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Proposed Risk-Based Approach for Nitrosamine Chemicals of Potential Concern

December 2018

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U.S. DEPARTMENT OF ENERGY

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Executive Summary

This report documents the re-evaluation of Hanford Tank Farm (HTF) occupational exposure limits (OEL) for five N-nitrosamines identified as Chemicals of Potential Concern (COPC), and two other N-nitrosamines being considered as COPCs. N-nitrosamines are genotoxic, and exposure has been historically regulated based on cancer as the endpoint of concern. Currently, $_{HTF}$OELs are based on German Maximum Arbeitsplatz Konzentration values that are no longer used. The National Institute of Occupational Safety and Health (NIOSH) recently released new policy applying a risk-based approach to develop OELs for occupational carcinogens and plans to release guidance on specific chemicals in the future. Consistent with this new NIOSH policy, Pacific Northwest National Laboratory proposes a risk-based approach to establish risk-specific doses for occupational exposures to N-nitrosamine COPCs. This approach establishes a range of N-nitrosamine inhalation exposures associated with risk levels that can be used as a tool for protecting HTF workers. Updated guidance from NIOSH or other authoritative bodies on N-nitrosamine OELs should trigger a re-evaluation of this proposed approach.

Acronyms and Abbreviations

ACGIH	American Conference of Government Industrial Hygienists
AT	averaging time
BA	bioavailability
BW	body weight
COPC	Chemicals of Potential Concern
CSF	cancer slope factor
ED	exposure duration
EF	exposure frequency
EPA	U.S. Environmental Protection Agency
HTF	Hanford Tank Farm
$_{HTF}$OEL	Hanford Tank Farm Occupational Exposure Limit
IR	inhalation rate
MAK	Maximum Arbeitsplatz Konzentration
NIOSH	National Institute of Occupational Safety and Health
OEL	occupational exposure limits
OSHA	Occupational Safety and Health Administration
PAC	Protective Action Criteria
PNNL	Pacific Northwest National Laboratory
RL	risk level
RML-CA	Risk Management Limits for Carcinogens
RPP	River Protection Project

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1.0 Introduction

The Industrial Hygiene Chemical Vapor Technical Basis (Meacham et al. 2006) is the current basis for identifying and managing Chemicals of Potential Concern (COPC) at the Hanford Tank Farm (HTF). That report documented occupational exposure limits (OEL) for the HTF COPCs and their technical bases. OELs provide guidance for safe HTF operations. The term $_{HTF}$OELs originally defined by Poet and Timchalk (2006) and Meacham et al. (2006) is used to refer to OELs established for use in HTF operations.

In 2016, Pacific Northwest National Laboratory (PNNL) conducted a review of $_{HTF}$OELs to determine if new toxicity data existed or if new OELs had been proposed by authoritative organizations (e.g., National Institute of Occupational Safety and Health [NIOSH], Occupational Safety and Health Administration [OSHA], American Conference of Government Industrial Hygienists [ACGIH]) that would warrant revisions of OELs proposed in 2006.[1] The review found sufficient new information for multiple chemicals that warrant $_{HTF}$OEL updates. This report documents the re-evaluation of nitrosamines.

[1] Smith JN, C Timchalk, and TJ Weber. 2016. *State of Knowledge Assessment: COPC/Exposure Limits*. PNNL-25790, Pacific Northwest National Laboratory, Richland, Washington. (unpublished)

2.0 Nitrosamine Background

Nitrosamines are chemicals that contain a nitroso group bound to an amine. Formed naturally and by industrial processes, nitrosamines are found in air, water, food, cosmetics, and tobacco products (Park et al. 2015). In 2012, an average annual total nitrosamine concentration of 5.2 ng/m^3 was measured in ambient particulate matter located in London, England.[2] That concentration substantially exceeds public guidelines for exposure on a daily basis (0.3 ng/m^3) (Farren et al. 2015). This illustrates that exposures to elevated nitrosamine concentrations can and often occur at places outside the HTF, such as urban environments. Five nitrosamines found at the HTF were selected by the assessment team as high-priority COPCs, and two other nitrosamines are being considered as COPCs (Table 1).

