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## **TIER II RISK ASSESSMENT IN SUPPORT OF NEW SOURCE REVIEW FOR A MOBILE PIPE REACTOR**

Prepared in Connection With a New Source Permit Application for Reacting Locations as Follows:

- CPS, Moses Lake, WA
- Helena Chemical Company, Pasco, WA
- NuChem Ltd., Central Ferry, WA
- Two Rivers Terminal, Pasco, WA
- Two Rivers Terminal, Moses Lake, WA

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## 1.0 INTRODUCTION

PNS owns and operates a Mobile Pipe Reactor (MPR). The MPR is used to manufacture ammonium polyphosphate fertilizer (i.e. 10-34-0 Fertilizer), or other ammonium polyphosphate blends, for its clients who are agricultural retail facilities and sell agriculture chemicals to the end user (i.e. farmer). The ammonium polyphosphate fertilizer is manufactured by blending anhydrous ammonia with phosphoric acid in the MPR. The resulting ammonium polyphosphate solution is blended with water and discharged to a “wet well.” Once in the wet well the product is cooled in a packed tower evaporative cooler/scrubber. The product is then further cooled in a non-contact heat exchanger while at the same vaporizing the liquid ammonia that is an input to the MPR. The anhydrous ammonia, water, and phosphoric acid are provided by the Client. At any given client Facility, the anhydrous ammonia or phosphoric acid is stored in either: stationary storage tank(s); commercial truck(s); or railcar(s).

The PNS MPR is designed to operate at a maximum rate of 1,400 lb/min (42 T/hr) of finished product, although it is more typically operated at 1,200 lb/min (36 T/hr). The emissions from the process are discharged from the evaporative packed tower cooler/scrubber. A process flow diagram for the process is provided in attached Figure 1.

## 2.0 EMISSIONS

The toxic pollutant emissions that may occur from the process are un-reacted ammonia and fluoride, which is an impurity in the phosphoric acid. The PNS MPR has been stack tested to define the emissions from the process.

### 2.1 Ammonia

Ammonia emissions are based on an April 2011 stack test when the MPR was running at a rate of 36 T/hr. A summary of the stack test data is provided below.

**Chart 1: Summary of Ammonia Emission Rates**

PARAMETER	RUN 1	RUN 2	RUN 3	AVERAGE
Concentration (ppm)	260	302	263	275
Emission Rate (lb/hr)	9.9	11.5	10.0	10.5

The emission rates reported in Chart 1 above are short-term emission rates because they reflect an average concentration over the 1.5 hour time period of the test. These emission rates are appropriate for evaluating acute impacts. The long-term emission rates that may be used to evaluate chronic impacts will be much smaller because the MPR is not present at a specific location for any extended period of time. Typically, the MPR will be set up and operated at a client facility for several days at a time and will be present at a particular client’s facility for no more than several times per year.

Consistent with the Notice of Construction Application, the long-term emission rate was developed based on the total length of time that the MPR will operate over the year (710 hours) divided by the total number of hours in a year (8,760). The long-term (i.e. annual average) emission rate is calculated as follows.

$$LTER = STER * 710 \text{ hr} / 8,760 \text{ hr}$$

Where:

LTER = Long-term emission rate averaged over 1 year

STER = Short-term emission rate from test data

710 hr = Total operational time for all 5 sites

8,760 hr = 24 hr/day x 365 days/yr

Thus, the long-term emission rate is calculated as 0.85 lb/hr based on the stack test data which represents the packed tower scrubber and demister pad and best management practice control technology. The total ammonia MPR emissions over the course of a year based on the stack test data are 3.7 tons (10.5 lb/hr \* 710 hours \* ton/2000 lb).

## 2.2 Fluoride

Fluoride emissions were also measured during the same stack test and process rate. A summary of the stack test data is provided below.

**Chart 2: Summary of Fluoride Emission Rates**

PARAMETER	RUN 1	RUN 2	RUN 3	AVERAGE
Concentration (ppm)	0.07	0.10	0.06	0.08
Emission Rate (lb/hr)	0.003	0.004	0.002	0.003

The emission rates shown in Chart 2 are less than the Small Quantity Emission Rate (SQER) for Fluorine Gas (2.08 lb/24-hr) assuming the unit operates for 24-hours as demonstrated below.

$$ER (24 - \text{hr}) = 0.003 \text{ lb/hr} \times 24\text{hr} / 24\text{hr} = 0.003 \text{ lb} / 24\text{hr avg}$$

If fluoride was the only toxic pollutant emitted by the MPR then no additional analysis is required to demonstrate compliance with WAC Regulation 173-460-1. However, because both ammonia and

fluoride are respiratory irritants, and the ammonia emission rate exceeds the SQER, fluoride must also be modeled to determine a Hazard Index relevant to respiratory irritation.

Also, the fluoride emission rate described above is based on a test conducted using a railcar of super-phosphoric acid containing a specific quantity of fluoride contamination. The fluoride contamination in any one railcar can vary to some extent. This issue was addressed by conducting an analysis of the maximum potential fluoride contamination that may be present in any one railcar (see Section 2.3.3 of the Technical Support Document submitted as part of the Notice of Construction Permit Application.) The analysis resulted in an adjustment of the short-term emission rate from 0.003 lb/hr to 0.016 lb/hr.

The emission rate used to evaluate chronic fluoride impacts was determined in a manner similar to ammonia and resulted in a long-term emission rate of 1.30E-3 lb/hr of fluoride based on the adjusted short-term emission rate.

### 2.3 Tier II Analysis Emission Rates

PNS has submitted a Notice of Construction Permit Application in conjunction with this Tier II Report. The Washington Department of Ecology (WDE) has selected the emission rates described in Sections 2.1 and 2.2 as BACT for the mobile pipe reacting process. The emission rates used to perform the Tier II analysis are summarized below.

**Chart 3: Summary of Emission Rates Used in the Tier II Risk Analysis**

TOXIC POLLUTANT	BASE EMISSION RATE			EMISSION RATE INPUT TO TIER II DISPERSION MODEL
	Type of Emission Rate	Value (lb/hr)	Basis	
Ammonia	Acute	10.5	PNS Stack Data - BMP	10.5
	Chronic	0.85	PNS Stack Data - BMP	0.85
Fluoride	Acute	0.016	PNS Stack Data Adjusted for Possible FI Contamination in Acid	0.016
	Chronic	1.30E-3	PNS Stack Data Adjusted for Possible FI Contamination in Acid	1.30E-3

### 2.4 Stack Parameters

The stack parameters that were used to support the air dispersion modeling are based on the average stack parameters for all the test data except the stack diameter is adjusted to the diameter of the actual stack. (The stack test was performed with the aid of a temporary stack).

**Chart 4: Stack Parameters**

PARAMETER	VALUE
Stack Height Above Ground (ft)	14
Equivalent Stack Diameter (ft)	7.4
Stack Temperature (°F)	159
Stack Flow Rate (ft <sup>3</sup> /min)	23,421

## 2.5 Fugitive Ammonia Emissions from Railcars

The analysis also included the fugitive emissions from railcars that supply the ammonia used in the reacting process at all of the sites. Ammonia may be released from stationary railcars as fugitive emissions from valves, flanges, and pressure relief valves (PRVs). Some of the facilities may already have provisions in existing air permits that address these emissions. Regardless of whether a facility has an existing permit provision for ammonia storage in railcars, the Tier II analysis included these emissions.

With the exception of fugitive emissions from PRVs, the factors used to estimate emissions are based on emission factors promulgated for the Synthetic Organic Chemical Manufacturing Industry (SOCMI), due to a lack of any information applicable to the agricultural chemical blending and distribution industry. The emissions from PRV's were refined for this application by identifying the maximum leakage rate that manufacturers of PRVs for anhydrous ammonia adhere to as an industry standard.

PRVs for anhydrous ammonia railcars are required to meet the leakage standards of API 527. That current standard requires that PRVs be manufactured with a maximum leakage rate of 0.0085 cubic meters per 24-hour period, or 0.00035 m<sup>3</sup>/hr, for PRVs in service at pressures of 115 to 1000 psig (Consolidated, Revision 4).

The vapor pressure of anhydrous ammonia at 78 °F (298.5 °K, the maximum expected ambient temperature during railcar storage operations) is approximately 110 psia (758,420 Pa) based on *Handbook of Vapor Pressure Volume 4* (Yaws, 1995). It can be reasonably inferred from Department of Transportation regulations and professional experience, that the quantity of anhydrous ammonia in single railcar will not typically exceed 32,000 gallons; which provides a headspace of 2,000 gallons (7.57 m<sup>3</sup>) in a 34,000 gallon railcar. The moles of ammonia in such a system calculated from the ideal gas law are 2,339 moles. The resulting ammonia vapor concentration in the headspace is 5,262 g/m<sup>3</sup>.

The emission rate from a leaking PRV is thus given by the concentration times the flow rate as:

$$5,262 \frac{g}{m^3} \times 0.00035 \frac{m^3}{hr} = 1.842 \frac{g}{hr}, \text{ or } 0.00406 \text{ lb/hr.}$$

This emission factor was used with the SOCMI factors for other valves and flanges to determine the total ammonia emissions resulting from a railcar. A more detailed description of the railcar fugitive ammonia emission calculation process is provided in Section 7.1 of the Technical Support Document submitted with the Application for Notice of Construction.

The railcar fugitive emissions were modeled as 7 separate volume sources located on the rail spurs with the following parameters.

**Chart 5: Railcar Fugitive Release Parameters**

<b>PARAMETER</b>	<b>VALUE</b>	<b>UNIT</b>
Emission Rate	0.0008	g/sec
Release Height	2.29	Meters
Length of Side	3.05	Meters
Building Height	4.57	Meters
Initial Lateral Dimension	0.71	Meters
Initial Vertical Dimension	2.13	Meters

### **3.0 MODELING PROCEDURES**

#### **3.1 Common Modeling Parameters**

The modeling parameters that were common to each of the locations include the following:

1. AERMOD Version 12060 was used to conduct the modeling;
2. AERMET Version 11059 was used to process the meteorological data;
3. AERSURFACE Version 08009 was used to process the land use data;
4. AERMAP Version 11103 was used to process the terrain data;
5. BPIP Version 04272 was used to calculate downwash;
6. Five years of meteorological data were evaluated spanning the time period of 2007 – 2011;
7. The maximum 24-hour average concentration was determined for comparison to the ASIL values for ammonia and fluoride;
8. The maximum 1-hour average concentration was determined for the evaluation of acute impacts, the maximum 2-hour average concentration was determined for evaluation of the ATSDR acute toxicity endpoint, and the maximum annual average concentration was determined for the evaluation of chronic impacts;
9. TD-3505 meteorological data from the closest airport to each location was used for surface data;
10. Radiosonde meteorological data from Spokane International Airport was used as the upper air data for all locations;
11. The seasonal Albedo, Bowen Ratio, and Surface Roughness were determined by AERSURFACE from 12 sectors using land use data (NLCD 1992) from the USGS Seamless Server.
12. Digital elevation data used for each location were the Shuttle Radar Topography Mission (SRTM) 1 arc-second data and processed by AERMAP;
13. A common datum of WGS-84 was used as a reference for all building, stack, and receptor grid locations;
14. Short-term (acute) ammonia and fluoride emission rates were those described in Section 2.3;
15. Long-term (chronic) ammonia and fluoride emission rates were those described in Section 2.3;
16. Stack parameters were those described in Section 2.4; and
17. Modeled receptors consisted of a fence line receptor grid extending from fence line or property boundary to 600 meters with a grid spacing of 10 meters out to 350 meters, and 25 meters out to 600 meters.

## 3.2 Site Specific Modeling Parameters

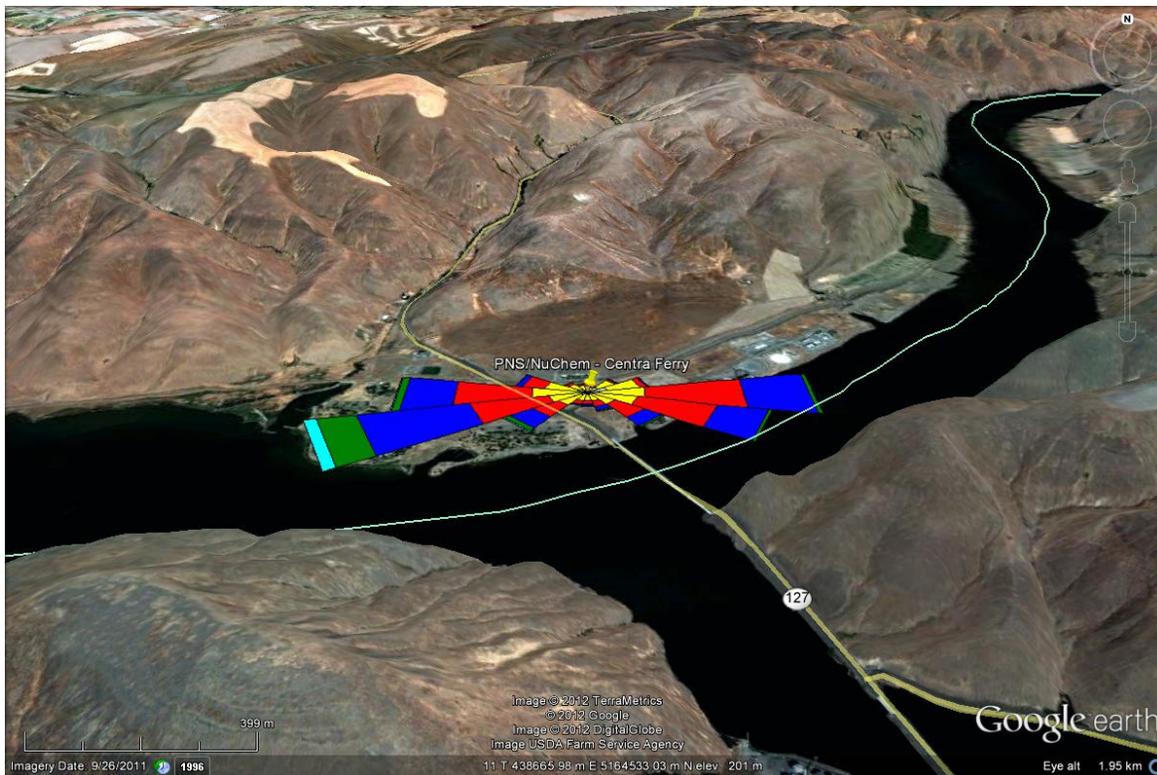
### 3.2.1 NuChem Ltd.

The MPR will be operated at the NuChem Ltd. site located in Central Ferry, Washington as shown in attached Figure 2. The proximate coordinates of the MPR stack are as follows:

- Latitude: 46.631553
- Longitude: -117.801265

TD-3505 data from the Pullman/Moscow Regional Airport was used as the surface data set. Diagram 1 shown below shows the wind rose of the site. The upper air data was from Spoken International Airport as previously described.

**Diagram 1: Wind Rose Created with Pullman/Moscow Airport Data (2007 – 2011) at NuChem, Central Ferry**



The maximum background ammonia emissions at this facility have been estimated by RME to be 3.44 lb/24-hr in a separate permit application document which includes the fugitive emissions from 7 ammonia railcars. There are no sources of fluoride emissions from this facility other than the MPR.

The MPR location at this site was subjected to downwash from nearby tanks and the reactor itself. These structures were geo-coded and downwash was considered in the modeling. The annual average Albedo, Bowen Ratio, and Surface Roughness determined from AERSURFACE are summarized as follows.

**Chart 6: Modeling Parameters for NuChem Site**

SEASON	ALBEDO	BOWEN RATIO	SURFACE ROUGHNESS
Winter	0.18	0.73	0.022
Spring	0.15	0.32	0.032
Summer	0.2	0.52	0.122
Autumn	0.2	0.73	0.12

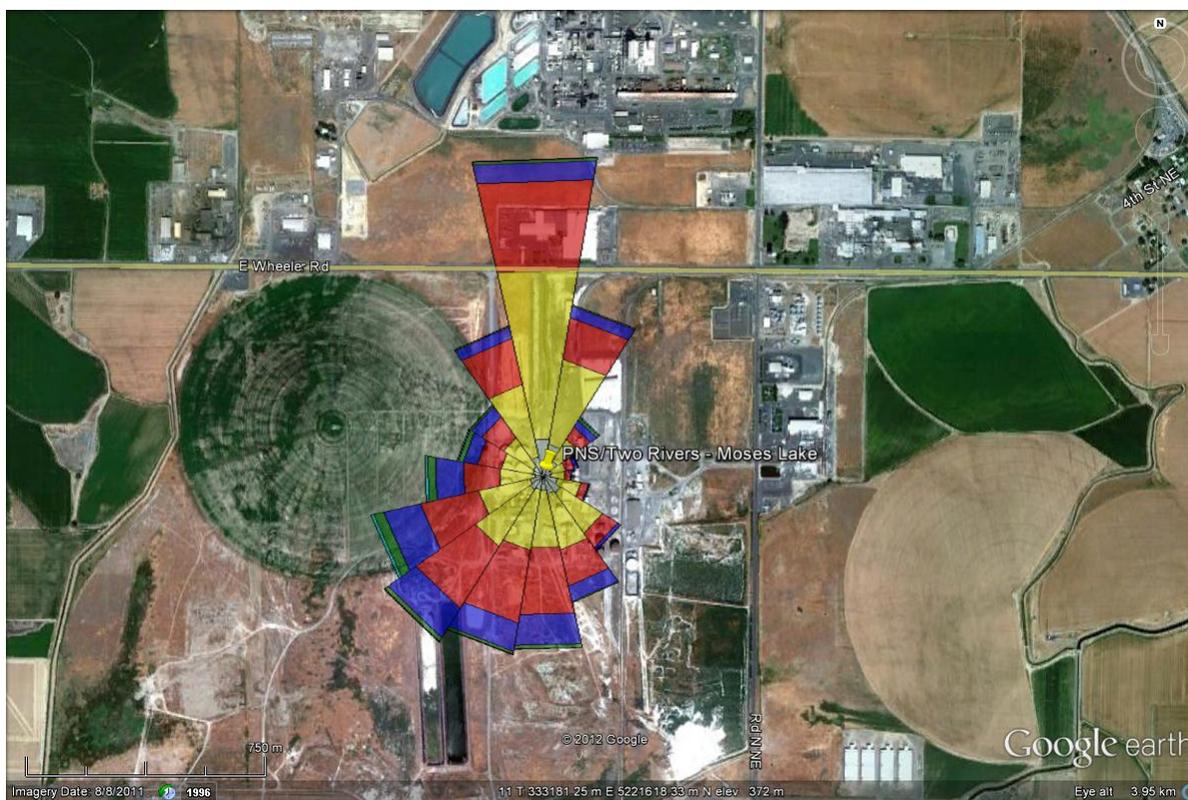
### 3.2.2 Two Rivers Terminal LLC, Moses Lake

The MPR will be operated at the Two Rivers Terminal site located in Moses Lake, Washington as shown in attached Figure 3. The proximate coordinates of the MPR stack are as follows:

- Latitude: 47.125029
- Longitude: -119.202023

TD-3505 data from the Grant County Airport was used as the surface meteorological data. A wind rose created from this data is shown in Diagram 2 below.

**Diagram 2: Wind Rose Created with Grant County Airport Data (2007 – 2011) at Two Rivers, Moses Lake**



There are no other sources of ammonia or fluoride emissions at this facility except for the ammonia railcars supplying the ammonia. The fugitive emissions from 7 ammonia railcars were considered in the modeling. There are multiple large tanks and buildings in the vicinity of the MPR location that will create downwash. The structures were geo-coded and considered in the modeling analysis. The annual

average Albedo, Bowen Ratio, and Surface Roughness determined from AERSURFACE are summarized as follows.

**Chart 7: Modeling Parameters for Two Rivers-Moses Lake Site**

SEASON	ALBEDO	BOWEN RATIO	SURFACE ROUGHNESS
Winter	0.18	0.94	0.036
Spring	0.17	0.52	0.044
Summer	0.18	0.71	0.051
Autumn	0.18	0.94	0.044

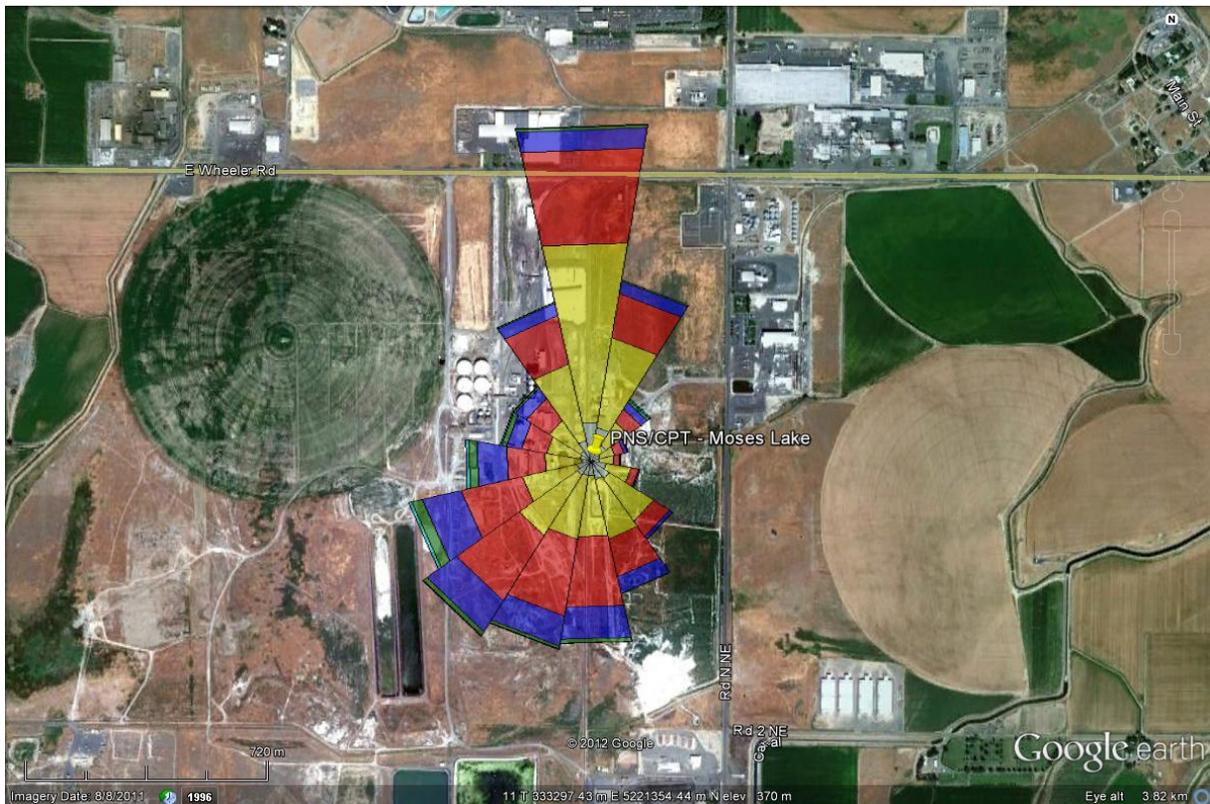
### 3.2.3 CPS, Moses Lake

The MPR will be operated at the CPS site located in Moses Lake, Washington as shown in attached Figure 4. The proximate coordinates of the MPR stack are as follows:

- Latitude: 47.123188
- Longitude: -119.198636

TD-3505 data from the Grant County Airport was used as the surface meteorological data set. A wind rose created from this data is shown in Diagram 3 below.

