL-1) were identified that were lower than the previously determined chronic regulatory values reported by ACGIH. The technical basis for acetonitrile regulatory values reported by EPA (13 ppm) and ACGIH (20 ppm) were compared to understand why an AEGL value that may be associated with observable adverse health effects (reversible) was lower than a chronic OEL, which should not be associated with adverse health effects over a working lifetime. EPA AEGL values are developed as emergency management guidelines for acute chemical exposures. Operations in emergency situations can tolerate varying levels of adverse health effects, particularly if they are transient and reversible, to enable emergency personnel to perform their duties. AEGLs are assigned to three different levels (AEGL-1, AEGL-2, and AEGL-3) according to the severity of effects. The AEGL-1 level represents effects producing notable discomfort, irritation, or certain asymptomatic non-sensory effects that are not disabling and are transient and reversible upon cessation of exposure. Therefore, AEGL-1 values are the most relevant values to compare to OELs, although AEGL values would still be higher than desired for an occupational exposure. AEGL-2 and AEGL-3 values produce irreversible or life-threatening health effects that are clearly unacceptable for consideration in an industrial hygiene program. The technical basis for EPA AEGL values developed for aliphatic nitriles, including acetonitrile, was documented in a technical report published by the National Research Council (NRC 2014).

The EPA AEGL-1 value was derived from human exposure data. Although multiple case reports of acetonitrile toxicity in humans existed at the time the AEGL-1 value was derived, exposure concentrations and durations were not available for the majority of the case studies, which precluded their inclusion in the quantitative risk assessment. Only one controlled experiment of the acute inhalation toxicity of acetonitrile was available (Pozzani et al. 1959), and no information about the potential human developmental and reproductive toxicity, genotoxicity, or carcinogenicity was found. Pozzani and his team studied three male volunteers (ages 31 to 47) who inhaled acetonitrile at 40 ppm for 4 hours. The two older subjects reported no subjective symptoms during or after the inhalation period. The youngest subject reported no adverse subjective response during exposure, but experienced slight chest tightness that evening. The following morning, he reported a cooling sensation in the lungs, which persisted for 24 hours. He described the sensation as being similar to that experienced when menthol is inhaled. The two older subjects were exposed 1 week later to acetonitrile at 80 ppm for 4 hours; no symptoms were reported. Nine days after the 80-ppm exposure, the same two subjects were exposed at 160 ppm for 4 hours. One subject reported a slight transitory flushing of the face 2 hours after inhalation and slight bronchial tightness 5 hours later, which resolved overnight. This study was used as the basis for AEGL-1 values. An inter-species uncertainty factor of 1 was applied because the critical study was conducted in humans. A factor of 1 also was applied for intra-species variability, because the mild effects were judged to have occurred in a sensitive subject. A modifying factor of 3 was applied to account for the sparse database for effects relevant to AEGL-1. The 4-hour AEGL-1 value of 13 ppm was held constant across the 10-minute, 30-minute, and 1-hour durations because no human data were available for exposure durations of less than 4 hours; thus, time scaling to shorter durations could result in values that would elicit symptoms above those defined by AEGL-1. A calculated value for an 8 hour duration was 14 ppm, which is essentially equal to the 4 hour AEGL-1 value of 13 ppm, so an 8 hour AEGL-1 value was not recommended by the EPA. In addition, the final National Research Council technical document on aliphatic nitriles (NRC 2014) listed a need for additional data in humans or animals to support AEGL-1 values because the current assessment was based on a single experimental study.

The ACGIH TLV–TWA value (20 ppm) was derived from the same Pozzani et al. (1959) study in combination with animal studies that were not considered when deriving AEGL-1 values. Inclusion of animal studies is consistent with the National Research Council AEGL report (NRC 2014), suggesting consideration of additional human and animal studies to support the AEGL-1 assessment. The ACGIH considered animal lifetime inhalation studies, shorter-term inhalation studies, and carcinogenicity, developmental, and genotoxicity studies (ACGIH 2002). It was noted that both short-term and lifetime inhalation studies indicated that a 200 ppm acetonitrile dose was not active in rodents. Inclusion of both human and animal exposure data provided increased weight-of-evidence in the ACGIH assessment, compared with the AEGL-1 assessment. Finally, it is noted that the ACGIH is a prioritized regulatory source for chronic OEL values due to contractual obligations with DOE. Based on the increased weight-of-evidence in the ACGIH assessment, the ACGIH TLV–TWA value for acetonitrile of 20 ppm is proposed for continued application to $_{HTF}$OELs. No evidence for a new mode-of-action was identified that may warrant consideration in $_{HTF}$OELs for additional nitrile-class COPCs.