Table 1. High-Priority COPC N-Nitrosamines

Compound	Chemical Abstract Service Registry Number	MAK[a]-Based OEL (ppb)
N-Nitrosodimethylamine (NDMA)	62-75-9	0.3
N-Nitrosodiethylamine	55-18-5	0.1
N-Nitrosomethylethylamine	10595-95-6	0.3
N-Nitrosomorpholine	59-89-2	0.6[b]
N-Nitrosodibutylamine	924-16-3	Not applicable
N-Nitrosopiperidine[c]	100-75-4	Not applicable
N-Nitrosodi-N-propylamine[c]	621-64-7	Not applicable

[a] Maximum Arbeitsplatz Konzentration (MAK), German Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area.
[b] Adjusted based on NDMA MAK. See Meacham et al. (2006).
[c] N-Nitrosamines currently being considered for COPCs.

Historically, nitrosamine exposure has been regulated based on cancer (primarily liver cancer) as the effect-of-concern. Once absorbed into the body, nitrosamines can be metabolized. The alpha carbon adjacent to the N-nitroso group can be hydroxylated by cytochrome P450 enzymes. Rearrangement products of these nitrosamine metabolites are reactive and can readily bind irreversibly to DNA, forming adducts. By virtue of their genotoxicity, many nitrosamines cause cancer in laboratory animals, and all seven nitrosamines identified in Table 1 have been classified as either possible or probable human carcinogens by the Environmental Protection Agency (EPA) Integrated Risk Information System and the International Agency for Research on Cancer.

Protective Action Criteria (PAC) were developed for N-nitrosomorpholine and NDMA (Table 2). PACs are short-term, acute criteria (i.e., 1 hour) that were developed based on rat oral acute toxicity data. PACs may have utility for establishing acute occupational guidelines but have limited utility for chronic occupational exposure guidelines. As such, these criteria were not used to recommend chronic $_{HTF}$OEL occupational guidelines.

The 2016 report prepared by PNNL recommended that $_{HTF}$OELs for all N-nitrosamines be re-evaluated.[1] $_{HTF}$OELs recommended in 2006 by Meacham et al. (2006) were adopted from MAK values (Table 1). Since that time, the approach for establishing exposure limits for carcinogenic N-nitrosamines has evolved considerably.

[2] A total nitrosamine concentration of 5.2 ng/m^3, if represented entirely by NDMA, would be approximately 0.0017 ppb. Similarly, 0.3 ng/m^3 would be approximately 0.0001 ppb.

Table 2. Protective Action Criteria for COPC N-Nitrosamines

Classification	Protective Action Criteria			
	NDMA		N-Nitrosomorpholine	
	mg/m^3	ppb	mg/m^3	ppb
PAC-1[a]	0.082	27	0.85	179
PAC-2[b]	0.9	297	9.3	1960
PAC-3[c]	10	3300	56	11,800

[a] PAC-1 is the airborne concentration in which the general population, including susceptible individuals, if exposed to for 1 hour could experience notable discomfort, irritation, or certain asymptomatic non-sensory effects.
[b] PAC-2 is the airborne concentration in which the general population, including susceptible individuals, if exposed to for 1 hour could experience irreversible or other serious, long-lasting adverse health effects or an impaired ability to escape.
[c] PAC-3 is the airborne concentration in which the general population, including susceptible individuals, if exposed to for 1 hour could experience life-threatening health effects or death.

The specific MAK values for N-nitrosamines were replaced with the recommendation that "… exposure should be minimized due to carcinogenicity concerns" (Deutsche Forschungsgemeinschaft 2015). Similarly, ACGIH and OSHA now recommend that OELs for N-nitrosamines be "… as low as reasonably achievable" (ACGIH 2012, NIOSH 2005). Reflecting the generally held principle that for genotoxic carcinogens there may be no exposure without risk (Dankovic et al. 2015), authoritative government bodies are increasingly recommending new approaches for establishing exposure limits more appropriate for this category of carcinogens.