**Diagram 3: Wind Rose Created with Grant County Airport Data (2007 – 2011) at CPS, Moses Lake**



There are no other sources of ammonia or fluoride emissions at this facility except for the ammonia railcars supplying the ammonia. The fugitive emissions from 7 ammonia railcars were considered in the modeling. There are a few large tanks and buildings in the vicinity of the MPR location that will create downwash. The structures were geo-coded and considered in the modeling analysis. The annual average Albedo, Bowen Ratio, and Surface Roughness determined from AERSURFACE are summarized as follows.

**Chart 8: Modeling Parameters for CPS-Moses Lake Site**

SEASON	ALBEDO	BOWEN RATIO	SURFACE ROUGHNESS
Winter	0.18	0.94	0.036
Spring	0.17	0.52	0.044
Summer	0.18	0.71	0.051
Autumn	0.18	0.94	0.044

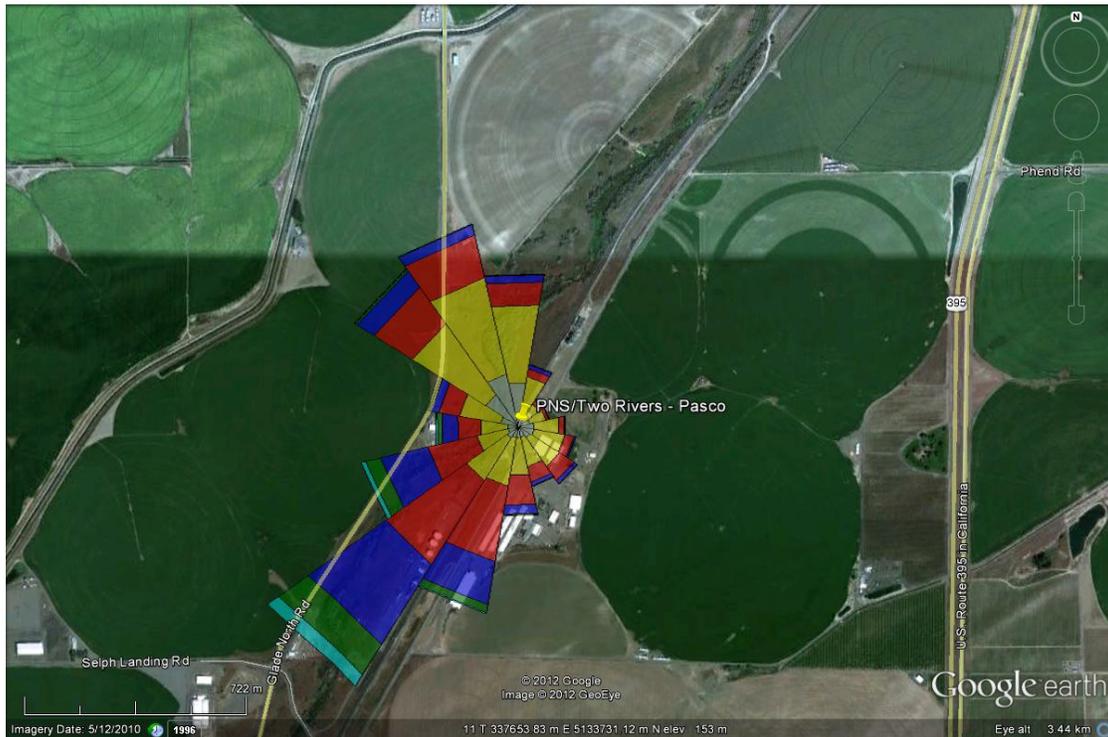
**3.2.4 Two Rivers Terminal LLC, Pasco**

The MPR will be operated at the Two Rivers Terminal site located in Pasco, Washington as shown in attached Figure 5. The proximate coordinates of the MPR stack are as follows:

- Latitude: 46.336119
- Longitude: -119.111333

TD-3505 data from the Tri-Cities Airport was used as the surface meteorological dataset. A wind rose created from this data is shown in Diagram 4 below.

**Diagram 4: Wind Rose Created with Tri-Cities Airport Data (2007 – 2011) at Two Rivers, Pasco**





The maximum ammonia background emissions at this facility have been estimated by RME to be 5.18 lb/24-hr in a separate permit application document, which includes the fugitive emissions from 7 ammonia railcars. There are no known background sources of fluoride emissions from this facility.

The MPR location at this site was subjected to downwash from nearby tanks and the reactor itself. These structures were geocoded and downwash was considered in the modeling. The annual average Albedo, Bowen Ratio, and Surface Roughness determined from AERSURFACE are summarized as follows.

**Chart 10: Modeling Parameters for Helena-Pasco Site**

<b>SEASON</b>	<b>ALBEDO</b>	<b>BOWEN RATIO</b>	<b>SURFACE ROUGHNESS</b>
Winter	0.18	0.92	0.069
Spring	0.16	0.55	0.078
Summer	0.18	0.69	0.085
Autumn	0.18	0.92	0.078

## **4.0 TOXICOLOGICAL ENDPOINTS**

RME identified multiple toxicological endpoints for ammonia and fluoride.

### **4.1 Ammonia**

Various agencies and organizations have developed acute and chronic exposure endpoints for ammonia as shown in Chart 11 below.

**Chart 11: Summary of Ammonia Toxicity Values**

Agency	Averaging Time	Acute Value ( $\mu\text{g}/\text{m}^3$ )	Acute Value (ppmv)	Chronic Value ( $\mu\text{g}/\text{m}^3$ )	Chronic Value (ppmv)	Comments
ATSDR	2 hours - acute; annual - chronic	1,184	1.70	70	0.10	The Acute MRL is based upon a 50 ppm exposure endpoint for irritation with an uncertainty factor of three (3) for the use of an LOAEL and ten (10) for human variability. The Chronic MRL is based on a study of workers that showed no difference in lung function or prevalence of symptoms between the exposed individuals and the control group. The health effects for which the MRL is reportedly protective of are aggravation of self-reported symptoms of cough, wheeze, nasal irritation, eye irritation, and throat soreness. The NOAEL was adjusted to continuous exposure from 8 hours/day, 40 hours per week with an uncertainty factor of 10 for sensitive individuals, and 3 for lack of reproductive and developmental studies.
EPA (RfC)	Annual	N/A	N/A	100	0.14	The RfC is based on the same study as the ATSDR Chronic MRL with the same uncertainty factors. The only difference is how the occupational exposure was adjusted to a continuous exposure.
California OEHHA Toxic Hot Spot RELs	1 hour-acute; annual - chronic	3,200	4.59	200	0.29	The Acute REL is based on 3 studies including the single study used by ATSDR to develop its Acute MRL. OEHHA adjusted the exposure concentration to 1-hour values. The odor threshold is reported at 17 ppm. The Chronic REL is based on the same study used by ATSDR and EPA to develop their chronic exposure endpoints without the additional modifying factor of 3. OEHHA obtained good agreement between its REL and animal studies.

Agency	Averaging Time	Acute Value ( $\mu\text{g}/\text{m}^3$ )	Acute Value (ppmv)	Chronic Value ( $\mu\text{g}/\text{m}^3$ )	Chronic Value (ppmv)	Comments
NRC (AEGL-1)	1 hour	20,897	30	N/A	N/A	The AEGL-1 value of 30 ppm for all time points is supported by observations that humans reported similar intensities of response after exposure to 50 ppm for 10 min. in 2 hours. Odor can be detected between 5 to 53 ppm.
ACGIH/NIOSH	15 min/8 hours	24,380	35	17,414	25	Recommended exposure limit is based upon a statement by AIHA that 300 to 500 ppm for 30 to 60 minutes has been reported as a maximum short exposure tolerance.
OSHA	8 hours	N/A	N/A	34,828	50	Permissible exposure limit is based upon current OSHA standards.

The source of the Tier I WDE acceptable source impact level (ASIL) endpoint of  $70.8 \text{ ug/m}^3$  as a 24-hour average could not be identified from the available information. The value is closest to the ATSDR Chronic MRL of  $70 \text{ ug/m}^3$  for an annual average exposure of 24 hours per day for 365 days per year. For this Tier II analysis, RME proposes to use the California Office of Environmental Health Hazard Assessment (OEHHA) Reference Exposure Levels (RELs) for both acute and chronic exposures. It is RME's opinion that these values are best supported by the scientific literature. The OEHHA REL acute value is based on a 1-hour exposure, whereas the ATSDR Acute MRL is based on a 2 hour exposure. The OEHHA Acute REL is based on three studies, whereas the ATSDR Acute MRL is based on a single study. Likewise, the OEHHA Chronic REL is better supported because OEHHA was able to obtain good agreement with its value based on the same human study used by ATSDR and EPA, and they were able to support their chronic exposure endpoint with good agreement from animal studies. Finally, it is noted that ATSDR specifically states in bolded lettering on its website "that MRLs are not intended to define clean up or action levels for ATSDR or other Agencies" (<http://www.atsdr.cdc.gov/mrls/index.asp>).

## 4.2 Fluoride

There are fewer exposure endpoints developed for fluoride than ammonia, especially for acute exposures. The available information is summarized in Chart 12 below. The data in Chart 12 suggest that the OEHHA chronic exposure REL of  $13 \text{ ug/m}^3$ , developed for continuous inhalation exposures to fluoride and hydrogen fluoride, is the basis for the WDE 24-hour average ASIL for fluoride containing chemicals (also  $13 \text{ ug/m}^3$ ). It also appears that the 24-hr average ASIL value for fluorine gas ( $15.8 \text{ ug/m}^3$ ) is based on the ATSDR 24-hr MRL ( $15.6 \text{ ug/m}^3$  with no rounding). For this Tier II analysis, RME proposes to use the AEGL-1 value for fluorine gas expressed as fluoride to evaluate acute exposures. This concentration is more consistent for a 1-hr exposure duration than the ATSDR MRL which is very similar to the chronic OEHHA REL. The AEGL-1 value is protective of sensitive individuals to mild irritation, which is the health effect of concern for short-term exposures to fluoride and fluorine gas.

RME proposes to use the OEHHA REL to evaluate chronic exposures because this is the only non-worker chronic exposure endpoint available for fluoride. The OEHHA chronic REL is protective of more serious long-term health effects including increased bone density.

**Chart 12: Summary of Fluoride Toxicity Values**

Agency	Averaging Time	Acute Value ( $\mu\text{g}/\text{m}^3$ ) <sup>1</sup>	Acute Value (ppmv)	Chronic Value ( $\mu\text{g}/\text{m}^3$ ) <sup>1</sup>	Chronic Value (ppmv)	Comments
ATSDR - For Fluorine Gas <sup>2</sup>	24 hours - acute	7.8	0.01	N/A	N/A	The Acute MRL was developed from a study where five volunteers were exposed to different concentrations of fluorine gas. The MRL is based on a NOAEL of 10 ppm for irritation to humans. The NOAEL was adjusted by a factor of 10 for human variability and from a 15-minute exposure to a 24-hr exposure by multiplying the 15-minute exposure concentration by 0.25 hr/24 hr.
EPA (RfC)	Annual	N/A	N/A	N/A	N/A	USEPA has not published a RfC for fluorine.
California OEHHA Toxic Hot Spot RELs - For Fluoride or Hydrogen Fluoride	Annual - chronic	N/A	N/A	13	0.02	The Chronic REL is based on a study of 74 fertilizer plant workers and an unexposed control group of 67 subjects. A benchmark concentration of 0.37 mg/m <sup>3</sup> was derived by fitting the probit model to the log dose via the use of USEPA's BMDS (version 3.1). The exposure period was adjusted from 8-hr/day, 5 days/week to continuous, and an uncertainty factor of 10 was used for human variability. An Acute REL has not been developed.
NRC (AEGL-1)- For Fluorine Gas	1 hour	1,321	1.7	N/A	N/A	The AEGL-1 is the airborne concentration of substance above which it is predicted the general population, including susceptible individuals, could experience noticeable discomfort, irritation, or certain asymptomatic, non-sensory health effects. The AEGL-1 is based on the same study that ATSDR used with a human variability factor of 3 and a modifying factor of 2 to address the short exposure duration and limited data set of the study. The NRC states that the concentration is protective for exposures up to 8 hours because at mildly irritating concentrations adaptation to slight sensory irritation occurs.

Agency	Averaging Time	Acute Value ( $\mu\text{g}/\text{m}^3$ ) <sup>1</sup>	Acute Value (ppmv)	Chronic Value ( $\mu\text{g}/\text{m}^3$ ) <sup>1</sup>	Chronic Value (ppmv)	Comments
NIOSH - For Fluorine Gas	8 hour-TWA	N/A	N/A	78	0.1	None.
OSHA - For Fluorine Gas	8 hour-TWA	N/A	N/A	78	0.1	None.

NOTES:

1. Mass per volume concentration reported as Fluoride.
2. The ATSDR Acute MRL for Hydrogen Fluoride is 0.02 ppmv.

## 5.0 MODELING RESULTS

Each site was modeled using Lakes Environmental's AERMOD View™ Version 8.1.0. The output from the modeling is shown graphically in Diagrams 6 – 21 and the results are summarized in Table 1 of Appendix A. The results show that the emission rates for fluoride and ammonia result in offsite concentrations that are well below the toxicological endpoints recommended by ATSDR, EPA, OEHHA, and the NRC (AEGL-1) for the 1<sup>st</sup> hour, 2<sup>nd</sup> hour, and annual average concentrations at each facility, with the exception of the 1 hour and 2 hour average ammonia concentrations for the CPS-Moses Lake Facility and the 2 hour average ammonia concentration for the Helena-Pasco Facility. Offsite ammonia concentrations at these two (2) facilities exceed the acute toxicological endpoint concentration values for residential land use based on one or more of the different agency toxicological endpoints, but the land use where the concentrations occur is industrial. The model results for each site are as follows.

### 5.1 NuChem Ltd.

Ammonia and fluoride emissions for the NuChem location were evaluated for the 1<sup>st</sup> high 1-hour average concentrations, 1<sup>st</sup> high 2-hour average concentrations (ammonia only), 1<sup>st</sup> high 24-hour average concentrations, and annual average concentrations for the years 2007 – 2011. The results are described in the following diagrams and discussion.

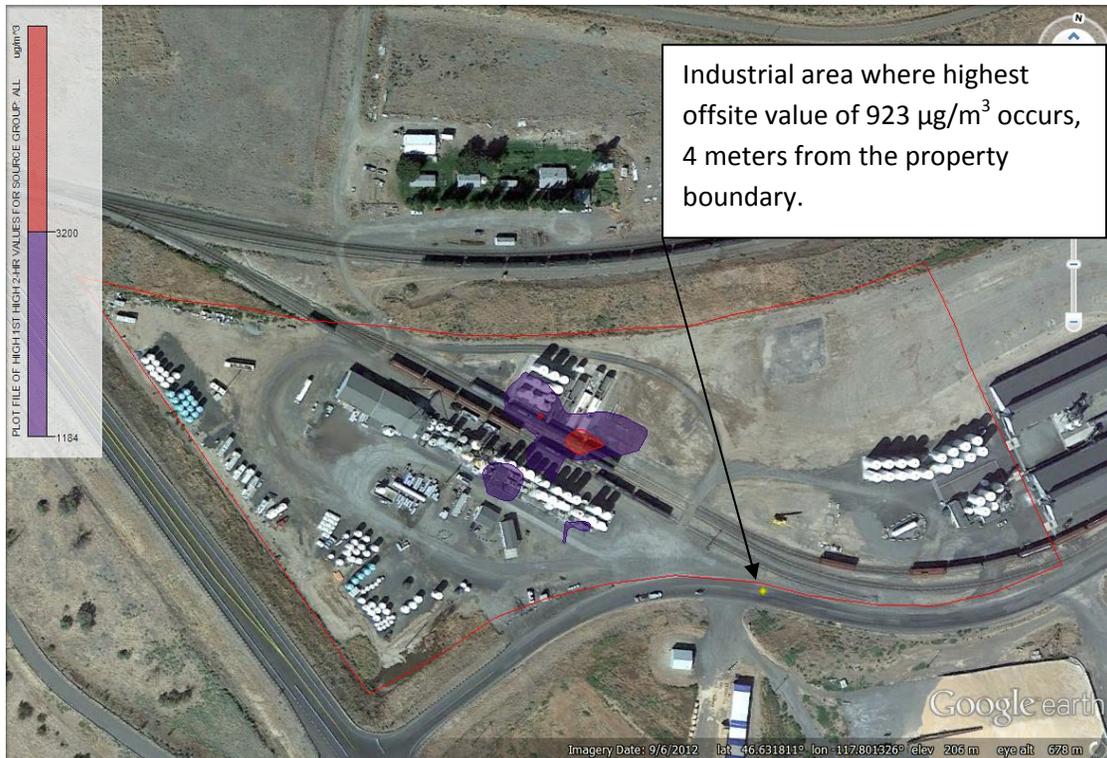
Diagram 6: 1<sup>st</sup> High – 1 Hour Concentrations of Fluoride (Comparison to NRC Value of 1,321  $\mu\text{g}/\text{m}^3$ )



Diagram 7: 1<sup>st</sup> High – 1 Hour Concentrations of Ammonia (Comparison to Cal OEHHA Value of 3,200  $\mu\text{g}/\text{m}^3$ )



Diagram 8: 1<sup>st</sup> High – 2 Hour Concentrations of Ammonia (Comparison to ATSDR Value of 1,184  $\mu\text{g}/\text{m}^3$ )



### 5.1.1 Fluoride

Modeling results for the 1<sup>st</sup> high – 1 hour average concentrations of fluoride were compared to the NRC AEGL-1 concentration for a 1-hour averaging period and show that the concentrations beyond the property line are well below the toxicological endpoint of 1,321  $\mu\text{g}/\text{m}^3$ . The highest offsite concentration is 1.57  $\mu\text{g}/\text{m}^3$ , located 23 meters from the property boundary. (The AEGL-1 is the airborne concentration of substance above which it is predicted the general population, including susceptible individuals, could experience noticeable discomfort, irritation, or certain asymptomatic, non-sensory health effects.) Although not shown in a specific diagram, the 1<sup>st</sup> high – 24 hour concentrations of fluoride were compared to the ATSDR toxicological endpoint for a 24 hour averaging period and show that the concentrations beyond the property boundary are well below the threshold of 7.8  $\mu\text{g}/\text{m}^3$ . The highest offsite concentration is 0.44  $\mu\text{g}/\text{m}^3$ , and is located on the property boundary. Finally, none of the annual average concentrations of fluoride exceed the California OHHEA chronic Relative Exposure Level (REL) of 13  $\mu\text{g}/\text{m}^3$ . The values for each year are listed in Table 1 of Appendix A.

### 5.1.2 Ammonia

Modeling results for the 1<sup>st</sup> high – 1 hour average concentrations of ammonia were compared to the California OEHHA 1-hr average acute REL (3,200  $\mu\text{g}/\text{m}^3$ ) and show that the concentrations beyond the property line are well below this toxicological endpoint. The highest offsite concentration is 1,054  $\mu\text{g}/\text{m}^3$ , located 23 meters from the property boundary. Modeling results for the 1<sup>st</sup> high – 2 hour average concentrations of ammonia were compared to the ATSDR 2-hour average toxicological endpoint (1,184  $\mu\text{g}/\text{m}^3$ ). The highest offsite concentration is 923  $\mu\text{g}/\text{m}^3$  and is located 4 meters from the property boundary.

For the purposes of completeness, the 1<sup>st</sup> high 24-hour average concentrations of ammonia were compared to the Tier I WDE 24-hour average ASIL concentration (70.8  $\mu\text{g}/\text{m}^3$ ). As expected, the modeled concentrations exceed the ASIL value with a high offsite concentration of 289  $\mu\text{g}/\text{m}^3$ . This concentration occurs 8 meters from the property boundary. The concentrations above the ASIL extend 190 meters from the property boundary. Finally, the highest annual average concentration of ammonia (including onsite concentrations) do not exceed the California OHHEA chronic REL of 200  $\mu\text{g}/\text{m}^3$ , the EPA chronic RfC of 100  $\mu\text{g}/\text{m}^3$ , or the ATSDR chronic MRL of 70  $\mu\text{g}/\text{m}^3$ . The values for each year are listed in Table 1 of Appendix A.

### 5.1.3 Summary

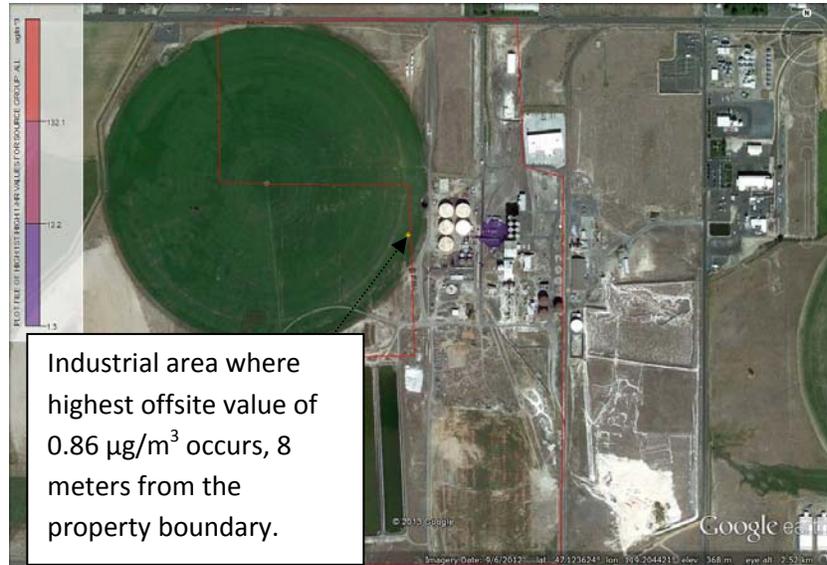
Overall, the emissions from the PNS mobile pipe reactor result in offsite concentrations of ammonia and fluoride that are well below any relevant toxicological endpoints. Although the offsite 24-hr average concentrations exceeds the WDE Tier I ASIL for ammonia, the Tier I ASIL appears to be based on ATSDR's Chronic MRL for an annual average exposure, and thus, is inappropriate for evaluating a 24-hr average concentration in a Tier II risk assessment.

## 5.2 Two Rivers Terminal LLC, Moses Lake

Ammonia and fluoride emissions for the Two Rivers Moses Lake location were evaluated for the 1<sup>st</sup> high 1-hour average concentrations, 1<sup>st</sup> high 2-hour average concentrations (ammonia only), 1st high 24-hour

average concentrations, and annual average concentrations for the years 2007 – 2011. The results are described in the following diagrams and discussion.