# 4.0 Recommended Chronic HTFOELs

A comprehensive evaluation of the technical basis for acute and chronic regulatory values for acetonitrile determined that differences between EPA and ACGIH guidelines were related to weight-of-evidence. The ACGIH assessment was the most comprehensive and the ACGIH is a prioritized regulatory authority by the DOE. No additional changes in regulatory values for nitrile-class COPCs or 2,4-dimethylpyridine were identified. Therefore, no changes to the existing HTFOEL values established in PNNL-15736 (Poet and Timchalk 2006) for these chemicals are proposed (see Table 1).

**Table 2**. Proposed Chronic HTFOEL Exposure Guidelines

| Chemical | Carbon # | Chemical Abstract Service Number | Current HTFOEL (ppm) | Proposed Regulatory Guideline (ppm) | Agency/ TLV specification |
|---|---|---|---|---|---|
| **Nitriles** | | | | | |
| 1. Acetonitrile | 1 | 75-05-8 | 20 | 20 | ACGIH TWA |
| 2. Propanenitrile | 2 | 107-12-0 | 6 | 6 | NIOSH TWA |
| 3. Butanenitrile | 3 | 109-74-0 | 8 | 8 | NIOSH TWA |
| 4. Pentanenitrile | 4 | 110-59-8 | 6 | 6 | (Surrogate) NIOSH TWA |
| 5. Hexanenitrile | 5 | 628-73-9 | 6 | 6 | (Surrogate) NIOSH TWA |
| 6. Heptanenitrile | 6 | 629-08-3 | 6 | 6 | (Surrogate) NIOSH TWA |
| 7. 2-Methylene butanenitrile | 3 | 1647-11-6 | 0.3 | 0.3 | (Surrogate) NIOSH TWA |
| 8. 2,4-Pentadienenitrile | 4 | 1615-70-9 | 0.3 | 0.3 | (Surrogate) NIOSH TWA |
| **Pyridines** | | | | | |
| 9. 2,4-Dimethylpyridine | N/A | 108-47-4 | 0.5 | 0.5 | DOE TEEL-1 |

## 4.1 Justification for Proposed Chronic HTFOELs

### 4.1.1 Nitriles

**Acetonitrile Recommendation**: 20 ppm TLV–TWA 8 hours

**Source/Justification**: ACGIH 2016 handbook. This proposed value is unchanged from PNNL-15736.

The primary concern with updating the HTFOEL for acetonitrile came from a difference in acute regulatory values reported for EPA AEGL-1 (13 ppm) compared with ACGIH TLV–TWA (20 ppm). The technical basis for this discrepancy was discussed in detail in Section 3.2 and was found to be a change in weight-of-evidence for the assessment reported by the ACGIH. In summary, the EPA AEGL-1 assessment was based on a single human exposure study described by Pozzani et al. (1959) with specified uncertainty factors included in the assessment. The EPA AEGL-1 technical basis specifically noted the single human study basis of the assessment as a weakness and recommended that future risk assessments include additional human and animal studies. The ACGIH assessment considered the same Pozzani et al (1959) study, as well as animal lifetime inhalation studies, short-term inhalation studies, carcinogenicity, developmental, and genotoxicity studies (ACGIH 2002). It was noted that both short-term and lifetime inhalation studies indicated that a 200 ppm acetonitrile dose was not active in rodents. Based on increased weight-of-evidence provided in the ACGIH assessment and prioritization of regulatory values based on a DOE contractual obligation, a 20 ppm acetonitrile TLV–TWA is proposed for continued application.