In December 2016, NIOSH released a new policy regarding occupational exposure to carcinogens in response to this topic. Because there may be no exposure to genotoxic chemical carcinogens without risk, NIOSH is no longer developing recommended exposure limits for carcinogens and, instead, is working to eliminate occupational exposure to these compounds using administrative and engineering controls. When exposures to carcinogens cannot be eliminated, NIOSH is developing Risk Management Limits for Carcinogens (RML-CA), which is the daily maximum 8-hour time-weighted average concentration of a carcinogen above which a worker should not be exposed (NIOSH 2017). NIOSH will set RML-CAs at the concentration corresponding to the 95% lower confidence limit of the 1 in 10,000 risk estimate when analytically possible to measure (NIOSH 2017). This new approach acknowledges that there is no known safe level for carcinogen exposure, and an RML-CA is a reasonable starting place for controlling occupational exposures (NIOSH 2017).

Development of exposure guidelines based on specific levels of risk is common practice for the EPA, which uses this method to calculate exposure limits for carcinogens for the general (non-occupational) population (EPA 2005). This approach produces "risk-specific doses" (exposures) defined as the dose associated with a specific level of cancer risk. The risk-specific dose is calculated from cancer slope factors and standard reference values for human body weight, breathing rates, and/or water ingestion rates. The cancer slope factor is the slope of a linear extrapolation of a plot of the cancer incidence vs. daily dose from animal carcinogenicity bioassay data for the compound of interest (EPA 2005). The risk-specific dose is obtained by dividing a selected risk level (e.g., 1 in 10,000) by the unit risk, which is the cancer slope factor after adjustment from animal daily dose (mg/kg/day) to human-equivalent exposure levels (dose/m^3 of air, dose/L of water) (Equations 1-4).

$$1.4 \times 10^{-3}(\mu g/L)^{-1} = 51\ (mg/kg/d)^{-1}/70\ kg \times 2\ (L/d)/\ 1000\ (\mu g/mg) \quad \text{Eq. 1}$$

$$7 \times 10^{-2}(\mu g/L) = 1 \times 10^{-4}\ (Acceptable\ risk)/\ 1.4 \times 10^{-3}(\mu g/L)^{-1} \quad \text{Eq. 2}$$

$$1.4 \times 10^{-2}(\mu g/m^3)^{-1} = 51\ (mg/kg/d)^{-1}/70\ kg \times 30\ (m^3/d) \times 0.67/1000\ (\mu g/mg) \quad \text{Eq. 3}$$

$$7 \times 10^{-3}(\mu g/m^3) = 1 \times 10^{-4}(Acceptable\ risk)/\ 1.4 \times 10^{-2}(\mu g/m^3)^{-1} \quad \text{Eq. 4}$$

As an illustration, EPA has established risk-specific doses for COPC N-nitrosamines in water (Table 3) and air (Table 4) for lifetime (non-occupational) exposures (EPA 1986). For N-nitrosomethylamine, a drinking water unit risk was calculated using a human-equivalent cancer slope factor of 51 $(mg/kg/day)^{-1}$, 70 kg body weight, and 2 L water consumption per day (Equation 1). The risk-specific dose in water was calculated by dividing the acceptable risk level by the drinking water unit risk (Equation 2). Similarly, the inhalation unit risk was derived using an inhalation rate (30 m^3/day) and a factor that adjusts for the differences in systemic bioavailability between the route of exposure in the animal study (oral) and the route the exposure limit is derived for (inhalation) (Equation 3). The inhalation risk-specific dose was calculated for a selected risk level and the inhalation unit risk (Equation 4). Note: the EPA document (EPA 1986) that makes these calculations is currently unavailable, and the estimated parameters we used are based on other standard sources commonly used in risk assessment (Rennen et al. 2004, EPA 2005). The parameter with most uncertainty is the relative bioavailability for N-nitrosamines (0.67), which was back calculated to achieve equivalent published inhalation unit risks as EPA.