**Diagram 9: 1<sup>st</sup> High – 1 Hour Concentrations of Fluoride (Comparison to NRC Value of 1,321  $\mu\text{g}/\text{m}^3$ )**



**Diagram 10: 1<sup>st</sup> High – 1 Hour Concentrations of Ammonia (Comparison to Cal OEHHA Value of 3,200  $\mu\text{g}/\text{m}^3$ )**

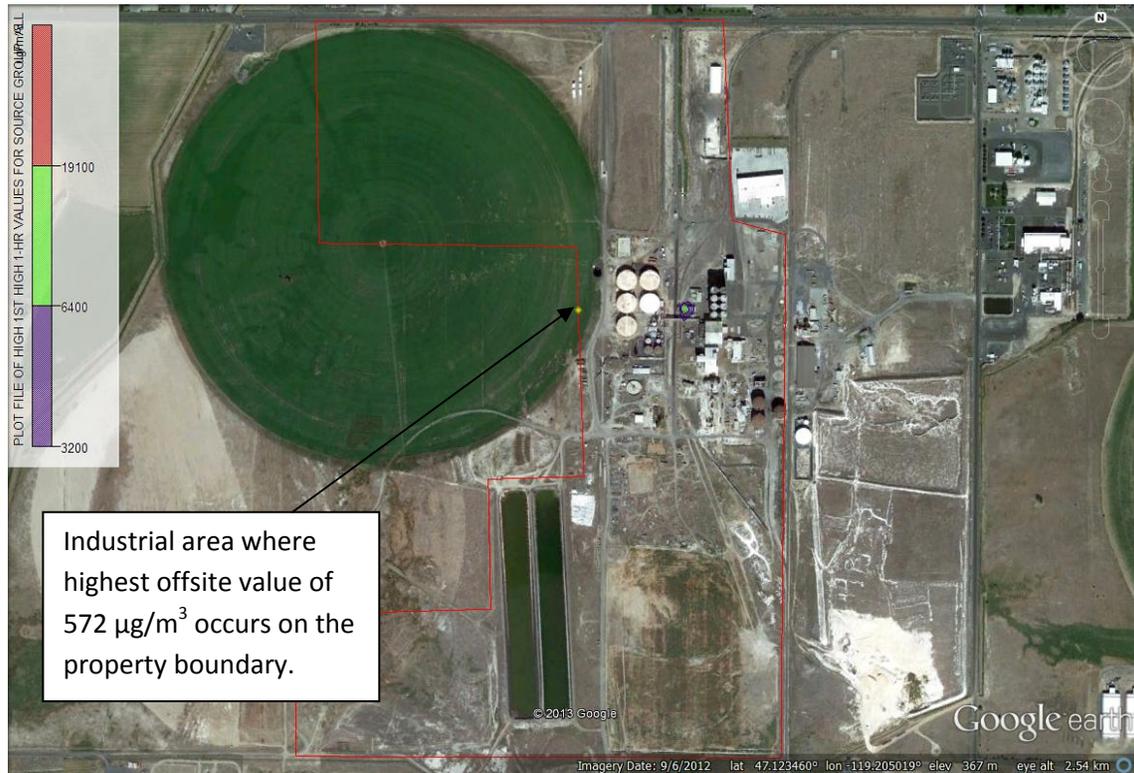
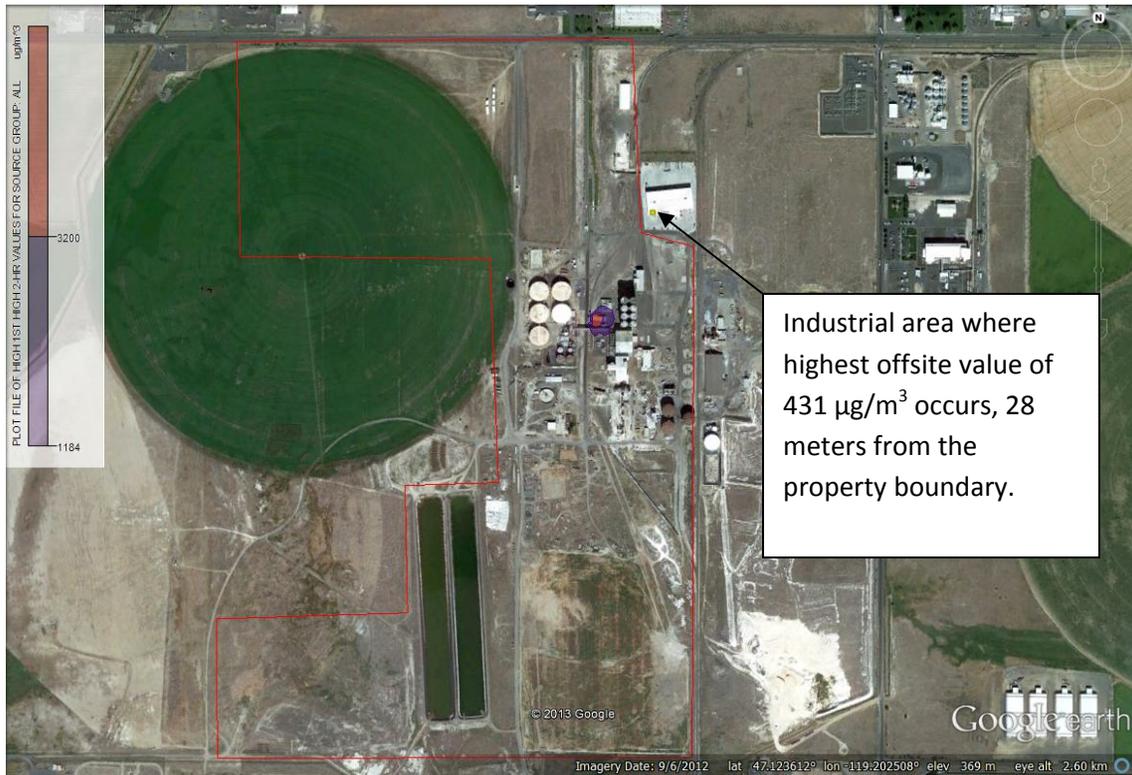


Diagram 11: 1<sup>st</sup> High – 2 Hour Concentrations of Ammonia (Comparison to ATSDR Value of 1,184  $\mu\text{g}/\text{m}^3$ )



### 5.2.1 Fluoride

Modeling results for the 1<sup>st</sup> high – 1 hour average concentrations of fluoride were compared to the NRC AEGL-1 concentration for a 1-hour averaging period and show that the concentrations beyond the property line are well below the toxicological endpoint of 1,321  $\mu\text{g}/\text{m}^3$ . The highest offsite concentration is 0.86  $\mu\text{g}/\text{m}^3$ , located 8 meters from the property boundary. (The AEGL-1 is the airborne concentration of substance above which it is predicted the general population, including susceptible individuals, could experience noticeable discomfort, irritation, or certain asymptomatic, non-sensory health effects.) Although not shown in a specific diagram, the 1<sup>st</sup> high – 24 hour concentrations of fluoride were compared to the ATSDR toxicological endpoint for a 24 hour averaging period and show that the concentrations beyond the property boundary are well below the threshold of 7.8  $\mu\text{g}/\text{m}^3$ . The highest offsite concentration is 0.11  $\mu\text{g}/\text{m}^3$ , and is located on the property boundary. Finally, none of the annual average concentrations of fluoride exceed the California OHHA chronic REL of 13  $\mu\text{g}/\text{m}^3$ . The values for each year are listed in Table 1 of Appendix A.

### 5.2.2 Ammonia

Modeling results for the 1<sup>st</sup> high – 1 hour average concentrations of ammonia were compared to the California OEHHA 1-hr average acute REL (3,200  $\mu\text{g}/\text{m}^3$ ) and show that the concentrations beyond the property line are well below this toxicological endpoint. The highest offsite concentration is 572  $\mu\text{g}/\text{m}^3$ , located on the property boundary. Modeling results for the 1<sup>st</sup> high – 2 hour average concentrations of

ammonia were compared to the ATSDR 2-hour average toxicological endpoint (1,184  $\mu\text{g}/\text{m}^3$ ). The highest offsite concentration is 431  $\mu\text{g}/\text{m}^3$  and is located 28 meters from the property boundary.

For the purposes of completeness, the 1<sup>st</sup> high 24-hour average concentrations of ammonia were compared to the Tier I WDE 24-hour average ASIL concentration (70.8  $\mu\text{g}/\text{m}^3$ ). The modeled offsite concentrations are just below the ASIL value with a high property boundary concentration of 70.2  $\mu\text{g}/\text{m}^3$ . Finally, the highest annual average concentrations of ammonia (including onsite concentrations) do not exceed the California OHHEA chronic REL of 200  $\mu\text{g}/\text{m}^3$ , the EPA chronic RfC of 100  $\mu\text{g}/\text{m}^3$ , or the ATSDR chronic MRL of 70  $\mu\text{g}/\text{m}^3$ . The values for each year are listed in Table 1 of Appendix A.

### 5.2.3 Summary

Overall, the emissions from the PNS mobile pipe reactor result in offsite concentrations of ammonia and fluoride emissions that are well below any relevant toxicological endpoints. Additionally, the offsite 24-hr average concentrations do not exceed the WDE Tier I ASIL for ammonia.

## 5.3 CPS, Moses Lake

Ammonia and fluoride emissions for the CPS Moses Lake location were evaluated for the 1<sup>st</sup> high 1-hour average concentrations, 1<sup>st</sup> high 2-hour average concentrations (ammonia only), 1<sup>st</sup> high 24-hour average concentrations, and annual average concentrations for the years 2007 – 2011. The results are described in the following diagrams and discussion.

Diagram 12: 1<sup>st</sup> High – 1 Hour Concentrations of Fluoride (Comparison to NRC Value of 1,321  $\mu\text{g}/\text{m}^3$ )



Diagram 13: 1<sup>st</sup> High – 1 Hour Concentrations of Ammonia (Comparison to Cal OEHHA Value of 3,200  $\mu\text{g}/\text{m}^3$ )

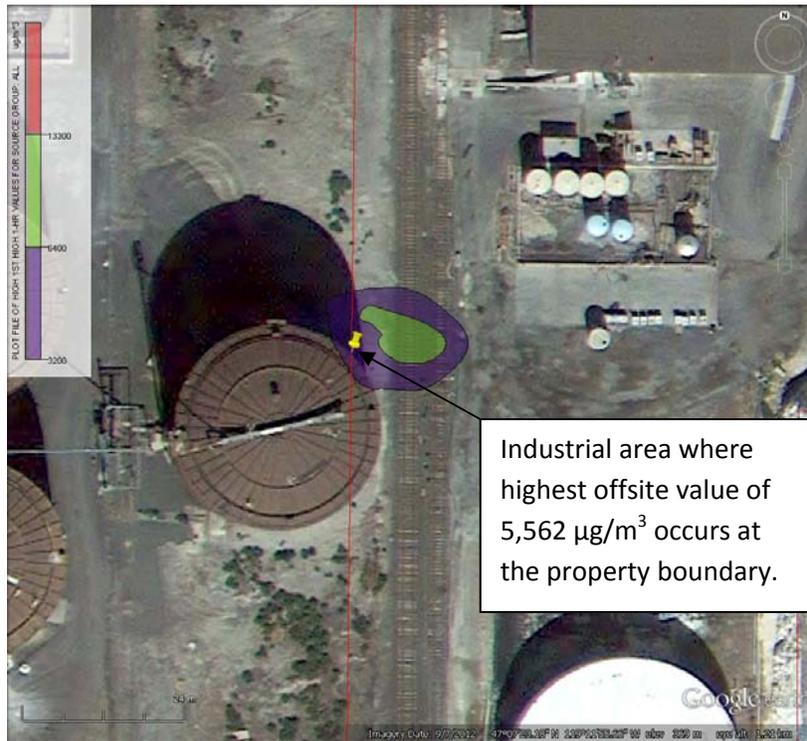


Diagram 14: 1<sup>st</sup> High – 1 Hour Concentrations of Ammonia, Overview of Site

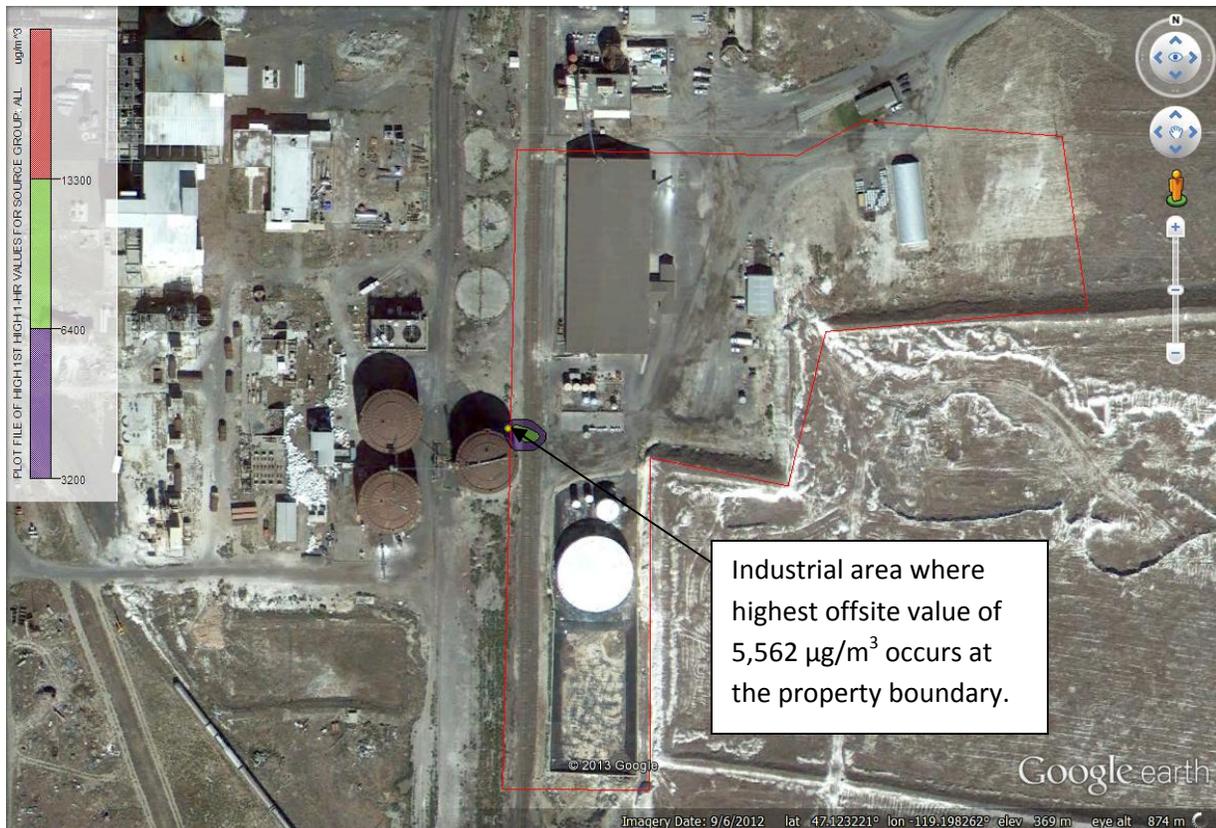
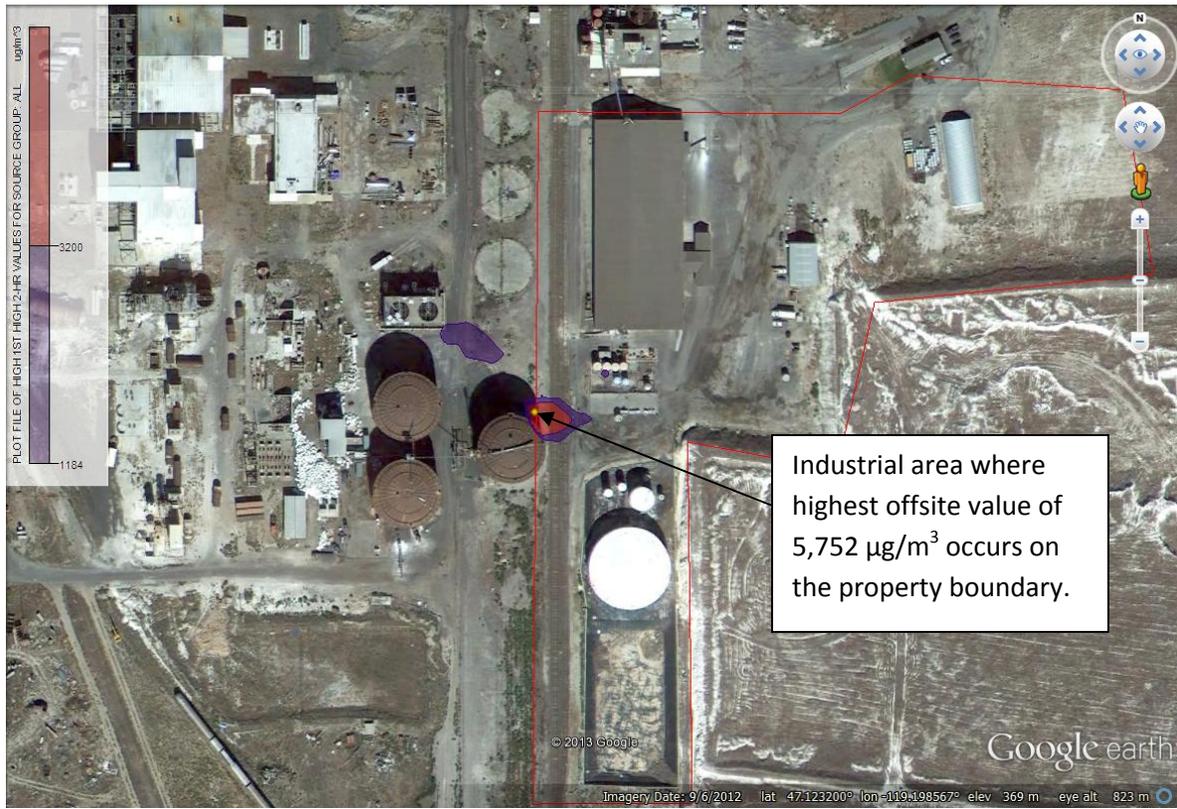


Diagram 15: 1<sup>st</sup> High – 2 Hour Concentrations of Ammonia (Comparison to ATSDR Value of 1,184  $\mu\text{g}/\text{m}^3$ )



### 5.3.1 Fluoride

Modeling results for the 1<sup>st</sup> high – 1 hour average concentrations of fluoride were compared to the NRC AEGL-1 concentration for a 1-hour averaging period and show that the concentrations beyond the property line are well below the toxicological endpoint of 1,321  $\mu\text{g}/\text{m}^3$ . The highest offsite concentration is 7.06  $\mu\text{g}/\text{m}^3$  located on the property boundary. (The AEGL-1 is the airborne concentration of substance above which it is predicted the general population, including susceptible individuals, could experience noticeable discomfort, irritation, or certain asymptomatic, non-sensory health effects.) Although not shown in a specific diagram, the 1<sup>st</sup> high – 24 hour concentrations of fluoride were compared to the ATSDR toxicological endpoint for a 24 hour averaging period and show that the concentrations beyond the property boundary are below the threshold of 7.8  $\mu\text{g}/\text{m}^3$ . The highest offsite concentration is 4.41  $\mu\text{g}/\text{m}^3$ , and is located on the property boundary. Finally, none of the annual average concentrations of fluoride exceed the California OHHEA chronic REL of 13  $\mu\text{g}/\text{m}^3$ . The values for each year are listed in Table 1 of Appendix A.

### 5.3.2 Ammonia

Modeling results for the 1<sup>st</sup> high – 1 hour average concentrations of ammonia were compared to the California OEHHA 1-hr average acute REL (3,200  $\mu\text{g}/\text{m}^3$ ). Concentrations above this endpoint extend 4 meters onto an adjacent industrial property. The highest offsite concentration is 5,562  $\mu\text{g}/\text{m}^3$  located on the property boundary. This concentration is less than the American Conference of Governmental Industrial Hygienist (ACGIH) 8-hr Threshold Limit Value of 17,414  $\mu\text{g}/\text{m}^3$ . Modeling results for the 1<sup>st</sup>

high – 2 hour average concentrations of ammonia were compared to the ATSDR 2-hour average toxicological endpoint (1,184  $\mu\text{g}/\text{m}^3$ ). The highest offsite concentration is 5,753  $\mu\text{g}/\text{m}^3$  and is located on the property boundary. Two-hr average concentrations above the ATSDR Acute MRL extend up to 43 meters (141 feet) onto the neighboring industrial property.

For the purposes of completeness, the 1<sup>st</sup> high 24-hour average concentrations of ammonia were compared to the Tier I WDE 24-hour average ASIL concentration (70.8  $\mu\text{g}/\text{m}^3$ ). As expected, the modeled concentrations exceed the ASIL value with a high offsite concentration of 2,896  $\mu\text{g}/\text{m}^3$ . This concentration occurs on the property boundary within an industrial complex. Finally, the highest annual average concentrations of ammonia (including onsite concentrations) do not exceed the California OEHHA chronic REL of 200  $\mu\text{g}/\text{m}^3$ , the EPA chronic RfC of 100  $\mu\text{g}/\text{m}^3$ , or the ATSDR chronic MRL of 70  $\mu\text{g}/\text{m}^3$ . The values for each year are listed in Table 1 of Appendix A.

### **5.3.3 Summary**

The emissions from the PNS mobile pipe reactor result in offsite concentrations of fluoride that are well below any relevant toxicological endpoints. The ammonia concentrations offsite do exceed the acute toxicological endpoints recommended by the California OEHHA and the ATSDR. However, concentrations that exceed the recommended acute toxicological endpoints occur on industrial property and the concentrations do not exceed the ACGIH 8-hr TLV. The annual average ammonia concentrations (both on and offsite) do not exceed any relevant chronic toxicological endpoints. Finally, although the offsite 24-hr average concentrations exceed the WDE Tier I ASIL for ammonia, the Tier I ASIL appears to be based on ATSDR's Chronic MRL for an annual average exposure, and thus, is inappropriate for evaluating a 24-hr average concentration in a Tier II risk assessment.

## **5.4 Two Rivers Terminal LLC, Pasco**

Ammonia and fluoride emissions for the Two Rivers Pasco location were evaluated for the 1<sup>st</sup> high 1-hour average concentrations, 1<sup>st</sup> high 2-hour average concentrations (ammonia only), 1<sup>st</sup> high 24-hour average concentrations, and annual average concentrations for the years 2007 – 2011. The results are described in the following diagrams and discussion.

Diagram 16: 1<sup>st</sup> High – 1 Hour Concentrations of Fluoride (Comparison to NRC Value of 1,321  $\mu\text{g}/\text{m}^3$ )



Diagram 17: 1<sup>st</sup> High – 1 Hour Concentrations of Ammonia (Comparison to Cal OEHHA Value of 3,200  $\mu\text{g}/\text{m}^3$ )



Diagram 18: 1<sup>st</sup> High – 2 Hour Concentrations of Ammonia (Comparison to ATSDR Value of 1,184  $\mu\text{g}/\text{m}^3$ )



#### 5.4.1 Fluoride

Modeling results for the 1<sup>st</sup> high – 1 hour average concentrations of fluoride were compared to the NRC AEGL-1 concentration for a 1-hour averaging period and show that the concentrations beyond the property line are well below the toxicological endpoint of 1,321  $\mu\text{g}/\text{m}^3$ . The highest offsite concentration is 1.34  $\mu\text{g}/\text{m}^3$  located on the property boundary. (The AEGL-1 is the airborne concentration of substance above which it is predicted the general population, including susceptible individuals, could experience noticeable discomfort, irritation, or certain asymptomatic, non-sensory health effects.) Although not shown in a specific diagram, the 1<sup>st</sup> high – 24 hour concentrations of fluoride were compared to the ATSDR toxicological endpoint for a 24 hour averaging period and show that the concentrations beyond the property boundary are well below the threshold of 7.8  $\mu\text{g}/\text{m}^3$ . The highest offsite concentration is 0.57  $\mu\text{g}/\text{m}^3$  and is located on the property boundary. Finally, none of the annual average concentrations of fluoride exceed the California OHHEA chronic REL of 13  $\mu\text{g}/\text{m}^3$ . The values for each year are listed in Table 1 of Appendix A.