**Propanenitrile Recommendation**: 6 ppm TLV–TWA 10 hours

**Source/Justification**: NIOSH Pocket Guide to Chemical Hazards. The NIOSH REL is unchanged from PNNL-15736.

**Butanenitrile Recommendation**: 8 ppm TLV–TWA 10 hours

**Source/Justification**: NIOSH Pocket Guide to Chemical Hazards. The NIOSH REL is unchanged from PNNL-15736.

**Pentanenitrile Recommendation**: 6 ppm TLV–TWA 10 hours

**Source/Justification**: The $_{HTF}$OEL for pentanenitrile is based on use of propanenitrile as surrogate with regulatory values taken from the NIOSH Pocket Guide to Chemical Hazards.

Propanenitrile was selected as a surrogate for alkyl nitrile-class COPCs when PNNL-15736 was being prepared because it has the most robust toxicological data and the most conservative regulatory value. The length of the carbon side chain significantly influences toxicity, and propanenitrile is recognized as a highly potent nitrile. The EPA Office of Pollution Prevention and Toxics has accepted a proposal from Eastman Kodak Co. and Solutia, Inc., to combine alkyl nitriles with up to three carbons (C–3) for the purposes of addressing data gaps, and PNNL adopted this approach. For the purpose of developing $_{HTF}$OELs, nitriles with longer side chains also are considered within this family. Research reported by Tanii and Hashimoto (1984a, 1984b) found cyanide metabolism in all the tested members of this family. The $LD_{50}$ values determined by Tanii and Hashimoto (1984a) formed the basis for the proposed $_{HTF}$OELs for chemicals in this family that for which no regulatory guidelines exist. As a conservatism, nitriles with carbon side chains longer than three (less toxic than propanenitrile) were conservatively set at the OEL for propanenitrile (6 ppm). Pentanenitrile has a four-carbon side chain length and is expected to be less toxic than propanenitrile; hence, application of the more conservative regulatory value for propanenitrile. The NIOSH REL value for propanenitrile is unchanged from PNNL-15736. Therefore, a 6 ppm TLV–TWA is proposed for continued application to pentanenitrile.

**Hexanenitrile Recommendation**: 6 ppm TLV–TWA 10 hours

**Source/Justification**: The $_{HTF}$OEL for hexanenenitrile is based on use of propanenitrile as a surrogate with regulatory values taken from the NIOSH Pocket Guide to Chemical Hazards.

Propanenitrile was selected as a surrogate for alkyl nitrile-class COPCs when PNNL-15736 was being prepared because it has the most robust toxicological data and the most conservative regulatory value. The length of the carbon side chain significantly influences toxicity and propanenitrile is recognized as a highly potent nitrile. The EPA Office of Pollution Prevention and Toxics has accepted a proposal from Eastman Kodak Co. and Solutia, Inc., to combine alkyl nitriles with up to three carbons (C–3) for the purposes of addressing data gaps, and PNNL adopted this approach. For the purpose of developing $_{HTF}$OELs, nitriles with longer side chains also are considered within this family. Research reported by Tanii and Hashimoto (1984a, 1984b) found cyanide metabolism in all the tested members of this family. The $LD_{50}$ values determined by Tanii and Hashimoto (1984a) formed the basis for the proposed $_{HTF}$OELs for chemicals in this family that lack regulatory guidelines. As a conservatism, nitriles with carbon side chains longer than three (less toxic than propanenitrile) were conservatively set at the OEL for propanenitrile (6 ppm). Hexanenenitrile has a five-carbon side chain length and is expected to be less

toxic than propanenitrile, hence application of the more conservative regulatory value for propanenitrile. The NIOSH REL value for propanenitrile is unchanged from PNNL-15736. Therefore, a 6 ppm TLV–TWA is proposed for continued application to hexanenenitrile.

**Heptanenitrile Recommendation**: 6 ppm TLV–TWA 10 hours

**Source/Justification**: The $_{HTF}$OEL for heptanenenitrile is based on use of propanenitrile as surrogate with regulatory values taken from the NIOSH Pocket Guide to Chemical Hazards.