Table 3. Risk-Specific Oral Doses of N-Nitrosamine COPCs Derived by EPA

Compound	Cancer Slope Factor $(mg/kg/day)^{-1}$	Drinking Water Unit Risk $(\mu g/L)^{-1}$	Water Risk Specific Dose (µg/L)		
			1:10,000	1:100.000	1:1,000,000
NDMA	51	1.40E-03	7.00E-02	7.0E-03	7.00E-04
N-Nitrosodiethylamine	150	4.30E-03	2.00E-02	2.0E-03	2.00E-04
N-Nitrosomethylethylamine	22	6.30E-04	2.00E-01	2.0E-02	2.00E-03
N-Nitrosomorpholine	4	1.10E-05			
N-Nitrosodibutylamine	5.4	1.60E-04	6.00E-01	6.0E-02	6.00E-03
N-Nitrosopiperidine	2.9				
N-Nitrosodipropylamine	7	2.00E-04	5.00E-01	5.00E-02	5.00E-03

Table 4. Risk-Specific Inhalation Doses of N-Nitrosamine COPCs Derived by EPA

Compound	Cancer Slope Factor $(mg/kg/day)^{-1}$	Inhalation Unit Risk $(\mu g/m^3)^{-1}$	Inhalation Risk-Specific Dose $(\mu g/m^3)$		
			1:10,000	1:100.000	1:1,000,000
NDMA	51	1.40E-02	7.00E-03	7.0E-04	7.00E-05
N-Nitrosodiethylamine	150	4.30E-02	2.00E-03	2.0E-04	2.00E-05
N-Nitrosomethylethylamine	22				
N-Nitrosomorpholine	4				
N-Nitrosodibutylamine	5.4	1.60E-03	6.00E-02	6.0E-03	6.00E-04
N-Nitrosopiperidine	2.9				
N-Nitrosodipropylamine	7				

NIOSH recently published a policy on occupational carcinogens that contained specific guidance regarding appropriate levels of acceptable risk for occupational exposures (NIOSH 2017).

> "NIOSH is working to establish RML-CA for an occupational carcinogen at the concentration corresponding to the 95% lower confidence limit of the 1 in 10,000 (10^{-4}) risk estimate when analytically possible to measure. Historically, NIOSH issued recommended exposure limits for carcinogens based on an excess risk level of 1 in 1,000 (10^{-3}), while acknowledging that there is no known safe level of exposure to a carcinogen. This level of risk was recommended because it

> could be analytically measured and achieved in many workplaces. However, in the last 25 years, advances in exposure assessment, sensor and control technologies, containment, ventilation, risk management, and safety and health management systems have made it possible, in many cases, to control occupational chemical carcinogens to a lower exposure level. Therefore, in order to incrementally move toward a level of exposure to occupational chemical carcinogens that is closer to background, NIOSH will begin issuing recommendations for RML-CAs that would advise employers to take additional action to control chemical carcinogens when workplace exposures result in excess risks greater than 10^{-4}."

Until further NIOSH review or action is taken on COPC N-nitrosamines, establishing exposure limits for specific levels of risk using the approach utilized by the EPA (Equations 1–4), which is consistent with the intent of the NIOSH RML-CA approach, is an attractive alternative. $_{HTF}$OELs derived using this approach would be expected to be similar to those derived using the NIOSH RML-CA approach.

3.0 Approach for Nitrosamines

PNNL proposes the risk-based approach described above, with modification for occupational exposures, to establish $_{HTF}$OELs for N-nitrosamine COPCs. This approach was explored and considered during previous efforts to establish $_{HTF}$OELs, where depending on assumptions made, the risk-based approach produced OELs similar to the MAK values that are no longer used (Meacham et al. 2006).