#### 5.4.2 Ammonia

Modeling results for the 1<sup>st</sup> high – 1 hour average concentrations of ammonia were compared to the California OEHHA 1-hr average acute REL (3,200  $\mu\text{g}/\text{m}^3$ ) and show that the concentrations beyond the property line are well below this toxicological endpoint. The highest offsite concentration is 882  $\mu\text{g}/\text{m}^3$  located on the property boundary. Modeling results for the 1<sup>st</sup> high – 2 hour average concentrations of ammonia were compared to the ATSDR 2-hour average toxicological endpoint (1,184  $\mu\text{g}/\text{m}^3$ ). The highest offsite concentration is 806  $\mu\text{g}/\text{m}^3$  and is located on the property boundary.

For the purposes of completeness, the 1<sup>st</sup> high 24-hour average concentrations of ammonia were compared to the Tier I WDE 24-hour average ASIL concentration (70.8  $\mu\text{g}/\text{m}^3$ ). As expected, the modeled concentrations exceed the ASIL value with the high offsite concentration of 374  $\mu\text{g}/\text{m}^3$ . This concentration occurs on the property boundary, but is located entirely within an industrial complex. The concentrations above the ASIL extend 168 meters from the property boundary. Finally, the highest annual average concentrations of ammonia (including onsite concentrations) do not exceed the California OHHEA chronic REL of 200  $\mu\text{g}/\text{m}^3$ , the EPA chronic RfC of 100  $\mu\text{g}/\text{m}^3$ , or the ATSDR chronic MRL of 70  $\mu\text{g}/\text{m}^3$ . The values for each year are listed in Table 1 of Appendix A.

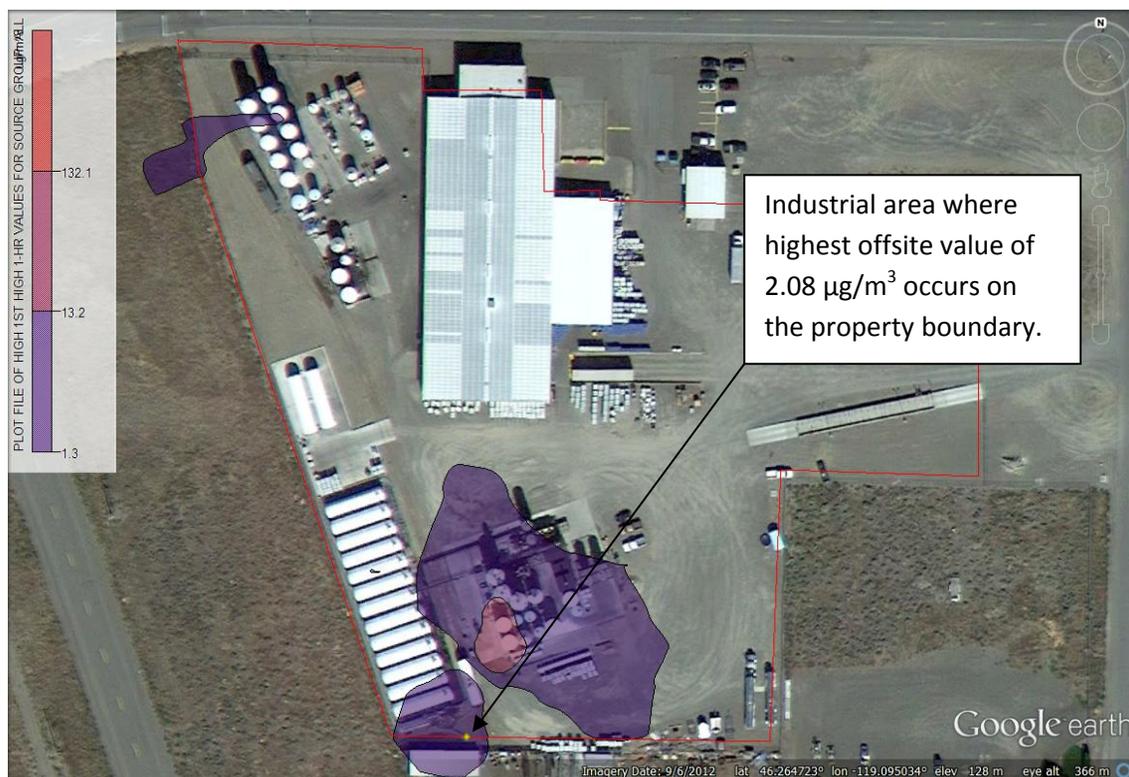
### 5.4.3 Summary

Overall, the emissions from the PNS mobile pipe reactor result in offsite concentrations of ammonia and fluoride concentrations that are well below any relevant toxicological endpoints. Although the offsite 24-hr average concentrations exceeds the WDE Tier I ASIL for ammonia, the Tier I ASIL appears to be based on ATSDR's Chronic MRL for an annual average exposure, and thus, is inappropriate for evaluating a 24-hr average concentrations in a Tier II risk assessment.

## 5.5 Helena Chemical Company, Pasco

Ammonia and fluoride emissions for the Helena Pasco location were evaluated for the 1<sup>st</sup> high 1-hour average concentrations, 1<sup>st</sup> high 2-hour average concentrations (ammonia only), 1<sup>st</sup> high 24-hour average concentrations, and annual average concentrations for the years 2007 – 2011. The results are described in the following diagrams and discussion.

Diagram 19: 1<sup>st</sup> High – 1 Hour Concentrations of Fluoride (Comparison to NRC Value of 1,321  $\mu\text{g}/\text{m}^3$ )



**Diagram 20: 1<sup>st</sup> High – 1 Hour Concentrations of Ammonia (Comparison to Cal OEHHA Value of 3,200  $\mu\text{g}/\text{m}^3$ )**



**Diagram 21: 1<sup>st</sup> High – 2 Hour Concentrations of Ammonia (Comparison to ATSDR Value of 1,184  $\mu\text{g}/\text{m}^3$ )**



### 5.4.1 Fluoride

Modeling results for the 1<sup>st</sup> high – 1 hour average concentrations of fluoride were compared to the NRC AEGL-1 concentration for a 1-hour averaging period and show that the concentrations beyond the property line are well below the toxicological endpoint of 1,321  $\mu\text{g}/\text{m}^3$ . The highest offsite concentration is 2.08  $\mu\text{g}/\text{m}^3$  located on the property boundary. (The AEGL-1 is the airborne concentration of substance above which it is predicted the general population, including susceptible individuals, could experience noticeable discomfort, irritation, or certain asymptomatic, non-sensory health effects.) Although not shown in a specific diagram, the 1<sup>st</sup> high – 24 hour concentrations of fluoride were compared to the ATSDR toxicological endpoint for a 24 hour averaging period and show that the concentrations beyond the property boundary are well below the threshold of 7.8  $\mu\text{g}/\text{m}^3$ . The highest offsite concentration is 0.47  $\mu\text{g}/\text{m}^3$  and is located on the property boundary. Finally, none of the annual average concentrations of fluoride exceed the California OHHEA chronic REL of 13  $\mu\text{g}/\text{m}^3$ . The values for each year are listed in Table 1 of Appendix A.

### 5.4.2 Ammonia

Modeling results for the 1<sup>st</sup> high – 1 hour average concentrations of ammonia were compared to the California OEHHA 1-hr average acute REL (3,200  $\mu\text{g}/\text{m}^3$ ) and show that the concentrations beyond the property line are well below this toxicological endpoint. The highest offsite concentration is 1,358  $\mu\text{g}/\text{m}^3$  located on the property boundary. Modeling results for the 1<sup>st</sup> high – 2 hour average concentrations of ammonia were compared to the ATSDR 2-hour average toxicological endpoint (1,184  $\mu\text{g}/\text{m}^3$ ). The highest offsite concentration is 1,346  $\mu\text{g}/\text{m}^3$  and is located on the property boundary. Two-hr average concentrations above the ATSDR Acute MRL extend up to 3.5 meters (12 feet) onto the neighboring industrial property. The concentrations on the neighboring industrial property are significantly less than the ACGIH 8-hr TLV of 17,414  $\mu\text{g}/\text{m}^3$ .

For the purposes of completeness, the 1<sup>st</sup> high 24-hour average concentrations of ammonia were compared to the Tier I WDE 24-hour average ASIL concentration (70.8  $\mu\text{g}/\text{m}^3$ ). As expected, the modeled concentrations exceed the ASIL value with the high offsite concentration of 303  $\mu\text{g}/\text{m}^3$ . This concentration occurs on the property boundary. The concentrations above the ASIL extend 202 meters from the property boundary. Finally, the highest annual average concentrations of ammonia (including onsite concentrations) do not exceed the California OHHEA chronic REL of 200  $\mu\text{g}/\text{m}^3$ , the EPA chronic RfC of 100  $\mu\text{g}/\text{m}^3$ , or the ATSDR chronic MRL of 70  $\mu\text{g}/\text{m}^3$ . The values for each year are listed in Table 1 of Appendix A.

### 5.4.3 Summary

The emissions from the PNS mobile pipe reactor result in offsite concentrations of fluoride that are well below any relevant toxicological endpoints. The ammonia concentration offsite do not exceed the acute toxicological endpoints recommended by the California OEHHA, but do exceed the 2-hr ATSDR acute MRL. However, concentrations that exceed the ATSDR acute MRL occur on industrial property and the concentrations do not exceed the ACGIH 8-hr TLV. The annual average ammonia concentrations (both on and offsite) do not exceed any relevant chronic toxicological endpoints. Finally, although the offsite

24-hr average concentrations exceed the WDE Tier I ASIL for ammonia, the Tier I ASIL appears to be based on ATSDR's Chronic MRL for an annual average exposure, and thus, is inappropriate for evaluating a 24-hr average concentration in a Tier II risk assessment.

## **6.0 RISK ASSESSMENT**

The Tier II risk assessment was completed by computing an acute Hazard Index (HI) and a chronic HI. The acute HI was computed by dividing the appropriate modeled concentrations of ammonia and fluoride by their respective acute toxicological endpoints to calculate an acute Hazard Quotient (HQ). The two hazard quotients were summed to obtain an acute HI. The acute HI was computed for different combinations of the acute toxicological endpoints because RME does not know which endpoint WDE will determine to be the most appropriate. (RME was directed to carry each of the endpoints through the analysis during the development of the Protocol.) The results of the acute Tier II risk assessment are detailed in Table 2 of Appendix A.

The only two sites with acute HIs for residential exposures greater than 1 are the CPS-Moses Lake site and the Helena Pasco site. The acute HI for the CPS Moses Lake site is 4.86 using the ATSDR acute MRL for ammonia and the NRC AEGL-1 for fluoride, and 1.74 using the California OEHHA acute REL for ammonia and the NRC AEGL-1 for fluoride. The acute HI for the Helena-Pasco site is 1.14 if the ATSDR acute MRL is used as the toxicological endpoint for ammonia. However, as discussed in Section 4, the ATSDR did not intend for its MRLs to be used as regulatory action levels or cleanup standards, which also means that they should not be used to support permitting actions. Further, the HI's occur on property that is industrial in its use. If the ACGIH TLV is used as the toxicological endpoint for ammonia, the HI becomes 0.09 for the CPS-Moses Lake site and 0.01 for the Helena-Pasco site.

An approach similar to that described above for the acute HI was used to compute a chronic HI, except that the highest annual average concentration and chronic toxicological endpoints were used to compute the HQs for the two chemicals. The results of the chronic Tier II risk assessment are detailed in Table 3 of Appendix A. The risk assessment results show that the chronic offsite HI for all sites ranged from a low of 0.07 for the Two Rivers-Moses Lake site to a high value of 0.35 at the Two Rivers-Pasco site.

## **7.0 CONCLUSIONS AND OPINIONS**

The results of the Tier II Risk Assessment can be summarized as follows.

1. The emissions from the PNS mobile pipe reactor will not result in a chronic HI greater than 1 at any of the sites where PNS intends to operate.
2. The emissions from the PNS mobile pipe reactor will not result in an acute HI greater than 1 at any of the sites where PNS intends to operate when the land use of the area is considered in the analysis.

3. If the area around the CPS-Moses Lake site were residential in nature, the acute HI would range from 4.86 (based on the ATSDR acute MRL) to 1.74 (based on the California OEHHA acute REL). However, as previously noted, ATSDR did not intend for its MRLs to be used as action levels by regulatory agencies.
4. If the area around the Helena-Pasco site were residential in nature, the acute HI would be 1.14 if the ATSDR acute MRL is used as the toxicological endpoint for ammonia in the analysis. However, as previously noted, ATSDR did not intend for its MRLs to be used as action levels by regulatory agencies.

## 8.0 REFERENCES

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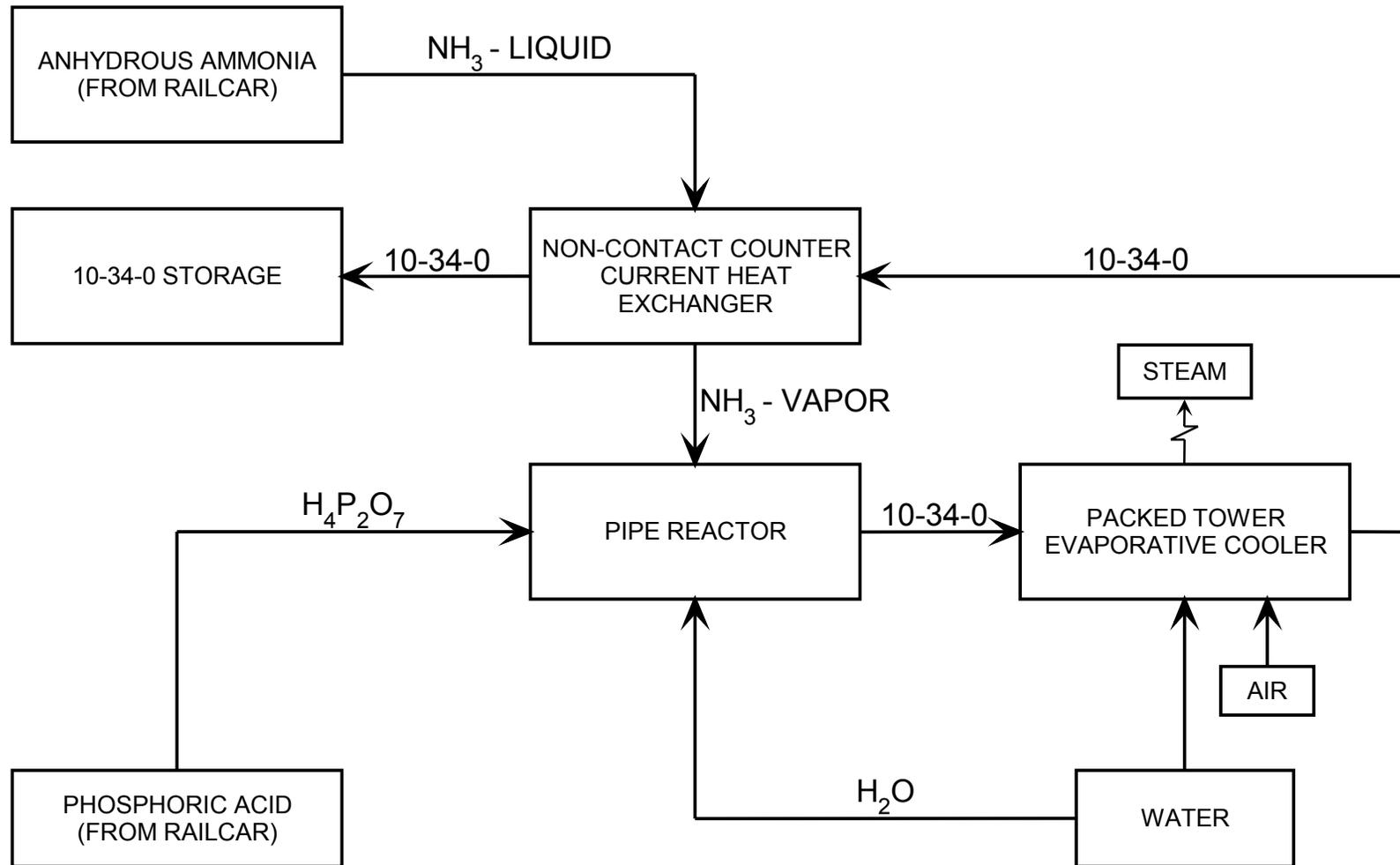
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**ATTACHED FIGURES**

§68.65(c)(1)(i)



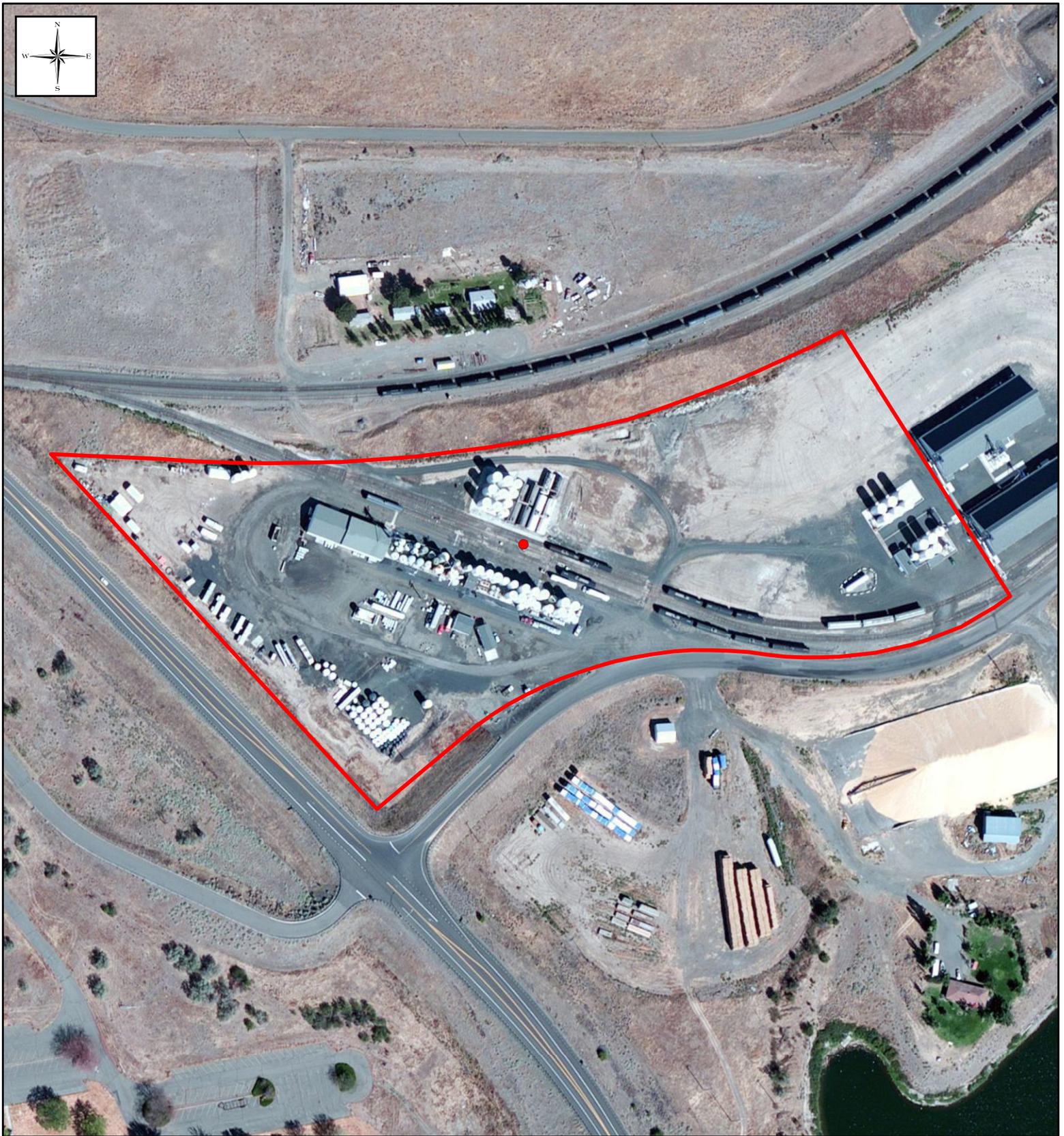
April 13, 2012

FIGURE 1  
10-34-0 REACTING  
PROCESS FLOW DIAGRAM

RME PROJECT #: 1087

PACIFIC NORTHWEST SOLUTIONS, INC.





LEGEND

- Pipe Reactor
- NuChem Property Boundary

FIGURE 2: PROPERTY BOUNDARY

NuCHEM LTD.

CENTRAL FERRY, WASHINGTON

MAY 23, 2012



RISK MANAGEMENT &  
ENGINEERING, LTD



LEGEND

- Pipe Reactor
- Property Boundary

FIGURE 3: PROPERTY BOUNDARY

TWO RIVERS TERMINAL MOSES LAKE

13583 WHEELER RD  
MOSES LAKE, WA 98837

MAY 23, 2012



RISK MANAGEMENT &  
ENGINEERING, LTD



LEGEND

- Pipe Reactor
- CPS

FIGURE 4: PROPERTY BOUNDARY

CPS MOSES LAKE

2624 RD N NE  
MOSES LAKE, WA 98837

MAY 23, 2012



RISK MANAGEMENT &  
ENGINEERING, LTD



LEGEND

- Pipe Reactor
- SelphLanding

**FIGURE 5: PROPERTY BOUNDARY**

TWO RIVERS SELPHLANDING

1670 SELPHLANDING RD  
PASCO, WA 99301

MAY 23, 2012



RISK MANAGEMENT &  
ENGINEERING, LTD



LEGEND

- Pipe Reactor
- PascoFence

FIGURE 6: PROPERTY BOUNDARY

HCC PASCO

1010 EAST KARTCHNER  
PASCO, WA 99301

MAY 23, 2012



RISK MANAGEMENT &  
ENGINEERING, LTD

## APPENDICES

## **APPENDIX A**

Tables

**TABLE 1: SUMMARY OF AMMONIA AND FLUORIDE AIR DISPERSION MODELING RESULTS**

PARAMETER	Central Ferry		Moses Lake - CPS		Moses Lake - Two Rivers		Pasco - Helena		Pasco - Two Rivers	
	Fl $\mu\text{g}/\text{m}^3$	NH3 $\mu\text{g}/\text{m}^3$								
Highest Offsite or Property Boundary Concentration										
<b>Comparison Value<sup>1</sup></b>	1,321	3,200	1,321	3,200	1,321	3,200	1,321	3,200	1,321	3,200
1st High 1-Hour Avg. Conc.	1.57	1,054	7.06	5,562	0.86	572	2.08	1,376	1.34	882
<b>Comparison Value<sup>2</sup></b>	NA	1,184								
1st High 2-Hour Avg. Conc.	NA	923	NA	5,753	NA	431	NA	1,346	NA	806
<b>Comparison Value<sup>3</sup></b>	7.8	NA								
1st High 24-Hour Avg. Conc.	0.44	289	4.41	2,896	0.11	70.16	0.47	303	0.57	374
Highest Annual Average Concentration For All Receptors (Always Occurs Onsite)										
<b>Comparison Value<sup>4</sup></b>	13	200	13	200	13	200	13	200	13	200
2007 - Ann. Avg. Conc.	0.011	20.3	0.010	16.2	0.011	12.9	0.020	19.2	0.029	22.1
2008 - Ann. Avg. Conc.	0.012	21.5	0.010	17.3	0.009	13.6	0.024	21.4	0.031	24.2
2009 - Ann. Avg. Conc.	0.009	20.1	0.011	18.1	0.012	13.9	0.017	17.1	0.026	20.4
2010 - Ann. Avg. Conc.	0.011	21.8	0.009	16.8	0.011	14.2	0.018	18.2	0.026	20.5
2011 - Ann. Avg. Conc.	0.009	21.4	0.008	16.1	0.008	14.1	0.023	19.9	0.033	25.0

NOTES:

1. Comparison value for Fluoride based on the National Research Council Acute Exposure Guideline Level (AEGL)-1; comparison value for Ammonia based on the California Office of Environmental Health and Hazard Assessment (OEHHA) acute Reference Exposure Level (REL). Both endpoints have a 1-hr averaging period.
2. Comparison value for Ammonia is based on the ATSDR acute MRL with a 2 hour averaging period.
3. Comparison value for Fluoride is based on the ATSDR acute MRL with a 24-hour averaging period.
4. Comparison value for Ammonia and Fluoride based on the Cal OEHHA REL.