Propanenitrile was selected as a surrogate for alkyl nitrile-class COPCs when PNNL-15736 was being prepared because it has the most robust toxicological data and the most conservative regulatory value. The length of the carbon side chain significantly influences toxicity and propanenitrile is recognized as a highly potent nitrile. The EPA Office of Pollution Prevention and Toxics has accepted a proposal from Eastman Kodak Co. and Solutia, Inc., to combine alkyl nitriles with up to three carbons (C–3) for the purposes of addressing data gaps, and PNNL adopted this approach. For the purpose of developing $_{HTF}$OELs, nitriles with longer side chains are also considered within this family. Research reported by Tanii and Hashimoto (1984a, 1984b) found cyanide metabolism in all the tested members of this family. The $LD_{50}$ values determined by Tanii and Hashimoto (1984a) formed the basis for the proposed $_{HTF}$OELs for chemicals in this family that lack regulatory guidelines. As a conservatism, nitriles with carbon side chains longer than three (less toxic than propanenitrile) were conservatively set at the OEL for propanenitrile (6 ppm). Heptanenenitrile has a six-carbon side chain length and is expected to be less toxic than propanenitrile, hence application of the more conservative regulatory value for propanenitrile. The NIOSH REL value for propanenitrile is unchanged from PNNL-15736. Therefore, a 6 ppm TLV–TWA is proposed for continued application to heptanenenitrile.

**2-Methylene butanenitrile Recommendation**: 0.3 ppm TLV–TWA 10 hours

**Source/Justification**: Regulatory information for 2-Methylene butanenitrile was not identified.

The $_{HTF}$OEL for 2-Methylene butanenitrile is based on alkene nitrile carbon side chain lengths and the use of methacrylonitrile as a structurally similar surrogate. Both methacrylonitrile and 2-Methylene butanenitrile are characterized by a three-carbon side chain length, indicating their toxic potencies may be similar. The NIOSH REL for methacrylonitrile is 1 ppm. Because of the lack of toxicity data for 2-Methylene butanenitrile, an additional 3× uncertainty factor was applied in PNNL-15736 and is proposed for continued application here. Therefore, a 0.3 ppm TWA is proposed for continued application to 2-Methylene butanenitrile, which is unchanged from PNNL-15736.

**2,4-Pentadienenitrile Recommendation**: 0.3 ppm TLV–TWA 10 hours

**Source/Justification**: Regulatory information for 2,4-Pentadienenitrile was not identified.

The $_{HTF}$OEL for 2,4-Pentadienenitrile is based on alkene nitrile carbon side chain length and the use of methacrylonitrile as a structurally similar surrogate. Methacrylonitrile is characterized by a three-carbon side chain length and 2,4-Pentadienenitrile is characterized by a four-carbon side chain length, suggesting 2,4-Pentadienenitrile will be less toxic. As a conservatism, the NIOSH REL for methacrylonitrile (1 ppm) was applied to 2,4-Pentadienenitrile with an additional 3× uncertainty factor due to the lack of toxicity data. The NIOSH REL for methacrylonitrile has not changed from the values used in PNNL-15736, therefore, a 0.3 ppm TLV–TWA is proposed for continued application to 2,4-Pentadienenitrile.

### 4.1.2 Pyridines

**2,4-Dimethylpyridine Recommendation**: 0.5 ppm TLV–TWA

**Source/Justification**: DOE TEEL-1.

Based on the comparison of acute and subchronic effects of 5-ethyl-2-picoline, pyridine, and 2,4-dimethylpyridine in laboratory animals and the effects from human exposures to pyridine mixtures, a DOE TEEL-1 of 0.5 ppm was proposed as the $_{HTF}$OEL for 2,4-dimethylpyridine in PNNL-15736.

TEEL-1 is similar to the ACGIH TLV of 1 ppm for pyridine and the AIHA TEEL of 2 ppm for 2-methylpyridine, 3-methylpyridine, and 4-methylpyridine. The definition of TEEL-1 is, "… the maximum airborne concentration below which it is believed that nearly all individuals could be exposed without experiencing other than mild transient adverse health effects or perceiving a clearly defined, objectionable odor." The TEEL-1 value usually is based on a 1-hour TWA. In addition, the World Health Organization recognizes 2,4-dimethylpyridine as having "no safety concern" for oral exposures (WHO 2012). Therefore, the TEEL-1 value is considered to be very conservative. No additional regulatory information on 2,4-dimethylpyridine was identified. This proposed value is unchanged from PNNL-15736.

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