To derive the inhalation unit risk for an occupational setting, the oral cancer slope factor, the body weight of females commonly used for OEL derivation (65 kg), the inhalation rate used for occupational exposures (10 m^3/day), and the calculated bioavailability factor for N-nitrosamines (0.67) were used (an example with N-Nitrosodimethylamine is shown in Equation 5). Because the inhalation unit risk is based on a lifetime exposure basis, an exposure period adjustment was made to account for the reduced exposure time for an occupational setting (less than 24 hours, less than 365 days per year, etc.). This adjustment was accomplished by applying the following assumptions: 250 working days per year for exposure frequency (Meacham et al. 2006), 45 working years for exposure duration (NIOSH 2017), 365 days/year, and a life span of 75 years (Kuempel et al. 2015) (Equation 6). Using the inhalation unit risk adjusted for a working lifetime, the risk-specific dose (i.e., the OEL) was calculated (Equation 7), and units were converted to parts per billion (ppb) assuming standard conditions (1 atm, 25°C) (Equation 8).

$$5.3 \times 10^{-3}(\mu g/m^3)^{-1} = 51\ (mg/kg/d)^{-1}/65\ \ kg \times 10\ (m^3/d) \times 0.67/1000\ (\mu g/mg) \qquad \text{Eq. 5}$$

$$2.2 \times 10^{-3}(\mu g/m^3)^{-1} = 5.3 \times 10^{-3}(\mu g/m^3)^{-1} \times \frac{250\ (d/yr) \times 45\ yr}{365\ (d/yr) \times 75\ yr} \qquad \text{Eq. 6}$$

$$4.6 \times 10^{-2}(\mu g/m^3) = 1 \times 10^{-4}(Acceptable\ risk)/\ 2.2 \times 10^{-3}(\mu g/m^3)^{-1} \qquad \text{Eq. 7}$$

$$\mathbf{1.5 \times 10^{-2}\ ppb = 24.45\ (L/mol) \times 4.6 \times 10^{-2}(\mu g/m^3)/74.08\ (g/mol) \times \left(\frac{g}{1 \times 10^6 \mu g}\right) \times \left(\frac{m^3}{1000\ L}\right)} \qquad \text{Eq. 8}$$

4.0 Results

The proposed approach derives a range of risk-specific doses for N-nitrosamine COPCs (Table 5 and Table 6). Risk-specific doses with levels of acceptable risk 1:1,000 are comparable to previously used OELs based on MAK guidelines (Table 6).

Table 5. Proposed $_{HTF}$OELs Derived Using a Risk-Based Approach

Compound	Inhalation Unit Risk $(\mu g/m^3)^{-1}$	Occupational Work Life Adjusted Inhalation Unit Risk $(\mu g/m^3)^{-1}$	Inhalation Risk-Specific Dose ($\mu g/m^3$)			
			1:1,000	1:10,000	1:100,000	1:1,000,000
NDMA	5.3E-03	2.2E-03	0.46	4.63E-02	4.63E-03	4.63E-04
N-Nitrosodiethylamine	1.5E-02	6.4E-03	0.16	1.57E-02	1.57E-03	1.57E-04
N-Nitrosomethylethylamine	2.2E-03	9.2E-04	1.08	1.08E-01	1.08E-02	1.08E-03
N-Nitrosomorpholine	4.1E-04	1.7E-04	5.90	5.90E-01	5.90E-02	5.90E-03
N-Nitrosodibutylamine	5.6E-04	2.3E-04	4.37	4.37E-01	4.37E-02	4.37E-03
N-Nitrosopiperidine	3.0E-04	1.2E-04	8.14	8.14E-01	8.14E-02	8.14E-03
N-Nitrosodipropylamine	7.2E-04	3.0E-04	3.37	3.37E-01	3.37E-02	3.37E-03

Table 6. Comparison between Proposed $_{HTF}$OELs Derived Using a Risk-Based Approach and Those Previously Used Derived from MAK Guidelines