NA = Not Available

**TABLE 2: ACUTE RISK ASSESSMENT**

<b>Central Ferry</b>					
Endpoints	NH3 Concentration µg/m <sup>3</sup> <sup>1</sup>	NH3 AHQ <sup>2</sup>	Fl Concentration µg/m <sup>3</sup> <sup>3</sup>	Fl AHQ <sup>4</sup>	AHI <sup>5</sup>
ATSDR <sup>6</sup> / NRC <sup>7</sup>	922.78	0.78	1.57	0.001	0.78
Cal OEHHA <sup>8</sup> / NRC	1,053.59	0.33	1.57	0.001	0.33
ACGIH <sup>9</sup> / NRC	263.40	0.02	1.57	0.001	0.02
<b>Moses Lake - CPS</b>					
Endpoints	NH3 Concentration µg/m <sup>3</sup> <sup>1</sup>	NH3 AHQ <sup>2</sup>	Fl Concentration µg/m <sup>3</sup> <sup>3</sup>	Fl AHQ <sup>4</sup>	AHI <sup>5</sup>
ATSDR <sup>6</sup> / NRC <sup>7</sup>	5,752.68	4.86	7.06	0.005	4.86
Cal OEHHA <sup>8</sup> / NRC	5,562.33	1.74	7.06	0.005	1.74
ACGIH <sup>9</sup> / NRC	1,390.58	0.08	7.06	0.005	0.09
<b>Moses Lake - Two Rivers</b>					
Endpoints	NH3 Concentration µg/m <sup>3</sup> <sup>1</sup>	NH3 AHQ <sup>2</sup>	Fl Concentration µg/m <sup>3</sup> <sup>3</sup>	Fl AHQ <sup>4</sup>	AHI <sup>5</sup>
ATSDR <sup>6</sup> / NRC <sup>7</sup>	431.29	0.36	0.86	0.001	0.36
Cal OEHHA <sup>8</sup> / NRC	572.07	0.18	0.86	0.001	0.18
ACGIH <sup>9</sup> / NRC	143.02	0.01	0.86	0.001	0.01
<b>Pasco - Helena</b>					
Endpoints	NH3 Concentration µg/m <sup>3</sup> <sup>1</sup>	NH3 AHQ <sup>2</sup>	Fl Concentration µg/m <sup>3</sup> <sup>3</sup>	Fl AHQ <sup>4</sup>	AHI <sup>5</sup>
ATSDR <sup>6</sup> / NRC <sup>7</sup>	1,345.92	1.14	2.08	0.002	1.14
Cal OEHHA <sup>8</sup> / NRC	1,375.60	0.43	2.08	0.002	0.43
ACGIH <sup>9</sup> / NRC	343.90	0.02	2.08	0.002	0.02
<b>Pasco - Two Rivers</b>					
Endpoints	NH3 Concentration µg/m <sup>3</sup> <sup>1</sup>	NH3 AHQ <sup>2</sup>	Fl Concentration µg/m <sup>3</sup> <sup>3</sup>	Fl AHQ <sup>4</sup>	AHI <sup>5</sup>
ATSDR <sup>6</sup> / NRC <sup>7</sup>	806.36	0.68	1.34	0.001	0.68
Cal OEHHA <sup>8</sup> / NRC	882.02	0.28	1.34	0.001	0.28
ACGIH <sup>9</sup> / NRC	220.51	0.01	1.34	0.001	0.01

Notes:

1. Maximum offsite or fence line modeled NH3 concentration for the relevant averaging period.
2. NH3 AHQ is derived by dividing the NH3 concentration by the toxicological endpoint for NH3.
3. Maximum offsite or fence line modeled FL concentration for the relevant averaging period.
4. FL AHQ is computed by dividing the FL concentration by the toxicological endpoint for FL.
5. AHI is computed by summing the NH3 AHQ and the FL AHQ.
6. ATSDR acute toxicological endpoint based on a 2-hour average concentration is 1,184 µg/m<sup>3</sup> for NH3.
7. NRC AEGL-1 for FL is 1,321 µg/m<sup>3</sup>.

8. Cal OEHHA acute REL for NH<sub>3</sub> is 3,200 µg/m<sup>3</sup>.
9. ACGIH and NIOSH standard for 8-hr TWA concentration of NH<sub>3</sub> is 17,414 µg/m<sup>3</sup>. The 8-hr TLV was used as a conservative endpoint.

**TABLE 3: CHRONIC RISK ASSESSMENT**

<b>Central Ferry</b>					
Endpoint	NH3 Concentration µg/m <sup>3</sup> <sup>1</sup>	NH3 HQ <sup>2</sup>	Fl Concentration µg/m <sup>3</sup> <sup>3</sup>	Fl HQ <sup>4</sup>	HI <sup>5</sup>
ATSDR <sup>6</sup> / Cal OEHHA <sup>7</sup>	21.83	0.31	0.01	0.0009	0.31
EPA <sup>8</sup> / Cal OEHHA	21.83	0.22	0.01	0.0009	0.22
Cal OEHHA <sup>9</sup> / Cal OEHHA	21.83	0.11	0.01	0.0009	0.11
<b>Moses Lake - CPS</b>					
Endpoint	NH3 Concentration µg/m <sup>3</sup> <sup>1</sup>	NH3 HQ <sup>2</sup>	Fl Concentration µg/m <sup>3</sup> <sup>3</sup>	Fl HQ <sup>4</sup>	HI <sup>5</sup>
ATSDR <sup>6</sup> / Cal OEHHA <sup>7</sup>	18.08	0.26	0.01	0.0008	0.26
EPA <sup>8</sup> / Cal OEHHA	18.08	0.18	0.01	0.0008	0.18
Cal OEHHA <sup>9</sup> / Cal OEHHA	18.08	0.09	0.01	0.0008	0.09
<b>Moses Lake - Two Rivers</b>					
Endpoint	NH3 Concentration µg/m <sup>3</sup> <sup>1</sup>	NH3 HQ <sup>2</sup>	Fl Concentration µg/m <sup>3</sup> <sup>3</sup>	Fl HQ <sup>4</sup>	HI <sup>5</sup>
ATSDR <sup>6</sup> / Cal OEHHA <sup>7</sup>	14.19	0.20	0.01	0.0009	0.20
EPA <sup>8</sup> / Cal OEHHA	14.19	0.14	0.01	0.0009	0.14
Cal OEHHA <sup>9</sup> / Cal OEHHA	14.19	0.07	0.01	0.0009	0.07
<b>Pasco - Helena</b>					
Endpoint	NH3 Concentration µg/m <sup>3</sup> <sup>1</sup>	NH3 HQ <sup>2</sup>	Fl Concentration µg/m <sup>3</sup> <sup>3</sup>	Fl HQ <sup>4</sup>	HI <sup>5</sup>
ATSDR <sup>6</sup> / Cal OEHHA <sup>7</sup>	21.43	0.31	0.02	0.0018	0.31
EPA <sup>8</sup> / Cal OEHHA	21.43	0.21	0.02	0.0018	0.22
Cal OEHHA <sup>9</sup> / Cal OEHHA	21.43	0.11	0.02	0.0018	0.11
<b>Pasco - Two Rivers</b>					
Endpoint	NH3 Concentration µg/m <sup>3</sup> <sup>1</sup>	NH3 HQ <sup>2</sup>	Fl Concentration µg/m <sup>3</sup> <sup>3</sup>	Fl HQ <sup>4</sup>	HI <sup>5</sup>
ATSDR <sup>6</sup> / Cal OEHHA <sup>7</sup>	24.17	0.35	0.03	0.0025	0.35
EPA <sup>8</sup> / Cal OEHHA	24.17	0.24	0.03	0.0025	0.24
Cal OEHHA <sup>9</sup> / Cal OEHHA	24.17	0.12	0.03	0.0025	0.12

Notes:

1. Highest of the modeled annual average NH3 concentrations for years 2007 - 2011.
2. NH3 HQ computed by dividing the modeled NH3 concentration by the relevant toxicological endpoint for NH3.
3. Highest of the modeled annual average FL concentrations for years 2007 - 2011.
4. FL HQ computed by dividing the modeled FL concentration by the relevant toxicological endpoint for FL.
5. HI computed by summing the NH3 HQ and the FL HQ.
6. ATSDR chronic MRL for NH3 is 70 µg/m<sup>3</sup>.
7. Cal OEHHA chronic REL for FL is 13 µg/m<sup>3</sup>.
8. EPA RfC for NH3 is 100 µg/m<sup>3</sup>.
9. Cal OEHHA chronic REL for NH3 is 200 µg/m<sup>3</sup>.

**APPENDIX B**

Model Output Files (CD PROVIDED)

## **APPENDIX C**

Key References for Ammonia Toxicity Values

**Agency for Toxic Substances and Disease Registry**  
**(ATSDR)**

## APPENDIX A. ATSDR MINIMAL RISK LEVELS AND WORKSHEETS

The Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA) [42 U.S.C. 9601 et seq.], as amended by the Superfund Amendments and Reauthorization Act (SARA) [Pub. L. 99–499], requires that the Agency for Toxic Substances and Disease Registry (ATSDR) develop jointly with the U.S. Environmental Protection Agency (EPA), in order of priority, a list of hazardous substances most commonly found at facilities on the CERCLA National Priorities List (NPL); prepare toxicological profiles for each substance included on the priority list of hazardous substances; and assure the initiation of a research program to fill identified data needs associated with the substances.

The toxicological profiles include an examination, summary, and interpretation of available toxicological information and epidemiologic evaluations of a hazardous substance. During the development of toxicological profiles, Minimal Risk Levels (MRLs) are derived when reliable and sufficient data exist to identify the target organ(s) of effect or the most sensitive health effect(s) for a specific duration for a given route of exposure. An MRL is an estimate of the daily human exposure to a hazardous substance that is likely to be without appreciable risk of adverse noncancer health effects over a specified duration of exposure. MRLs are based on noncancer health effects only and are not based on a consideration of cancer effects. These substance-specific estimates, which are intended to serve as screening levels, are used by ATSDR health assessors to identify contaminants and potential health effects that may be of concern at hazardous waste sites. It is important to note that MRLs are not intended to define clean-up or action levels.

MRLs are derived for hazardous substances using the no-observed-adverse-effect level/uncertainty factor approach. They are below levels that might cause adverse health effects in the people most sensitive to such chemical-induced effects. MRLs are derived for acute (1–14 days), intermediate (15–364 days), and chronic (365 days and longer) durations and for the oral and inhalation routes of exposure. Currently, MRLs for the dermal route of exposure are not derived because ATSDR has not yet identified a method suitable for this route of exposure. MRLs are generally based on the most sensitive chemical-induced end point considered to be of relevance to humans. Serious health effects (such as irreparable damage to the liver or kidneys, or birth defects) are not used as a basis for establishing MRLs. Exposure to a level above the MRL does not mean that adverse health effects will occur.

## APPENDIX A

MRLs are intended only to serve as a screening tool to help public health professionals decide where to look more closely. They may also be viewed as a mechanism to identify those hazardous waste sites that are not expected to cause adverse health effects. Most MRLs contain a degree of uncertainty because of the lack of precise toxicological information on the people who might be most sensitive (e.g., infants, elderly, nutritionally or immunologically compromised) to the effects of hazardous substances. ATSDR uses a conservative (i.e., protective) approach to address this uncertainty consistent with the public health principle of prevention. Although human data are preferred, MRLs often must be based on animal studies because relevant human studies are lacking. In the absence of evidence to the contrary, ATSDR assumes that humans are more sensitive to the effects of hazardous substance than animals and that certain persons may be particularly sensitive. Thus, the resulting MRL may be as much as 100-fold below levels that have been shown to be nontoxic in laboratory animals.

Proposed MRLs undergo a rigorous review process: Health Effects/MRL Workgroup reviews within the Division of Toxicology, expert panel peer reviews, and agency-wide MRL Workgroup reviews, with participation from other federal agencies and comments from the public. They are subject to change as new information becomes available concomitant with updating the toxicological profiles. Thus, MRLs in the most recent toxicological profiles supersede previously published levels. For additional information regarding MRLs, please contact the Division of Toxicology, Agency for Toxic Substances and Disease Registry, 1600 Clifton Road NE, Mailstop F-32, Atlanta, Georgia 30333.

## APPENDIX A

**MINIMAL RISK LEVEL (MRL) WORKSHEET**

Chemical Name: Ammonia  
CAS Number: 7664-41-7  
Date: July 2004  
Profile Status: Third Draft Post-Public  
Route:  Inhalation  Oral  
Duration:  Acute  Intermediate  Chronic  
Graph Key: 14  
Species: Human

Minimal Risk Level: 1.7  mg/kg/day  ppm

Reference: Verberk MM. 1977. Effects of ammonia in volunteers. Int Arch Occup Environ Health 39:73-81.

Experimental design: The study examined the effects of exposure to ammonia in a group of 16 volunteers. Eight of them (experts) knew the effects of ammonia from the literature, but had had no personal contact, whereas the remaining eight subjects (non-experts) were students from a non-science faculty and were not familiar with ammonia or experiments in laboratory situations. All members of a group were exposed on the same day to one of the concentrations tested (50, 80, 110, or 140 ppm). The testing was repeated with a 1-week interval. Immediately before and after exposure, vital capacity, forced expiratory volume, and forced inspiratory volume were measured. During exposure, each subject recorded subjective feelings every 15 minutes as no sensation (0), just perceptible (1), distinctly perceptible (2), nuisance (3), offensive (4), or unbearable (5). No statistical analysis was performed and there was no group exposed to air only. A few weeks after the experiments, the subjects were tested to measure (pre-existing) non-specific reactivity of the airways to exogenous stimuli.

Effects noted in study and corresponding doses: None of the participants was hypersusceptible to non-specific irritants. Results of the pulmonary function tests after exposure were not statistically significantly different from pre-exposure values. For the non-experts, there was a clear increase in the number of reported symptoms for smell, eye irritation, throat irritation, cough, and general discomfort as the exposure concentration increased. The latter was not as clear for the experts. The number of symptoms recorded with a score >3 (nuisance) for smell, eye irritation, nose, throat, and urge to cough for the 50, 80, 110, and 140 ppm exposure groups was 2, 2, 7, and 11, respectively, for the experts and 6, 12, 18, and 29, respectively, for the non-experts. It should also be mentioned that the subjective responses appeared more pronounced in the non-expert group than in the expert group.

Dose and end point used for MRL derivation: 50 ppm for mild irritation to the eyes, nose, and throat in humans exposed to ammonia gas for 2 hours.

Because the effects observed were local irritation effects, they were not time-dependent (but rather concentration-dependent), an adjustment to 24-hour exposure was not necessary.

NOAEL  LOAEL

## APPENDIX A

Uncertainty Factors used in MRL derivation:

- [ X ] 3 for use of a minimal LOAEL
- [ ] 10 for extrapolation from animals to humans
- [ X ] 10 for human variability

Was a conversion used from ppm in food or water to a mg/body weight dose?

N/A

If an inhalation study in animals, list the conversion factors used in determining human equivalent dose:

N/A

Other additional studies or pertinent information which lend support to this MRL: Although the Verberk et al. (1977) study has limitations (no statistical analysis, subjective end points, no control group), it demonstrates that concentrations of 50 ppm ammonia can produce minimal discomfort in healthy members of the general population and therefore, should be avoided. Additional relevant information is provided by a study by Ferguson et al. (1977). In that study, a group of six healthy volunteers, not previously accustomed to working in an ammonia environment, were exposed 5 days/week to 25 ppm (2 hours/day), 50 ppm (4 hours/day), or 100 ppm (6 hours/day) of ammonia, or to 50 ppm of ammonia 6 hours/day for 6 weeks. End points monitored included subjective and objective measures of eye and throat irritation as well as pulse rate, respiration rate, pulmonary function (FVC, FEV), assessment of neurological function (reflex, balance, and coordination), and body weight. The exposure protocol consisted of a pre-exposure evaluation by a physician, 3 hours of exposure (this conflicts with exposure data on table 2 of the study and mentioned above), a mid-point physician's observation, lunch break, 3 additional hours of exposure, and a third physician's observation 30 minutes after exposure ceased. The conjunctiva and mucosa of the nose and throat were examined by a physician before and after each daily exposure and the degree of irritation noted was described as mild, moderate, or marked. Exposure to ammonia had no significant effect on the measures of respiratory function or in the neurological tests conducted. The results of the evaluations of irritation conducted by the physician showed no significant differences between the exposure groups, including the 0 ppm exposure group (pre-exposure). All subjects experienced some watering of the eyes and a sensation of dryness in the nose and throat and there was one observation of definite redness in the mucosa of the nose after a 6-hour exposure to 100 ppm during which time, there was an excursion to 200 ppm ammonia. No redness was observed in this subject the following morning. Throughout the study, the physician observed 6 cases of eye irritation, 20 of nose irritation, and 9 of throat irritation, and most cases appeared to have occurred the first week of the study during exposure to 50 ppm. It is difficult to determine in this study a NOAEL or LOAEL for irritation due to the different exposure durations experienced by the subjects, but it would appear that an exposure concentration of 100 ppm ammonia for 6 hours caused no significant changes in the vital functions measured and that 50 ppm can cause eye, nose, and throat irritation.

NIOSH (1974) reviewed 15 studies of case reports in which subjects were exposed to very high, but unquantified, concentrations of ammonia. The 15 reports provided a representative array of documented clinical findings including death, permanent eye lesions, and chronic respiratory symptoms, as well as acute lower and upper respiratory symptoms. The only quantitative information available was that a worker died 6 hours after estimated exposure to 10,000 ppm ammonia for an unspecified time (Mulder and Van der Zalm 1967). Studies with volunteers, also reviewed by NIOSH (1974), generally used concentrations of ammonia much higher than those in the studies by Verberk et al. (1977) or Ferguson et al. (1977) and/or exposure durations of only minutes. For example, exposure to a concentration of 500 ppm for 30 minutes caused respiratory irritation graded as severe by 2 out of 7 subjects (Silverman et al. 1949). Four out of 6 volunteers exposed to 50 ppm ammonia for 10 minutes graded the irritation as "moderate" and none described it as "discomforting" or "painful" (MacEwen et al. 1970). All of the

## APPENDIX A

subjects rated the odor as “highly penetrating” at 50 ppm and 3 subjects gave the same rating to 30 ppm. IBT (1973) exposed 10 subjects to 32, 50, 72, and 134 ppm for 5 minutes and the frequency of positive findings was as follows: at 32 ppm, 1 subject complained of dryness of the nose; at 50 ppm, 2 subjects complained of dryness of the nose; at 72 ppm, 3 subjects experienced eye irritation, 2 had nasal irritation, and 3 had throat irritation; and at 134 ppm, 5 subjects had signs of lacrimation, 5 had eye irritation, 7 had nasal irritation, 8 had throat irritation, and 1 had chest irritation.

Collectively, the available information from studies in humans supports the 50 ppm exposure level from the Verberk et al. (1977) study as a minimal LOAEL for irritation in acute studies. In general, studies in animals have used higher exposure concentrations. For ammonia, a corrosive irritant gas that affects the portal of entry and produces irritation of the eyes and respiratory tract, use of human data should be preferred over animal studies.

Agency Contact (Chemical Manager): Nickolette Roney, MPH

## APPENDIX A

**MINIMAL RISK LEVEL (MRL) WORKSHEET**

Chemical Name: Ammonia and Ammonium Compounds  
CAS Number: 7664-41-7  
Date: July 2004  
Profile Status: Third Draft Post Public  
Route:  Inhalation  Oral  
Duration:  Acute  Intermediate  Chronic  
Graph Key: 47  
Species: Humans

Minimal Risk Level: 0.1  mg/kg/day  ppm

Reference: Holness DL, Purdham JT, Nethercott JR. 1989. Acute and chronic respiratory effects of occupational exposure to ammonia. Am Ind Hyg Assoc J 50:646-650.

Experimental design: The study evaluated sense of smell, prevalence of respiratory symptoms (cough, bronchitis, wheeze, dyspnea, and others), eye and throat irritation, and lung function parameters (FVC, FEV<sub>1</sub>, FEV<sub>1</sub>/FVC, FEF<sub>50</sub>, and FEF<sub>75</sub>) in humans exposed for an average of 12.2 years in a soda ash plant (Holness et al. 1989). The cohort consisted of 52 workers and 35 controls. The subjects were assessed on two workdays: on the first workday of their workweek and on the last workday of their workweek. Spirometry was performed at the beginning and end of each work shift, so that each worker had four tests done. To determine the exposure levels, exposed and control workers were sampled over one work shift; the average sample collection period was 8.4 hours. All of the participants in the study were males.

Effects noted in study and corresponding doses: Analysis of the results showed no significant differences in the prevalence of reported symptoms, but the exposed workers reported that exposure in the plant aggravated some of their reported symptoms (cough, wheeze, nasal complaints, eye irritation, and throat discomfort). Odor threshold was not affected by exposure to ammonia and there were no significant differences in baseline lung functions between exposed and control subjects. Analysis of each worker separately showed no significant relationship between the level of ammonia exposure and changes in lung function. Also, when the workers were divided into groups of individuals that were exposed to low (<6.25 ppm), medium (6.25–12.5 ppm), and high (>12.5 ppm) ammonia levels, no significant association was found between reporting of symptoms, decline in baseline function, or increasing decline in function over the work shift and exposure to ammonia. Furthermore, no association was evident between increasing years of exposure and decreasing lung function. However, the power of the indices of both level and length of exposure is low because only eight workers were in areas with relatively high ammonia exposure.

The MRL was calculated by adjusting the NOAEL of 9.2 ppm (the mean TWA exposure concentration) for continuous exposure (9.2 x 8/24 hours x 5/7 days) and dividing by an uncertainty factor of 10 for the protection of sensitive individuals. A modifying factor of 3 was used for the lack of reproductive and developmental studies.

Dose and end point used for MRL derivation: 9.2 ppm for no significant alterations in lung function in chronically exposed workers.

NOAEL  LOAEL

## APPENDIX A

Uncertainty Factors used in MRL derivation:

- 10 for use of a LOAEL
- 10 for extrapolation from animals to humans
- 10 for human variability

Modifying Factors used in MRL derivation:

- 3 for lack of reproductive and developmental studies

Was a conversion used from ppm in food or water to a mg/body weight dose?

N/A.

If an inhalation study in animals, list the conversion factors used in determining human equivalent dose:

N/A.

Other additional studies or pertinent information which lend support to this MRL: Earlier studies summarized by NIOSH (1974) found that workers accustomed to 20 ppm ammonia did not complain of irritation symptoms, but showed slight redness in the conjunctiva. Those not accustomed had eye and respiratory discomfort and irritation. Another report stated that air levels below 5 ppm were associated with barely noticeable eye irritation. In yet an additional report, concentrations of 15–28 ppm in the work area produced slight eye irritation. More recent data reported respiratory effects associated with chronic-duration exposure to pollutants, including ammonia, in livestock confinement buildings and an increase in respiratory symptoms (such as bronchial reactivity/hyperresponsiveness, inflammation, cough, wheezing, or shortness of breath) and/or a decrease in lung function (such as forced expiratory volume in the first second [FEV<sub>1.0</sub>], maximum expiratory flow rates [MEF<sub>50</sub> and MEF<sub>75</sub>], and maximal mid-expiratory flow rate [MMEF]) in farmers exposed to ammonia levels of 2.3–20.7 ppm (Choudat et al. 1994; Cormier et al. 2000; Donham et al. 1995, 2000; Heederik et al. 1990; Reynolds et al. 1996; Vogelzang et al. 1997, 2000). The farmers were also exposed to other possible respiratory toxins, such as dust and endotoxins. A cross-sectional study of male workers at two fertilizer factories in Saudi Arabia showed a significant association between exposure to ammonia gas and respiratory symptoms and bronchial asthma (Ballal et al. 1998). No continuous exposure levels could be calculated for these workers because the number of days worked per week was not provided. There were no chronic-duration inhalation studies in animals.

Agency Contact (Chemical Manager): Nickolette Roney, MPH

**Environmental Protection Agency**

**(RfC)**



## Ammonia (CASRN 7664-41-7)

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Reference Dose for Chronic Oral Exposure (RfD)

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### Ammonia; CASRN 7664-41-7

Human health assessment information on a chemical substance is included in the IRIS database only after a comprehensive review of toxicity data, as outlined in the [IRIS assessment development process](#). Sections I (Health Hazard Assessments for Noncarcinogenic Effects) and II (Carcinogenicity Assessment for Lifetime Exposure) present the conclusions that were reached during the assessment development process. Supporting information and explanations of the methods used to derive the values given in IRIS are provided in the [guidance documents located on the IRIS website](#).

STATUS OF DATA FOR Ammonia

File First On-Line 05/01/1991

Category (section)	Status	Last Revised
Oral RfD Assessment (I.A.)	no data	
Inhalation RFC Assessment (I.B.)	on-line	05/01/1991
Carcinogenicity Assessment (II.)	no data	

## I. Chronic Health Hazard Assessments for Noncarcinogenic Effects

### I.A. Reference Dose for Chronic Oral Exposure (RfD)

Substance Name — Ammonia  
CASRN — 7664-41-7

Not available at this time.

### I.B. Reference Concentration for Chronic Inhalation Exposure (RfC)

Substance Name — Ammonia  
 CASRN — 7664-41-7  
 Last Revised — 05/01/1991

The inhalation Reference Concentration (RfC) is analogous to the oral RfD and is likewise based on the assumption that thresholds exist for certain toxic effects such as cellular necrosis. The inhalation RfC considers toxic effects for both the respiratory system (portal-of-entry) and for effects peripheral to the respiratory system (extrarespiratory effects). It is expressed in units of mg/cu.m. In general, the RfC is an estimate (with uncertainty spanning perhaps an order of magnitude) of a daily inhalation exposure of the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime. Inhalation RfCs were derived according to the Interim Methods for Development of Inhalation Reference Doses (EPA/600/8-88/066F August 1989) and subsequently, according to Methods for Derivation of Inhalation Reference Concentrations and Application of Inhalation Dosimetry (EPA/600/8-90/066F October 1994). RfCs can also be derived for the noncarcinogenic health effects of substances that are carcinogens. Therefore, it is essential to refer to other sources of information concerning the carcinogenicity of this substance. If the U.S. EPA has evaluated this substance for potential human carcinogenicity, a summary of that evaluation will be contained in Section II of this file.

**\_\_\_I.B.1. Inhalation RfC Summary**

Critical Effect	Exposures*	UF	MF	RfC
Lack of evidence of decreased pulmonary function or changes in subjective syptomatology	NOAEL: 6.4 mg/cu.m (9.2 ppm) NOAEL(ADJ): 2.3 mg/cu.m NOAEL(HEC): 2.3 mg/cu.m  LOAEL: None	30	1	1E-1 mg/cu.m
Occupational Study				
Holness et al., 1989				
Increased severity of rhinitis and pneumonia with respiratory lesions				
NOAEL: None  LOAEL: 17.4 mg/cu.m (25 ppm) LOAEL(ADJ): 17.4 mg/cu.m LOAEL(HEC): 1.9 mg/cu.m				
Rat Subchronic Inhalation Study Broderson et al., 1976				

\*Conversion Factors: MW = 17.03 Holness et al., 1989: Assuming 25C and 760 mm Hg, NOAEL (mg/cu.m) = 9.2 ppm x 17.03/24.45 = 6.4 mg/cu.m. The NOAEL is based on an 8-hour TWA occupational exposure. MVho = 10 cu.m/day, MVh = 20 cu.m/day. NOAEL(ADJ) = 6.4 mg/cu.m x (MVho/MVh) x 5 days/7 days = 2.3 mg/cu.m.

Broderson et al., 1976: Assuming 25C and 760 mm Hg, the LOAEL (mg/cu.m) = 25 ppm x 17.03/24.45 = 17.4 mg/cu.m. The LOAEL(HEC) was calculated for a gas:respiratory effect in the ExtraThoracic region. MVa = 0.14 cu.m/day, MVh = 20 cu.m/day, Sa(ET) = 11.6 sq. cm., Sh(ET) = 177 sq. cm. RGDR(ET) = (MVa/Sa) / (MVh/Sh) = 0.1068. NOAEL(HEC) = 17.4 x RGDR = 1.9 mg/cu.m.

**\_\_\_I.B.2. Principal and Supporting Studies (Inhalation RfC)**

Holness, D.L., J.T. Purdham and J.R. Nethercott. 1989. Acute and chronic respiratory effects of occupational exposure to ammonia. *Am. Ind. Hyg. Assoc. J.* 50: 646-650.

Broderson, J.R., J.R. Lindsey and J.E. Crawford. 1976. The role of environmental ammonia in respiratory mycoplasmosis of rats. *Am. J. Pathol.* 85: 115-130.

Holness et al. (1989) investigated production workers exposed to ammonia in a soda ash facility. All of the available 64 production workers were invited to participate and 82% agreed to be evaluated. The control group consisted of 31 other plant workers from stores and office areas of the plant without previous exposure to ammonia. The mean age of the workers was 38.9 years and duration of exposure was 12.2 years. Weight was the only statistically significant difference in demographics found after comparing height, weight, years worked, % smokers and pack-years smoked. The mean TWA ammonia exposures based on personal sampling over one work shift (average sample collection 8.4 hours) of the exposed and control groups were 9.2 ppm (6.4 mg/cu.m) and 0.3 ppm (0.21 mg/cu.m), respectively.

A questionnaire was administered to obtain information on exposure and work histories and to determine eye, skin and respiratory symptomatology (based on the American Thoracic Society [ATS] questionnaire [Ferris, 1978]). Spirometry (FVC, FEV-1, FEF50 and FEF75) was performed according to ATS criteria at the beginning and end of each work shift on the first workday of the week (day 1) and the last workday of the week (day 2). Differences in reported symptoms and lung function between groups were evaluated using the actual values and with age, height and pack-years smoked as covariates in linear regression analysis. Baseline lung function results were expressed as percent of predicted values calculated from Crapo et al. (1981) for FVC and FEV-1 and from Lapp and Hyatt (1967) for FEF50 and FEF75.

No statistical difference in the prevalence of the reporting symptoms was evident between the exposed and control groups, although workers reported that exposure at the plant had aggravated specific symptoms including coughing, wheezing, nasal complaints, eye irritation, throat discomfort and skin problems. The percentage of exposed workers reporting hay fever or familial history of hay fever was significantly less than controls, suggesting possible self-selection of atopic individuals out of this work force. The atopic status of the worker and control groups was not determined by skin prick tests to common aeroallergens. Furthermore, the workers complained that their symptomatology was exacerbated even though there was no statistical difference between groups. Since the study was cross-sectional in design with a small population, it is possible that selection bias may have occurred.

Baseline lung functions (based on the best spirometry values obtained during the four testing sessions) were similar in the exposed and control groups. No changes in lung function were demonstrated over either work shift (days 1 or 2) or over the workweek in the exposed group compared with controls. No relationship was demonstrated between chronic ammonia exposure and baseline lung function changes either in terms of the level or duration of exposure, probably due to lack of adequate exposure data for categorizing exposures and thus precluding development of a meaningful index accounting for both level and length of exposure.

Based on the lack of subjective symptomatology and changes in spirometry, this study establishes a free-standing TWA NOAEL of 9.2 ppm (6.4 mg/cu.m). Adjustment for the TWA occupational scenario results in a NOAEL(HEC) of 2.3 mg/cu.m.

Broderson et al. (1976) exposed groups of F344 rats (6/sex/dose) continuously to 25, 50, 150 or 250 ppm ammonia (HEC = 1.9, 3.7, 11.2 or 18.6 mg/cu.m, respectively) for 7 days prior to inoculation with *Mycoplasma pulmonis* and from 28-42 days following *M. pulmonis* exposure. Each treatment group had a corresponding control group exposed only to background ammonia and inoculated with *M. pulmonis* in order to produce murine respiratory mycoplasmosis (MRM). The

following parameters were used to assess toxicity: clinical observations and histopathological examination of nasal passages, middle ear, trachea, lungs, liver and kidneys. All levels of ammonia, whether produced naturally or derived from a purified source, significantly increased the severity of rhinitis, otitis media, tracheitis and pneumonia characteristic of *M. pulmonis*. Furthermore, there was a significant concentration response between observed respiratory lesions and increasing environmental ammonia concentration for gross and microscopic lesions. All lesions observed were characteristic of MRM. Gross bronchiectasis and/or pulmonary abscesses and the extent of gross atelectasis and consolidation was consistently more prevalent in exposed animals at all concentrations than in their corresponding controls. The severity of the microscopic lesions in the nasal passages, middle ears, tracheas and lungs was significantly greater in all exposed groups compared with controls. Increasing ammonia concentration was not associated with an increasing frequency of *M. pulmonis* isolations. Additionally, rats not exposed to *M. pulmonis* and exposed to ammonia at 250 ppm developed nasal lesions (epithelial thickening and epithelial hyperplasia) unlike those observed in inoculated rats. Based upon these data in *M. pulmonis* exposed rats, a LOAEL(HEC) of 1.9 mg/cu.m was identified.

A group of 295 pathogen free F344 rats was inoculated with *M. pulmonis* and exposed to either trace or 100 ppm ammonia (HEC=7.4 mg/cu.m) (Schoeb et al., 1982). Growth of *M. pulmonis* was greater in exposed rats than in controls. Similarly, serum immunoglobulin antibody responses to the inoculum were greater in the exposed population. It was further demonstrated that the nasal passages absorbed virtually all the ammonia at concentrations <500 ppm, indicating that the increased numbers of *M. pulmonis* in the lungs and the consequent exacerbation of lung lesions in MRM are secondary to events in the nasal passages rather than a direct effect of ammonia in the lung itself. These results are consistent with those of Broderson et al. (1976) detailed above.

The use of Holness et al. (1989) as the principal study can only be supported in the context of the data array. It is not surprising that no effects were seen on screening spirometry since the exposure levels were low. Comparing the 9.2 TWA of Holness et al. (1989) with other data on the respiratory effects of ammonia, a trend is observed that at lower concentrations the extrathoracic region of the respiratory system is affected due to the chemical's solubility and reactivity; while at higher concentrations, the lower part of the respiratory system is involved in both experimental animals (Dahlman, 1956; Gamble and Clough, 1976) and humans (Flury et al., 1983). Thus, no effects were observed in the lower respiratory system as reflected by pulmonary function. Pulmonary function may not be a particularly sensitive test because exposure to this type of agent at low concentrations is not expected to result in significant exposure of the lower respiratory region. No objective investigation of the workers' nasal epithelium was performed and the complaint of exacerbated upper respiratory symptoms suggests sensory irritation and supports the extrathoracic region as the critical region for an effect. The possibility of selection bias against atopic predispositions in the population is suggested by the significantly lower prevalence of hay fever in the exposed versus control cohort. Thus, there is a concentration-response in the extrathoracic region in experimental animals beginning at a LOAEL at essentially the same HEC as the NOAEL in Holness et al. (1989) and the NOAEL may be based on a less sensitive endpoint. Also the apparent discrepancy of a lower LOAEL(HEC) from Broderson et al. (1976) and the identified NOAEL(HEC) of the Holness et al. (1989) study may be the result of differences in air flow patterns since rats are obligate nose- breathers and humans breathe oronasally. The use of the NOAEL from Holness et al. (1989) can be supported as marginal in this context due to the symptomatology complaints and because human data engenders less uncertainty than extrapolation from the experimental animal data.

### **\_\_\_I.B.3. Uncertainty and Modifying Factors (Inhalation RfC)**

UF — An uncertainty factor of 10 is used to allow for the protection of sensitive individuals. A factor of 3 was used to account for several data base deficiencies including the lack of chronic data, the proximity of the LOAEL to the NOAEL and the lack of reproductive and developmental toxicology studies. This factor is not larger than 3, however, since studies in rats (Schaerdel et al., 1983) have

shown no increases in blood ammonia levels at exposures 32 ppm and only minimal increases at 300-1000 ppm, suggesting that no significant distribution is likely to occur at the HEC level calculated.

MF — None

#### **\_\_\_I.B.4. Additional Studies/Comments (Inhalation RfC)**

Groups of four healthy human volunteers were exposed weekly (5 days/week) to 25 (2 hours/day), 50 (4 hours/day) or 100 (6 hours/day) ppm ammonia (1.0, 4.1 or 12.1 mg/cu.m) for 6 weeks; or to 50 ppm (6.2 mg/cu.m) 6 hours/day for 6 weeks. Subjective and objective indications of eye and respiratory tract irritation, pulse rate, respiration rate, FVC, FEV and difficulty in performing simple cognitive tasks were used to assess toxicity. No abnormalities of the chest, heart, vital organs, neurological response, apparent motor function, or significant weight changes were observed during weekly medical examinations. Transient irritation of the nose and throat was observed at 50 ppm (duration-adjusted to 4.1 mg/cu.m) or greater (Ferguson et al., 1977).

Flury et al. (1983) reported on a 5-year follow-up case study of a 50-year-old male patient who sustained a high-concentration exposure to ammonia fumes when a refrigerator coolant tank exploded. The patient had no prior history of smoking, pulmonary disease, wheezing or atopy and no family history of atopy or asthma before the industrial accident. The patient was hospitalized with acute respiratory failure. Laryngoscopy demonstrated membranous formation involving the entire tracheal wall. Chest examination revealed bilateral rhonchi, and chest x-rays on admission revealed bilateral perihilar infiltrates. Subsequent serial pulmonary function testing (spirometry and diffusion capacity) was performed and although the initial peripheral airway abnormality resolved over the 5-year period, a persistent expiratory obstruction and recurrent bronchospasm, suggestive of hyperreactive airways, was demonstrated. It is proposed that reepithelialization and probable reinnervation of the bronchial mucosa following the initial inflammation resulted in drastically altered irritant receptors.

Eight human volunteers were exposed to 50, 80, 110 and 140 ppm ammonia (35, 56, 76 and 97 mg/cu.m, respectively) for 2 hours, with a 1-week interval between exposures. The subjects tolerated a concentration of 76 mg/cu.m, although they rated the throat irritation as a nuisance. An ammonia concentration of 97 mg/cu.m was intolerable, and all of the subjects left the exposure chamber prematurely (Verberk, 1977).

Human volunteers were exposed to 21 or 35 mg/cu.m ammonia for 10 minutes. At 35 mg/cu.m, the irritation was not found to be "discomforting or painful" and was rated "moderate" by 4/6 volunteers, "faint" by 1/6 and "none" by 1/6; at 21 mg/cu.m, irritation was rated "faint" by 2/5 and "none" by 3/5 (MacEwen et al., 1970).

Six volunteers were exposed to 500 ppm ammonia (348 mg/cu.m) for 30 minutes. Nasal and throat irritation was reported. An increase in minute volume ranging from 50-250% over control values was observed (Silverman et al., 1949).

Kane et al. (1979) determined an RD50 value (exposure concentration to evoke a 50% decrease in respiratory rate) for sensory irritation in Swiss- Webster mice for ammonia of 303 ppm (95% C.I. 159-644) by plotting the percent decrease in respiratory rate versus the logarithm of the exposure concentration. A minimal irritation level for humans was predicted at 0.01RD50 (3 ppm).

Dahlman (1956) microscopically monitored the ciliary movement in the tracheas of rats exposed to ammonia via mouth-piece continuously for 8 minutes to concentrations of 90, 45, 20 and 10 ppm (3 rats/dose); and 6.5 and 3 ppm (2 rats/dose). Ciliary activity ceased in a concentration-dependent rate upon exposure to ammonia. Time to ciliary stasis was 5, 10, 20 and 150 seconds at concentrations of 90, 45, 20 and 6.5 ppm, respectively. Time to ciliary stasis was 7-8 minutes at

the 3 ppm concentration.

Gamble and Clough (1976) whole-body exposed female Porton rats to ammonia concentrations of 200 (+/- 50) ppm for 4, 8 or 12 days or 435 (+/- 135) ppm for 7 days. Duration of exposure was not otherwise specified. The total number of animals was 16, but the apportionment into exposure groups was not provided. Hyperplasia of the tracheal epithelium was shown to be concentration- and time-dependent. At 4 days of exposure to 200 ppm, the epithelium had changed to transitional-stratified and by 8 days there was gross change: disappearance of cilia and stratification increasing to folds forming on the luminal surface. A mucilaginous exudate was also evident with a slight increase in submucosal cellularity. At 12 days at the 200 ppm concentration, the epithelialization had increased in thickness. Rats exposed for 7 days to 435 ppm showed acute inflammatory reactions with infiltration of neutrophils, large mononucleated cells, monocytes and immature fibroblasts in the trachea. Evidence of necrotic changes at the luminal surface included pyknotic nuclei and karyorrhectic cells.

Groups of 10 guinea pigs and 20 Swiss albino mice were exposed continuously to an ammonia-air concentration of 20 ppm (13.9 mg/cu.m) for up to 6 weeks. A separate group of six guinea pigs was similarly exposed to an ammonia concentration of 50 ppm (35 mg/cu.m) for 6 weeks, and a group of 21 Leghorn chickens was exposed to a 20 ppm concentration for up to 12 weeks. Controls (number not specified) were maintained under identical conditions, except for the ammonia. Smaller groups of chickens were exposed continually to either 200 ppm for up to 3 weeks or 1000 ppm for up to 2 weeks. The effects of ammonia were found to be both time- and concentration-dependent. While no effects were observed in guinea pigs, mice, or chickens sacrificed after 1, 2, 3 or 4 weeks of exposure at 20 ppm, darkening/reddening, edema, congestion, and hemorrhage were seen in the lungs of all three species at sacrifice after 6 weeks of exposure at that concentration. In guinea pigs exposed to 50 ppm ammonia for 6 weeks, grossly enlarged and congested spleens, congested livers and lungs, and pulmonary edema were seen. In chickens exposed to 200 ppm for 17-21 days, liver congestion and slight clouding of the cornea were observed in addition to those effects observed in the chickens exposed to 20 ppm ammonia for 6 weeks. At 1000 ppm, the same effects, in addition to congestion of the spleen, were seen in chickens after just 2 weeks of exposure, and corneal opacities developed within just 8 days of exposure. In a second series of experiments, it was found that a 72-hour exposure to 20 ppm ammonia significantly increased the infection rate of chickens subsequently exposed to an aerosol of Newcastle disease virus, while the same effect was observed in just 48 hours in chickens exposed to 50 ppm. Changes in gross and micropathology did not accompany the change in disease rate (Anderson et al., 1964).

Guinea pigs were exposed to 0 or 170 ppm (118 mg/cu.m) 6 hours/day, 5 days/week for up to 18 weeks. No adverse effects were observed in animals exposed to ammonia for 6-12 weeks (HEC=21 mg/cu.m). Mild changes in the spleen, kidney suprarenal glands and livers were observed (HEC=19 mg/cu.m) in guinea pigs exposed for 18 weeks. No effects on the lungs were observed. The upper respiratory tract was not examined (Weatherby, 1952).

Swiss-Webster mice (16-24/group) were exposed to 0 or 305 ppm ammonia (212 mg/cu.m) 6 hours/day for 5 days. Nasal lesions were observed at 212 mg/cu.m which when dose duration adjusted for the RGDR, equals a LOAEL(HEC) of 4.5 mg/cu.m (Buckley et al., 1984).

Continuous exposure of rats to ammonia at 0, 40, 127, 262, 455 or 470 mg/cu.m for a minimum of 90 days (114 days for the 40 mg/cu.m group) was conducted in male and female Sprague-Dawley and Long-Evans rats. A LOAEL of 262 mg/cu.m (HEC=28 mg/cu.m) was determined based upon nasal discharge in 25% of the rats, and nonspecific circulatory and degenerative changes in the lungs and kidneys that were difficult to relate specifically to ammonia inhalation. A frank-effect-level of 455 mg/cu.m (HEC=48.7 mg/cu.m) was observed due to high mortality in the rats (90-98%). Nasal passages were not histologically examined (Coon et al., 1970).

Duroc pigs were exposed to ammonia concentrations of 10, 50, 100 and 150 ppm. Exposure to

ammonia significantly decreased both food intake and body weight gain. Higher concentrations caused nasal, lacrimal and mouth secretions, which became less severe over time. No treatment-related gross or microscopic changes were observed in the bronchi, lungs or turbinates at necropsy (Stombaugh et al., 1969).

Various animal species were exposed to 0, 155 and 770 mg/cu.m for 8 hours/day, 5 days/week for 30 exposures (rats, guinea pigs, rabbits, dogs and monkeys). The LOAEL for lung inflammation is 770 mg/cu.m for rats (HEC=82.4 mg/cu.m) and guinea pigs. Ocular and nasal irritation was observed at 770 mg/cu.m in rabbits and dogs. The upper respiratory tract was not examined (Coon et al., 1970).

Atmospheric ammonia is present in relatively low concentrations in both urban and nonurban environments. Typical levels of ammonia are on the order of 5 and 20 ug/cu.m for nonurban and urban sites, respectively (WHO, 1986). The total intake of ammonia by inhalation is approximately 0.1-0.5 mg/day. Ammonia also may be excreted through expired air. Estimates of ammonia expired by humans during mouth breathing have been reported to be between 90 and 1509 ug/cu.m (Hunt and Williams, 1977) and 29-518 ug/cu.m (Larson et al., 1977). These measured values are considerably higher than the expected values from the equilibration concentrations of plasma and lung parenchyma ammonia levels (28-49 ug/cu.m). The higher-than-expected levels of ammonia in air expired by humans and other experimental animals suggests that ammonia may be synthesized by oral microflora. Furthermore, reaction products may be formed from the expired ammonia and other ambient chemicals thereby altering the toxicity and reactivity of this endogenous ammonia source. Barrow and Steinhagen (1980) measured the average expired air ammonia concentration in nose breathing rats (mean=54 ug/cu.m) and found the concentration to be in reasonable agreement with the values measured by Larson et al. (1977) in humans. However, comparison of tracheal cannulated animals to humans is not possible because in the Larson et al. (1977) study only one subject was sampled (29 ug/cu.m). Also, due to the inadequate sample size and inherent variability of breath ammonia values, some caution must be expressed in accepting the validity of the human values. Furthermore, because the oral cavity can be a "sink" or source of ammonia, comparisons to mouth breathing humans should not be made.