Compound	MAK-Based OEL (ppb)	Inhalation Risk-Specific Dose (ppb)			
		1:1,000	1:10,000	1:100,000	1:1,000,000
NDMA	0.3	0.15	1.5E-02	1.5E-03	1.5E-04
N-Nitrosodiethylamine	0.1	0.04	3.8E-03	3.8E-04	3.8E-05
N-Nitrosomethylethylamine	0.3	0.30	3.0E-02	3.0E-03	3.0E-04
N-Nitrosomorpholine	0.6	1.24	1.2E-01	1.2E-02	1.2E-03
N-Nitrosodibutylamine	NA	0.68	6.8E-02	6.8E-03	6.8E-04
N-Nitrosopiperidine	NA	1.74	1.7E-01	1.7E-02	1.7E-03
N-Nitrosodipropylamine	NA	0.63	6.3E-02	6.3E-03	6.3E-04

The risk-based approach proposed here for nitrosamine COPCs is similar to an alternative approach for deriving OELs previously considered in 2006. In the Industrial Hygiene Basis, a risk-based approach was considered prior to adopting MAK values for $_{HTF}$OELs (Meacham et al. 2006). A function (Equation 9) was proposed to determine OELs where RL is the risk level, AT is the averaging time, BW is the body weight, IR is the inhalation rate, EF is the exposure frequency, ED is the exposure duration, and CSF is the cancer slope factor. When bioavailability (BA) is included (Equation 9), the function proposed in 2006 is identical to calculations described here (Equations 1–7). When comparing assumptions used previously with those used here, some of these parameters are the same (e.g., body weight and inhalation rate), while others have been updated (e.g., averaging time and exposure duration) based on recent references (Table 7). However, further adjustment of these parameters may be warranted to better reflect actual HTF operations. Overall, these approaches and assumptions are similar.

$$OEL\ (\mu g/m^3) = \frac{RL \times AT\ (d) \times BW\ (kg) \times 1000\ (\mu g/mg)}{IR\ (m^3/d) \times EF\ (d/yr) \times ED\ (yr) \times CSF\ (mg/kg/d)^{-1} \times BA} \qquad \text{Eq. 9}$$

Table 7. Comparison of Parameters used for Risk-Based Calculations in 2006 (Industrial Hygiene basis range) and 2017 (current analysis) for Nitrosamine COPCs

Factor	Industrial Hygiene Basis Range (River Protection Project [RPP])	Current Analysis (Health Process Plan)	Comments
Inhalation rate (m^3/d)	5–10 (half day to full day)	10	
Cancer slope factor (kg-d/mg)	15/51 (CA vs. EPA)	51	RPP considered both
Averaging time (days)	25,000 (70 yrs × 365 days/yr)	27,375 (75 yrs × 365 days/yr)	Lifetime, 75 yrs (Kuempel 2015)
Body weight (kg)	65	65	
Exposure frequency (days/year)	200/250	250	RPP justified 200 and used 250
Exposure duration (years)	40	45	Working lifetime, 45 yrs (NIOSH 2017)
Risk level	10^{-3}–10^{-4}	10^{-3}–10^{-4}	
Bioavailability	1	0.67	Inhalation/oral, back calculated from EPA

5.0 Recommendations

PNNL proposes a risk-based approach to establish risk-specific doses for occupational exposures to N-nitrosamine COPCs. This approach establishes a range of N-nitrosamine inhalation exposures associated with risk levels that can be used as a tool for protecting HTF workers. The proposed approach is consistent with current approaches used by EPA to protect the public, approaches being implemented by NIOSH for occupational safety, and previously considered approaches for establishing $_{HTF}$OELs. Further refinement of the HTF-specific parameters used for the risk-based calculations may be warranted to better reflect actual HTF operations. Updated guidance from NIOSH or other authoritative bodies on nitrosamine OELs should trigger a re-evaluation of this proposed approach.

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