#### **\_\_\_I.B.5. Confidence in the Inhalation RfC**

Study — Medium  
Database — Medium  
RfC — Medium

Confidence in the principal study is medium. Although a relatively small sample size (males only) was studied and a free standing NOAEL was determined, mild extrathoracic effects were observed in rats near the same HEC as reported in the Holness study. Additional human subchronic and acute studies support the NOAEL. Confidence in the database is medium to high. Although developmental, reproductive or chronic toxicity following ammonia exposure has not been adequately tested, pharmacokinetic data suggests systemic distribution at the HEC level is unlikely. Reflecting medium confidence in the principal studies and medium to high confidence in the database, confidence in the RfD is medium.

#### **\_\_\_I.B.6. EPA Documentation and Review of the Inhalation RfC**

Source Document — This assessment is not presented in any existing U.S. EPA document.

Other EPA Documentation — U.S. EPA, 1987; U.S. EPA, 1989

Agency Work Group Review — 10/13/1988, 09/19/1989, 05/16/1990, 09/19/1990, 02/20/1991

Verification Date — 02/20/1991

Screening-Level Literature Review Findings — A screening-level review conducted by an EPA contractor of the more recent toxicology literature pertinent to the RfC for ammonia conducted in August 2003 identified one or more significant new studies. IRIS users may request the references for those studies from the IRIS Hotline at [hotline.iris@epa.gov](mailto:hotline.iris@epa.gov) or 202-566-1676.

#### **\_\_I.B.7. EPA Contacts (Inhalation RfC)**

Please contact the IRIS Hotline for all questions concerning this assessment or IRIS, in general, at (202)566-1676 (phone), (202)566-1749 (FAX) or [hotline.iris@epa.gov](mailto:hotline.iris@epa.gov) (internet address).

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## **\_II. Carcinogenicity Assessment for Lifetime Exposure**

Substance Name — Ammonia  
CASRN — 7664-41-7

This substance/agent has not undergone a complete evaluation and determination under US EPA's IRIS program for evidence of human carcinogenic potential.

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**\_III. [reserved]**  
**\_IV. [reserved]**  
**\_V. [reserved]**

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## **\_VI. Bibliography**

Substance Name — Ammonia  
CASRN — 7664-41-7  
Last Revised — 05/01/1991

### **\_VI.A. Oral RfD References**

None

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### **\_VI.B. Inhalation RfC References**

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### **\_VI.C. Carcinogenicity Assessment References**

None

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### **\_VII. Revision History**

Substance Name — Ammonia  
CASRN — 7664-41-7

<b>Date</b>	<b>Section</b>	<b>Description</b>
05/01/1991	I.B.	Inhalation RfC summary on-line
05/01/1991	VI.	Bibliography on-line
01/01/1992	IV.	Regulatory Action section on-line
04/01/1997	III., IV., V.	Drinking Water Health Advisories, EPA Regulatory Actions, and Supplementary Data were removed from IRIS on or before April 1997. IRIS users were directed to the appropriate EPA Program Offices for this information.
10/28/2003	I.B.6.	Screening-Level Literature Review Findings message has been added.

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### **\_VIII. Synonyms**

Substance Name — Ammonia  
CASRN — 7664-41-7  
Last Revised — 05/01/1991

- 7664-41-7
- Ammonia
- AM-FOL

- AMMONIA GAS
- Ammonia Solution, Strong
- Ammoniac [French]
- Ammoniaca [Italian]
- Ammoniak [German]
- Amoniaco [Spanish]
- Amoniak [Polish]
- ANHYDROUS AMMONIA
- Aromatic Ammonia, Vaporole
- Caswell No. 041
- EPA Pesticide Chemical Code 005302
- HSDB 162
- Nitro-Sil
- R 717
- SPIRIT OF HARTSHORN
- UN 1005
- UN 2073
- UN 2672

<p><b>IRIS Home</b></p> <p><b>Chronic Health Hazards for Non-Carcinogenic Effects</b></p> <p><b>Reference Dose for Chronic Oral Exposure (RfD)</b></p> <ul style="list-style-type: none"> <li>• Oral RfD Summary</li> <li>• Principal and Supporting Studies</li> <li>• Uncertainty and Modifying Factors</li> <li>• Additional Studies/Comments</li> <li>• Confidence in the Oral RfD</li> <li>• EPA Documentation and Review</li> </ul> <p><b>Reference Concentration for Chronic Inhalation Exposure (RfC)</b></p> <ul style="list-style-type: none"> <li>• Inhalation RfC Summary</li> <li>• Principal and Supporting Studies</li> <li>• Uncertainty and Modifying Factors</li> <li>• Additional Studies/Comments</li> <li>• Confidence in the Inhalation RfC</li> <li>• EPA Documentation and Review</li> </ul> <p><b>Carcinogenicity Assessment for Lifetime Exposure</b></p> <p><b>Evidence for Human Carcinogenicity</b></p>
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**California Environmental Protection Agency**  
**Office of Environmental Health Hazard Assessment**  
**(OEHHA)**

## ACUTE TOXICITY SUMMARY

### AMMONIA

(anhydrous ammonia, aqueous ammonia)

**CAS Registry Number: 7664-41-7**

#### I. Acute Toxicity Summary (for a 1-hour exposure)

*Inhalation reference exposure level* **3,200 µg/m<sup>3</sup>**  
*Critical effect(s)* eye and respiratory irritation  
*Hazard Index target(s)* Eyes; Respiratory System

#### II. Physical and Chemical Properties (HSDB, 1994 except as noted)

<i>Description</i>	colorless gas
<i>Molecular formula</i>	NH <sub>3</sub>
<i>Molecular weight</i>	17.03
<i>Density</i>	0.695 g/L @ 25°C
<i>Boiling point</i>	-33.5°C
<i>Melting point</i>	-77.7°C
<i>Vapor pressure</i>	6,460 mm Hg @
<i>Flashpoint</i>	unknown
<i>Explosive limits</i>	unknown
<i>Solubility</i>	very soluble in water, alcohol and ether
<i>Odor threshold</i>	17 ppm (geometric mean) (AIHA, 1989)
<i>Odor description</i>	sharp and very irritating
<i>Metabolites</i>	unknown
<i>Conversion factor</i>	1 ppm = 0.71 mg/m <sup>3</sup> @ 25°C

#### III. Major Uses or Sources

Ammonia is a strongly alkaline chemical which is widely used in industry as a feed stock for nitrogen based chemicals such as fertilizers, plastics and explosives (ATSDR, 1990). Nationwide, ammonia is the third most common chemical to be released accidentally (U.S.EPA, 1989). Among hazardous material incidents such as intentional and threatened releases, those involving ammonia are the sixth most common. The volatility of ammonia, along with its common method of storage as large quantities under pressure, results in a potential for release of large amounts of ammonia gas (NRC, 1987).

#### IV. Acute Toxicity to Humans

Ammonia vapors cause irritation of the eyes and respiratory tract. Higher concentrations cause conjunctivitis, laryngitis, and pulmonary edema, possibly accompanied by a feeling of suffocation (OSHA, 1989). Contact with the skin causes burns and blistering. The eye is especially sensitive to alkali burns. Ammonia combines with moisture in the eyes and mucous membranes to form ammonium hydroxide. Ammonium hydroxide causes saponification and liquefaction of the exposed, moist epithelial surfaces of the eye and can easily penetrate the cornea and damage the iris and the lens (CCOHS, 1988; Way *et al.*, 1992). Damage to the iris may eventually lead to cataracts (CCOHS, 1988). Inhalation exposure to ammonia may result in an increase in systemic arterial blood pressure (Zitnik *et al.*, 1969). Exposure can also cause a decrease in minute ventilation volume (Cole *et al.*, 1977). Ammonia gas is especially irritating to upper respiratory passages, which prompts exposed victims to attempt escape from the fumes as quickly as possible. MacEwen and Vernot (1972) described pulmonary edema as the most frequent cause of death in humans exposed to ammonia.

Silverman and coworkers (1949) exposed 7 volunteers to 500 ppm (355 mg/m<sup>3</sup>) ammonia for 30 minutes using an oral-nasal mask. Symptoms due to ammonia inhalation varied widely among the 7 subjects. All seven subjects experienced upper respiratory irritation, which was graded as severe in 2 subjects. Only 2 subjects were able to continue nasal breathing throughout the 30 minute exposure. Reactions included irritation of the nose and throat, hypoesthesia of the exposed skin, and lacrimation. In two subjects, the nasopharyngeal irritation persisted for 24 hours after the exposure. One of the 7 subjects was only exposed to ammonia for 15 minutes rather than the full 30 minutes. The reason for this deviation in the exposure regimen was not given. In a previous experiment, brief exposure to 1,000 ppm reportedly resulted in immediate coughing in human subjects.

Ferguson and coworkers (1977) used six human subjects to demonstrate that a tolerance to ammonia exposure of 100 ppm (71 mg/m<sup>3</sup>) can be developed with a two-to-three week inurement period during which volunteers were exposed to lesser concentrations. The results tended to support the belief that persons with no recent history of ammonia exposure are more sensitive to the irritating effects than those who are acclimated to the noxious gas.

Verberk (1977) exposed sixteen subjects, eight previously exposed and eight naive, for two hours to ammonia in concentrations of 50, 80, 110, and 140 ppm (36, 57, 78, 99 mg/m<sup>3</sup>). The naive group could not tolerate 140 ppm for two hours and had several complaints during exposure to 110 ppm for 1 hour. None of the subjects in the study demonstrated a decrease in measured pulmonary function tests, including vital capacity, forced expiratory volume (1 second), and forced inspiratory volume (1 second), following ammonia exposure. The results showed a greater sensitivity to ammonia exposure for the naive group for responses of smell, eye irritation, cough, general discomfort, headache, and irritation of the chest. At the end of the initial 30 minutes of the 2-hour exposure period, nuisance level smell, eyes, nose, or throat irritation, or cough urge were reported by 7 of 16 (44%), 9 of 16 (56%), 12 of 16 (75%), or 15 of 16 (94%) individuals at concentrations of 50, 80, 110, or 140 ppm, respectively.

MacEwen *et al.* (1970) exposed groups of 5 and 6 human subjects to respective ammonia concentrations of 30 and 50 ppm (21 and 36 mg/m<sup>3</sup>). The volunteers subjectively rated irritation for the 10-minute exposures. No moderate or higher irritation was discerned by the group at the lower exposure level; however, 4 of the 6 subjects rated the 10 minute exposure at 50 ppm as causing moderate irritation.

The Industrial Bio-Test Laboratories (1973) evaluated ten human subjects for the irritation threshold of ammonia from exposures to ammonia gas at four different concentrations: 32, 50, 72, and 134 ppm (23, 36, 51, and 95 mg/m<sup>3</sup>). Irritation was taken to be any annoyance to the eyes, nose, mouth, throat, or chest which persisted throughout the 5-minute exposure period. At 72 ppm three subjects experienced eye irritation, two had nasal irritation, and three had throat irritation. At 134 ppm, five of the ten subjects experienced lacrimation and eye irritation, seven complained of nasal irritation, eight had throat irritation, and one experienced chest irritation. The authors only used 5-minute exposure durations; and it is possible that irritation symptoms could have developed with longer exposure durations at the lower exposures. The authors discounted the significance of nasal dryness reported at the two lowest levels.

Douglas and Coe (1987) determined a lachrymatory threshold of 55 ppm for ammonia following approximately 15 second exposures of volunteers via tight-fitting goggles. The threshold for bronchoconstriction, determined as a 20% increase in airway resistance, was slightly higher at 85 ppm following 10 breaths of ammonia via mouthpiece.

Estimates of odor thresholds for ammonia vary from 0.04-103 ppm (0.03-73 mg/m<sup>3</sup>) (Ferguson *et al.*, 1977; Henderson and Haggard, 1943; Ruth, 1986). Near the odor threshold, persons exposed to ammonia can experience annoyance and believe the odor to be a nuisance. Exposure to ammonia may result in an exacerbation of preexisting asthma. Shim and Williams (1986) surveyed 60 patients with a history of asthma worsened by certain odors. Nearly 80% of these patients claimed to have an exacerbation of asthma following exposure to household cleaners containing ammonia.

#### *Predisposing Conditions for Ammonia Toxicity*

**Medical:** Persons with asthma and other respiratory ailments including underlying cardiopulmonary disease (Shim and Williams, 1986) and persons with no tolerance, developed from recent exposures to ammonia (Ferguson *et al.* 1977), may be more susceptible to the toxic effects of ammonia.

**Chemical:** Chronic high dose aspirin therapy and therapy with valproic acid elevate blood ammonia levels (Reprotext, 1999).

#### **V. Acute Toxicity to Laboratory Animals**

The pulmonary lesions observed following acute, potentially lethal, inhalation of ammonia are similar in man and experimental animals (Withers, 1986; Payne *et al.*, 1990). Male rats and mice were determined to be more sensitive to the lethal effects of ammonia than the females of either species (Appelman *et al.*, 1982; Stupfel *et al.*, 1971).

Several animal lethality studies published dose-response data from which the MLE<sub>05</sub> (maximum likelihood estimate corresponding to 5% lethality) and BC<sub>05</sub> (benchmark dose at the 95% lower confidence interval of the MLE<sub>05</sub>) could be determined (see Table 1).

Table 1. Animal Lethality Effective and Benchmark Dose Levels for Ammonia

Reference	Species	Time (min)	MLE <sub>05</sub> (ppm)	BC <sub>05</sub> (ppm)
MacEwen & Vernot (1972)	rat	60	5,999	4,908
MacEwen & Vernot (1972)	mouse	60	4,006	3,406
Kapeghian <i>et al.</i> (1982)	mouse	60	3,664	3,366
Appelman <i>et al.</i> (1982)	rat	(10)*	11,862	9,950
Appelman <i>et al.</i> (1982)	rat	(20)*	13,010	10,206
Appelman <i>et al.</i> (1982)	rat	(40)*	11,137	4,881
Silver and McGrath (1948)	mouse	(10)*	2,846	2,298

\* *Exposure time was adjusted to 60 min using a modification of Haber's Law to facilitate comparisons of MLE<sub>05</sub> and BC<sub>05</sub> values. Exponent n = 2 was determined, based on Appelman *et al.* (1982) rat lethality data, by varying the term in a log-normal probit analysis (Crump, 1984; Crump and Howe, 1983).*

Appelman *et al.* (1982) observed signs of restlessness, wet noses and nasal discharge in rats immediately after the start of inhalation exposure to ammonia. Mouth breathing and dyspnea occurred soon after the start of exposure. Eye discharge began about 30 minutes into the exposure, and signs of eye irritation after 60 minutes of exposure. Dose versus exposure time varied from 7,000 ppm (4,970 mg/m<sup>3</sup>) for 60 minutes to 26,850 ppm (19,064 mg/m<sup>3</sup>) for 10 minutes.

## VI. Reproductive or Developmental Toxicity

There are no confirmed studies which show conclusively that reproductive or developmental toxicity can be linked experimentally or epidemiologically to ammonia exposure (Reprotext, 1999).

**VII. Derivation of Acute Reference Exposure Level and Other Severity Levels (for a 1-hour exposure)**

**Reference Exposure Level (protective against mild adverse effects): 3,200 µg/m<sup>3</sup>**

<i>Study</i>	Industrial Biotest Laboratories, 1973; MacEwen <i>et al.</i> , 1970; Silverman <i>et al.</i> , 1949; Verberk, 1977
<i>Study population</i>	humans
<i>Exposure method</i>	inhalation
<i>Critical effects</i>	eye and respiratory irritation
<i>LOAEL</i>	varied (see Section IV of text)
<i>NOAEL</i>	varied (see Section IV of text)
<i>Exposure duration</i>	varied (see Section IV of text)
<i>Extrapolated 1 hour concentration</i>	13.6 ppm (BC <sub>05</sub> )
<i>LOAEL uncertainty factor</i>	not needed in BC approach
<i>Interspecies uncertainty factor</i>	1
<i>Intraspecies uncertainty factor</i>	3
<i>Cumulative uncertainty factor</i>	3
<i>Reference Exposure Level</i>	4.5 ppm (3.2 mg/m <sup>3</sup> ; 3,200 µg/m <sup>3</sup> )

The exposure concentrations from the 4 studies were adjusted to 1-hour durations using the formula  $C^n \times T = K$  (Table 2). The value for the exponent n was empirically derived from the preceding data sets. The value of n (in the formula  $C^n \times T = K$ ) was sequentially varied for the log-normal probit relationship analysis. Using a chi-square analysis, a value of n = 4.6 was found to be the best fit.

The REL was calculated by a benchmark concentration (BC) approach using a log-normal probit analysis (Crump and Howe, 1983; Crump, 1984). The 95% lower confidence limit of the concentration expected to produce a response rate of 5% is defined as the BC<sub>05</sub>. The maximum likelihood estimate for a 5% response was 20.1 ppm and the 95% LCL on this value (BC<sub>05</sub>) for ammonia from this analysis was 13.6 ppm.

Response rate	MLE (ppm)	95% LCL (ppm)
1%	13.4	7.8
5%	20.1	13.6 (BC <sub>05</sub> )

An uncertainty factor (UF) of 3 was used to account for intraspecies variation in the human population. Refer to section IX of this toxicity summary for the graphic representation of benchmark dose derivation.

Table 2. Ammonia, Human Irritation, 60 Minute Exposures (adjusted), ppm

Study Concentration	32	30	50	50	72	50	80	134	110	140	500
Exposure Time (min.)	5	10	5	10	5	120	120	5	60	60	30
<b>60 min. adjusted Concentration</b>	19	20	29	34	42	43	69	78	95	120	430
Response	0/10	0/5	0/10	4/6	3/10	7/16	9/16	8/10	12/16	15/16	7/7
Study	2	3	2	3	2	1	1	2	1	1	4

Table adapted from: (1) Verberk, 1977; (2) Industrial Biotest Laboratories, 1973; (3) MacEwen *et al.*, 1970; (4) and Silverman *et al.*, 1949. The two lowest concentrations were combined for the log-probit analysis since this improved the fit of the data.

### Level Protective against Severe Adverse Effects

Exposure to 140 ppm (99.4 mg/m<sup>3</sup>) ammonia was considered ‘unbearable’ resulting in termination of exposure by all of 8 non-expert student volunteers after 30 to 75 minutes (Verberk, 1977). These exposures were tolerated for the full 2-hour exposure period by all 8 expert volunteers who were familiar with irritant vapors. Based on these findings in which ammonia inhalation resulted in a subjective response of panic or the need in naive subjects to take shelter, a 2-hour NOAEL of 110 ppm and a 30-minute LOAEL of 140 ppm were noted. Short exposures to ammonia did not result in increased nasal resistance of atopic subjects when compared to nonatopic subjects (McLean *et al.*, 1979). The non-expert group was considered to be more like the general public in their response. The final value to protect against severe adverse effects from ammonia exposure is thus 110 ppm (78 mg/m<sup>3</sup>).

### Level Protective against Life-threatening Effects

Kapeghian *et al.* (1982) determined a 1-hour LC<sub>50</sub> of 4,230 ppm and a 1-hour no observed lethality level of 3,440 ppm in male mice. The MLE<sub>05</sub> and BC<sub>05</sub> were estimated as 3,664 and 3,366 ppm (Table 1), respectively. The report by Kapeghian *et al.* (1982) provides one of the most detailed exposure and monitoring methods used for ammonia among the various animal lethality reports reviewed. In addition, a sensitive experimental animal species was used for the experiments (MacEwen & Vernot, 1972). An uncertainty factor of 1 was applied to account for animal to human extrapolation since (1) the BC accounts for some degree of variation and (2) OEHHA’s comparison of human irritation thresholds with concentrations lethal to mice suggests humans are not more susceptible than mice to ammonia toxicity. That is, in examining the Verberk (1977) study and comparing it to the mouse lethality study, additional uncertainty factors to the mouse study results in a concentration below the Verberk (1977) human study. A factor of 10 was applied to account for individual human variation. The cumulative uncertainty factor was 10. The resulting level for ammonia to protect against life-threatening effects is 340 ppm (240 mg/m<sup>3</sup>).

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## CHRONIC TOXICITY SUMMARY

# AMMONIA

(Anhydrous ammonia; aqueous ammonia)

CAS Registry Number: 7664-41-7

### I. Chronic Toxicity Summary

<i>Inhalation reference exposure level</i>	<b>200 mg/m<sup>3</sup> (300 ppb)</b>
<i>Critical effect(s)</i>	Pulmonary function tests or subjective symptomatology in workers
<i>Hazard index target(s)</i>	Respiratory system

### II. Physical and Chemical Properties (HSDB, 1994; 1999)

<i>Description</i>	Colorless gas
<i>Molecular formula</i>	NH <sub>3</sub>
<i>Molecular weight</i>	17.03 g/mol
<i>Density</i>	0.7710 g/L @ 0°C
<i>Boiling point</i>	-33.35° C
<i>Vapor pressure</i>	7510 torr @ 25°C
<i>Solubility</i>	Soluble in water, alcohol, and ether
<i>Conversion factor</i>	1 ppm = 0.71 mg/m <sup>3</sup>

### III. Major Uses or Sources

This strongly alkaline chemical is widely used in industry as a feed stock for nitrogen-based chemicals such as fertilizers, plastics and explosives (ATSDR, 1990). Ammonia is also used as a refrigerant. The general public is exposed by off-gassing from cleaning solutions containing aqueous ammonia. Household ammonia solutions contain 5-10% ammonia in water while industrial strength can be up to 28%. The annual statewide industrial emissions from facilities reporting under the Air Toxics Hot Spots Act in California based on the most recent inventory were estimated to be 21,832,909 pounds of ammonia (CARB, 1999).

### IV. Effects of Human Exposures

Comparisons were made between 52 workers and 31 control subjects in a soda ash plant for pulmonary function and eye, skin and respiratory symptomatology (Holness *et al.*, 1989). The pulmonary function tests included FVC (forced vital capacity – the total amount of air the subject can expel during a forced expiration), FEV<sub>1</sub> (forced expiratory volume in one second), FEF<sub>50</sub> (forced expiratory flow rate at 50% of the FVC) and FEF<sub>75</sub> (forced expiratory flow rate at

75% of the FVC). Age, height, and pack-years smoked were treated as covariates for the comparisons. The workers were exposed on average for 12.2 years to mean (time-weighted average) ammonia concentrations of 9.2 ppm (6.4 mg/m<sup>3</sup>) ± 1.4 ppm, while controls were exposed to 0.3 ppm (0.21 mg/m<sup>3</sup>) ± 0.1 ppm. No differences in any endpoints (respiratory or cutaneous symptoms, sense of smell, baseline lung function, or change in lung function over a work shift at the beginning and end of a workweek) were reported between the exposed and control groups.

Groups of human volunteers were exposed to 25, 50, or 100 ppm (0, 17.8, 35.5, or 71 mg/m<sup>3</sup>) ammonia 5 days/week for 2, 4, or 6 hours/day, respectively, for 6 weeks (Ferguson *et al.*, 1977). Another group of 2 volunteers was exposed to 50 ppm ammonia for 6 hours/day for 6 weeks.

Group	Exposure	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6
A	ppm NH <sub>3</sub> hours	25 2	50 4	100 6	25 2	50 4	100 6
B	ppm NH <sub>3</sub> hours	50 6	50 6	50 6	50 6	50 6	50 6
C	ppm NH <sub>3</sub> hours	100 6	50 4	25 2	25 6	50 4	100 2

Pulmonary function tests (respiration rate, FVC and FEV<sub>1</sub>) were measured in addition to subjective complaints of irritation of the eyes and respiratory tract. The difficulty experienced in performing simple cognitive tasks was also measured, as was pulse rate. There were reports of transient irritation of the nose and throat at 50 or 100 ppm. Acclimation to eye, nose, and throat irritation was seen after two to three weeks (in addition to the short-term subjective adaptation). No significant differences between subjects or controls on common biological indicators, in physical exams, or in performance of normal job duties were found. After acclimation, continuous exposure to 100 ppm, with occasional excursions to 200 ppm, was easily tolerated and had no observed effect on general health.

## V. Effects of Animal Exposures

Rats were continuously exposed to ammonia at 0, 25, 50, 150, or 250 ppm (0, 18, 36, 107, or 179 mg/m<sup>3</sup>) ammonia for 7 days prior to intratracheal inoculation with *Mycoplasma pulmonis*, and from 28 to 42 days following *M. pulmonis* exposure (Broderson *et al.*, 1976). All exposures to ammonia resulted in significantly increased severity of rhinitis, otitis media, tracheitis, and pneumonia characteristic of *M. pulmonis* infection, therefore 25 ppm was a LOAEL in this subchronic study. Exposure to 250 ppm ammonia alone resulted in nasal lesions (epithelial thickening and hyperplasia) which were not like those seen in *M. pulmonis*-infected rats.

The growth of bacteria in the lungs and nasal passages, and the concentration of serum immunoglobulin were significantly increased in rats exposed to 100 ppm (71 mg/m<sup>3</sup>) ammonia over that seen in control rats (Schoeb *et al.*, 1982).

Guinea pigs (10/group) and mice (20/group) were continuously exposed to 20 ppm (14.2 mg/m<sup>3</sup>) ammonia for up to 6 weeks (Anderson *et al.*, 1964). Separate groups of 6 guinea pigs and 21 chickens were exposed to 50 ppm and 20 ppm ammonia for up to 6 and 12 weeks, respectively. All species displayed pulmonary edema, congestion, and hemorrhage after 6 weeks exposure, whereas no effects were seen after only 2 weeks. Guinea pigs exposed to 50 ppm ammonia for 6 weeks exhibited enlarged and congested spleens, congested livers and lungs, and pulmonary edema. Chickens exposed to 200 ppm for 17-21 days showed liver congestion and slight clouding of the cornea. Anderson and associates also showed that a 72-hour exposure to 20 ppm ammonia significantly increased the infection rate of chickens exposed to Newcastle disease virus, while the same effect was observed in chickens exposed to 50 ppm for just 48 hours.

Coon *et al.* (1970) exposed groups of rats (as well as guinea pigs, rabbits, dogs, and monkeys) continuously to ammonia concentrations ranging from 40 to 470 mg/m<sup>3</sup>. There were no signs of toxicity in 15 rats exposed continuously to 40 mg/m<sup>3</sup> for 114 days or in 48 rats exposed continuously to 127 mg/m<sup>3</sup> for 90 days. Among 49 rats exposed continuously to 262 mg/m<sup>3</sup> for 90 days, 25% had mild nasal discharge. At 455 mg/m<sup>3</sup> 50 of 51 rats died. Thus 127 mg/m<sup>3</sup> (179 ppm) is a subchronic NOAEL for upper respiratory effects in rats. Coon *et al.* (1970) also found no lung effects in 15 guinea pigs exposed continuously to 40 mg/m<sup>3</sup> (28 ppm) ammonia for 114 days.

## VI. Derivation of Chronic Reference Exposure Level

<i>Study</i>	Holness <i>et al.</i> , 1989 (supported by Broderon <i>et al.</i> , 1976)
<i>Study population</i>	52 workers; 31 controls
<i>Exposure method</i>	Occupational inhalation
<i>Critical effects</i>	Pulmonary function, eye, skin, and respiratory symptoms of irritation
<i>LOAEL</i>	25 ppm (Broderon <i>et al.</i> , 1976) (rats)
<i>NOAEL</i>	9.2 ppm (Holness <i>et al.</i> , 1989)
<i>Exposure continuity</i>	8 hours/day (10 m <sup>3</sup> /day occupational inhalation rate), 5 days/week
<i>Exposure duration</i>	12.2 years
<i>Average occupational exposure</i>	3 ppm for NOAEL group (9.2 x 10/20 x 5/7)
<i>Human equivalent concentration</i>	3 ppm for NOAEL group
<i>LOAEL uncertainty factor</i>	1
<i>Subchronic uncertainty factor</i>	1
<i>Interspecies uncertainty factor</i>	1
<i>Intraspecies uncertainty factor</i>	10
<i>Cumulative uncertainty factor</i>	10
<i>Inhalation reference exposure level</i>	0.3 ppm ( 300 ppb; 0.2 mg/m <sup>3</sup> ; 200 µg/m <sup>3</sup> )

The Holness *et al.* (1989) study was selected because it was a chronic human study and was published in a respected, peer-reviewed journal. It is also the only chronic study available. The USEPA (1995) based its RfC of 100 µg/m<sup>3</sup> on the same study but included a Modifying Factor

(MF) of 3 for database deficiencies. The criteria for use of modifying factors are not well specified by U.S. EPA. Such modifying factors were not used by OEHHA.

For comparison with the proposed REL of 200  $\mu\text{g}/\text{m}^3$  based on human data, we estimated RELs from 2 animal studies. (1) Anderson *et al.* (1964) exposed guinea pigs continuously to 50 ppm (35  $\text{mg}/\text{m}^3$ ) ammonia for 6 weeks and observed pulmonary edema. Use of an RGDR of 0.86 and a cumulative uncertainty factor of 3000 (10 for use of a LOAEL, 10 for subchronic, 3 for interspecies, and 10 for intraspecies) resulted in a REL of 10  $\mu\text{g}/\text{m}^3$ . Staff note that the nearly maximal total uncertainty factor of 3000 was used in this estimation. (2) Coon *et al.* (1970) exposed rats continuously to 127  $\text{mg}/\text{m}^3$  ammonia for 90 days and saw no signs of toxicity. Use of an RGDR(ET) of 0.16 for nasal effects (observed in rats exposed to higher levels of ammonia in Broderson *et al.* (1976)) and a cumulative uncertainty factor of 100 (3 for subchronic, 3 for interspecies, and 10 for intraspecies) resulted in a REL of 200  $\mu\text{g}/\text{m}^3$ .

## VII. Data Strengths and Limitations for Development of the REL

Significant strengths in the ammonia REL include (1) the availability of long-term human inhalation exposure data (Holness *et al.*, 1989), (2) the demonstration of consistent effects in experimentally exposed human volunteers following short-term exposures (Ferguson *et al.*, 1977), and (3) reasonable consistency with animal data (Coon *et al.*, 1970).

Major areas of uncertainty are (1) the lack of a NOAEL and LOAEL in a single study, (2) a lack of animal data with chronic exposure and histopathological analyses, and (3) difficulties in estimated human occupational exposures. The overall database for this common chemical is limited.

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**Acute Exposure Guideline Level  
(AEGs)**

## 2

### Ammonia<sup>1</sup>

## Acute Exposure Guideline Levels

### PREFACE

Under the authority of the Federal Advisory Committee Act (P.L. 92-463) of 1972, the National Advisory Committee for Acute Exposure Guideline Levels for Hazardous Substances has been established to identify, review, and interpret relevant toxicological and other scientific data and develop acute exposure guideline levels (AEGLs) for high-priority, acutely toxic chemicals.

AEGLs represent threshold exposure limits for the general public and are applicable to emergency exposure periods ranging from 10 minutes (min) to 8 hours (h). Three levels—AEGL-1, AEGL-2, and AEGL-3—are developed for each of five exposure periods (10 min, 30 min, 1 h, 4 h, and 8 h) and are distinguished by varying degrees of severity of toxic effects. The three AEGLs are defined as follows:

AEGL-1 is the airborne concentration (expressed as parts per million [ppm] or milligrams per cubic meter [ $\text{mg}/\text{m}^3$ ]) of a substance above which it is predicted that the general population, including susceptible individuals, could

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<sup>1</sup>This document was prepared by the AEGL Development Team composed of Kowetha Davidson (Oak Ridge National Laboratory) and Susan Ripple (Chemical Manager and National Advisory Committee [NAC] on Acute Exposure Guideline Levels for Hazardous Substances member). The NAC reviewed and revised the document and AEGLs as deemed necessary. Both the document and the AEGL values were then reviewed by the National Research Council (NRC) Committee on Acute Exposure Guideline Levels. The NRC committee has concluded that the AEGLs developed in this document are scientifically valid conclusions based on the data reviewed by the NRC and are consistent with the NRC guideline reports (NRC 1993, 2001).

an individual exposed to a high unknown concentration of ammonia. Other case reports also contained no exposure estimates but showed that high concentrations of ammonia caused severe damage to the respiratory tract, particularly in the tracheobronchial and pulmonary regions. Death was most likely to occur when damage caused pulmonary edema. Nonlethal, irreversible, or long-term effects occurred when damage progressed to the tracheobronchial region, manifested by reduced performance on pulmonary function tests, bronchitis, bronchiolitis, emphysema, and bronchiectasis. Nondisabling reversible effects were manifested by irritation to the eyes, throat, and nasopharyngeal region of the respiratory tract. The odor of ammonia can be detected by humans at concentrations >5 ppm; the odor is highly penetrating at 50 ppm (10 min). Human volunteers exposed to ammonia showed slight irritation at 30 ppm (10 min); moderate irritation to the eyes, nose, throat, and chest at 50 ppm (10 min to 2 h); moderate to highly intense irritation at 80 ppm (30 min to 2 h); highly intense irritation at 110 ppm (30 min to 2 h); unbearable irritation at 140 ppm (30 min to 2 h), and excessive lacrimation and irritation at 500 ppm. Reflex glottis closure, a protective response to inhaling irritant vapors, occurred at 570 ppm for 21- to 30-year-old subjects, 1,000 ppm for 60-year-old subjects, and 1,790 ppm for 86- to 90-year-old subjects.

Acute lethality studies in animals showed that the lethal concentration in 50% ( $LC_{50}$ ) of the rats ranged from 40,300 ppm for a 10-min exposure to 7,338 and 16,600 ppm for 60-min exposures. For the mouse,  $LC_{50}$  values were 21,430 ppm for a 30-min exposure (almost all animals died in less than 13 min), 10,096 ppm for a 10-min exposure, and 4,230 and 4,837 ppm for 60-min exposures. Comparative data for the same exposure duration show that mice were more sensitive than rats to the acute exposure to ammonia (10-min  $LC_{50}$  values for mice and rats are 10,096 and 40,300 ppm, respectively). The lowest lethal concentration was 1,000 ppm for a cat exposed via an endotracheal tube, which probably exacerbated the effects in the tracheobronchial region (bronchopneumonia, bronchitis, bronchiolitis, and emphysema) by bypassing the scrubbing action of the nasopharyngeal region. Rats exposed by inhalation to lethal concentrations of ammonia showed signs of dyspnea, irritation to the eyes and nose, and hemorrhage in the lungs. Mice exposed to lethal concentrations of ammonia showed signs of irritation to the eyes and nose, along with tremors, ataxia, convulsions, seizures, and pathological lesions in the alveoli. Effects at nonlethal concentrations in mice and rats consisted of mild effects on the respiratory epithelium of the nasal cavity (mice and rats), reduction in the respiratory rate (mice), and evidence of eye irritation (rat). The  $RD_{50}$  (concentration causing a 50% reduction in respiratory rate) for the mouse was 300 ppm for a 30-min exposure.

The AEGL-1 value was based on a study in which 2/6 human subjects experienced faint irritation after exposure to ammonia at 30 ppm for 10 min (MacEwen et al. 1970). An interspecies uncertainty factor is not applied because human data are used to derive the AEGL-1. An intraspecies uncertainty factor of 1 was applied because ammonia is a contact irritant and is efficiently scrubbed

in the upper respiratory tract, particularly at the low AEGL-1 concentration. Irritation would be confined to the upper respiratory tract, and members of the population are not expected to respond differently. Atopic subjects, including asthmatics, responded similarly to nonatopics to brief nasal exposure to ammonia, and exercising subjects experienced only nonsignificant clinical changes in pulmonary function after exposure to ammonia. Asthmatic and exercising individuals are not expected to respond differently from nonasthmatic or resting individuals. Time scaling is not applied because upper respiratory tract irritation at low ammonia concentrations is not expected to become more severe with duration of exposure; adaptation may occur during prolonged exposure to ammonia. Therefore, the AEGL-1 value is 30 ppm for all exposure durations.

The AEGL-2 values were based on “offensive irritation” to the eyes and respiratory tract experienced by nonexpert human subjects (unfamiliar with the effects of ammonia or with laboratory studies) exposed to 110 ppm of ammonia for 2 h (Verberk 1977). The response of the nonexpert subjects ranged from “no sensation” to “offensive” eye irritation, cough, or discomfort and from “just perceptible” or “distinctly perceptible” to “offensive” throat irritation. However, AEGL-2 derivation was based on the response of the most sensitive nonexpert subjects. No residual effects were reported after termination of exposure, and pulmonary function was not affected by exposure. At the next higher concentration, some subjects reported the effects as unbearable and left the chamber after 30 min to 1 h; none remained for the full 2 h. An intraspecies uncertainty factor of 1 was selected because ammonia is a contact irritant, it is efficiently scrubbed in the upper respiratory tract, and any perceived irritation is not expected to be greater than that of the most sensitive nonexpert subject. The range of responses for this group is considered comparable to the range of responses that would be encountered in the general population, including asthmatics. Investigations have shown a link between nasal symptoms or allergic rhinitis and asthma, with rhinitis preceding the development of asthma, and studies have shown that atopic subjects, including asthmatics, and nonatopic subjects do not respond differently to a brief nasal exposure to ammonia. Exposure to exercising subjects showed only nonsignificant clinical changes in pulmonary function during exposure to ammonia at concentrations up to 336 ppm. In addition, a child experienced less severe effects than an adult exposed to very high concentrations of ammonia. The equation  $C^n \times t = k$ , where  $n = 2$ , was used to extrapolate to 5-, 10-, and 30-min exposure durations. This equation was based on mouse and rat lethality data. The AEGL-2 values are 220, 220, 160, 110, and 110 ppm for exposure durations of 10 and 30 min and 1, 4, and 8 h, respectively. The value of 110 ppm was adopted for the 4- and 8-h values, because the maximum severity rating for irritation in the Verberk (1977) study changed very little between 30 min and 2 h and is not expected to change for exposures up to 8 h. The 30-min value was also adopted as the 10-min AEGL-2 value because time scaling would yield a 10-min AEGL-2 of 380 ppm, which might impair escape.

The AEGL-3 values were based on  $LC_{01}$  values of 3,317 and 3,374 ppm derived by probit analysis of mouse lethality data reported by Kapeghian et al.

(1982) and MacEwen and Vernot (1972), respectively. An interspecies uncertainty factor of 1 was applied to the mouse data because the mouse was the most sensitive species among mammals and the mouse is considered unusually sensitive to respiratory irritants. An uncertainty factor of 3 was applied to account for intraspecies variability because concentrations of ammonia that are life threatening cause severe tracheobronchial and pulmonary damage and these effects are not expected to be more severe in asthmatics than in nonasthmatics, in children than adults, or in exercising than nonexercising individuals (see rationale for AEGL-2), but tracheobronchial and pulmonary effects may occur at a lower concentration in the elderly. Investigations showed that reflex glottis closure (protective mechanism) is 3-fold less sensitive in the elderly than in young subjects; this mechanism may be applicable only when concentrations of ammonia exceed 570 ppm. In addition, a larger interspecies or intraspecies uncertainty factor would lower the 30-min AEGL-3 to approximately 500 ppm, which was tolerated by humans without lethal or long-term consequences. ten Berge's equation ( $C^n \times t = k$ ) was used to extrapolate to the relevant exposure durations. The value of  $n$  was calculated from the regression coefficients ( $b_1/b_2$ ) for the mouse lethality data reported by ten Berge et al. (1986). The 5-min AEGL value was requested by the ammonia industry. The AEGL values and toxicity end points are summarized in Table 2-1.

## 1. INTRODUCTION

Ammonia is a colorless, corrosive, alkaline gas that has a very pungent odor, detectable by humans at concentrations >5 ppm. It can be liquefied under pressure. Ammonia is very soluble in water; it forms ammonium hydroxide when it contacts moist surfaces, producing heat because of its exothermic prop-

**TABLE 2-1** Summary of AEGL Values for Ammonia

Classification	10 min	30 min	1 h	4 h	8 h	End Point (Reference)
AEGL-1 (non disabling)	30 ppm (21 mg/m <sup>3</sup> )	30 ppm (21 mg/m <sup>3</sup> )	30 ppm (21 mg/m <sup>3</sup> )	30 ppm (21 mg/m <sup>3</sup> )	30 ppm (21 mg/m <sup>3</sup> )	Mild irritation (MacEwen et al. 1970)
AEGL-2 (disabling)	220 ppm (154 mg/m <sup>3</sup> )	220 ppm (154 mg/m <sup>3</sup> )	160 ppm (112 mg/m <sup>3</sup> )	110 ppm (77 mg/m <sup>3</sup> )	110 ppm (77 mg/m <sup>3</sup> )	Irritation: eyes and throat; urge to cough (Verberk 1977)
AEGL-3 (lethal)	2,700 ppm (1,888 mg/m <sup>3</sup> )	1,600 ppm (1,119 mg/m <sup>3</sup> )	1,100 ppm (769 mg/m <sup>3</sup> )	550 ppm (385 mg/m <sup>3</sup> )	390 ppm (273 mg/m <sup>3</sup> )	Lethality (Kapeghian et al. 1982; MacEwen and Vernot 1972)

erty. Ammonia and air will explode when ignited under some conditions (not otherwise described). Although it is generally regarded as nonflammable, ammonia is classified as a flammable gas by the National Fire Protection Association (Budavari et al. 1989; Lewis 1993; Pierce 1994). Table 2-2 summarizes the physical and chemical properties of ammonia.

**TABLE 2-2** Physical and Chemical Data

Property	Descriptor or Value	Reference
Chemical name	Ammonia	
Synonyms	Anhydrous ammonia, ammonia gas, AM-Fol, nitro-sil, R 717, spirit of hartshorn, UN1005 (DOT)	
CAS registry no.	7664-41-7	
Chemical formula	NH <sub>3</sub>	Weast et al 1984
Molecular weight	17.03	Weast et al 1984
Physical state	colorless gas (or liquid)	Lewis 1993
Vapor pressure	8.5 atm at 20°C	Lewis 1993
Density (liquid)	0.6818 at 33.35°C, 1 atm 0.6585 at 15°C, 2.332 atm 0.6386 at 0°C, 4.238 atm 0.6175 at 15°C, 7.188 atm 0.5875 at 35°C, 13.321 atm	O'Neil et al. 2001
Specific volume	22.7 ft <sup>3</sup> /lb at 70°C	Lewis 1993
Critical temperature	132.9°C	Pierce 1994
Pressure at critical temperature	111.5 atm	Pierce 1994
Solubility	89.9 g/100 mL cold water	Weast et al. 1984
Boiling/freezing point	-33.5°C/-77°C	Lewis 1993
Autoignition temperature	650°C (1,204°F)	Lewis 1993
Explosive limit	16-25% by volume in air	Pierce 1994
Ionization constants	$K_b$ $1.774 \times 10^{-5}$ , $K_a$ $5.637 \times 10^{-10}$ at 25°C	Pierce 1994
Alkalinity	1% solution, pH = 11.7	Pierce 1994
Conversion	1 ppm = 0.7 mg/m <sup>3</sup> at 25°C, 1 atm 1 mg/m <sup>3</sup> = 1.43 ppm	Pierce 1994

Ammonia is produced commercially by a modified Haber reduction process using atmospheric nitrogen and a hydrogen source. Ammonia is used as a compressed gas, as an aqueous solution (28%) called aquammonia, and as a household cleaning product (10%). It is widely used as a fertilizer, where the anhydrous gas or aqueous solution is injected directly into the soil. Ammonia is also used as a refrigerant in commercial installations, and it is used in the manufacture of other chemicals (Pierce 1994).

Ammonia is transported on highways (in tanker trucks), by railways, in pipelines, and on barges. Exposure to the general public can occur from accidents during transportation on highways and railways, during transfer between transportation vessels and storage vessels, by accidental releases at manufacturing facilities, and from farming accidents during soil application.

The data evaluated for AEGL derivation were obtained from case studies of accident victims exposed to high concentrations of ammonia, experimental studies in humans exposed to lower but irritating concentrations of ammonia, and experimental studies on lethality and irritation in animals. Additional data are available on long-term exposure to ammonia in the agricultural industry (feeding lots and poultry houses) but are not considered relevant for deriving acute exposure values for ammonia.

## **2. HUMAN TOXICITY DATA**

### **2.1. Human Lethality**

Quantitative exposure estimates of acute lethality of ammonia in humans are not well documented. In one case study the exposure concentration was estimated, but the duration was not. Another study reconstructs the exposure due to an accidental spill resulting in deaths. The remaining studies document the types of effects encountered when humans are acutely exposed to lethal concentrations of ammonia.

A worker was exposed to a very high concentration of ammonia vapor, estimated as 10,000 ppm. Duration of exposure was not reported, but it could have been a few minutes; nevertheless, the worker continued to perform his duties for an additional 3 h after the exposure. He experienced coughing, dyspnea, and vomiting soon after exposure. Three hours after initial exposure, his face was "red and swollen," his mouth and throat were "red and raw," his tongue was swollen, his speech was difficult, and he had conjunctivitis. He died of cardiac arrest 6 h after exposure. An autopsy revealed marked respiratory irritation, denudation of the tracheal epithelium, and pulmonary edema (Mulder and Van der Zalm 1967).

Caplin (1941) reported on 47 persons accidentally exposed to ammonia in an enclosed area (air raid shelter). The patients were divided into three groups depending on the degree to which they were affected: mildly, moderately, or severely. No deaths occurred among the nine mildly affected patients. Three of

27 moderately affected patients showed signs and symptoms similar to pulmonary edema and died within 36 h. Nine moderately affected patients developed bronchopneumonia within 2-3 days, and three died 2 days after the onset. The mortality rate for the moderately affected patients was 22% (6/27). The 11 severely affected patients developed pulmonary edema; seven died within 48 h. The mortality rate for the severely affected patients was 63% (7/11). Walton (1973) reported on the death of one of seven workers exposed to ammonia in an industrial accident. The autopsy report noted marked laryngeal edema, acute congestion, pulmonary edema, and denudation of the bronchial epithelium. These studies show that individuals who develop pulmonary edema (evidence of damage to alveolar region) after inhaling ammonia are more likely to die than those who do not.

Individuals who are acutely exposed to high concentrations of ammonia and survive the immediate effects may die weeks to months later, probably due to secondary effects of exposure. A 25-year-old man died 60 days after exposure to a high concentration of ammonia in a farming accident (Sobonya 1977). The autopsy report noted damage to the bronchial epithelium, bronchiectasis, mucus and mural thickening of the smallest bronchi and bronchioles, fibrous obliteration of small airways, and a purulent cavitary pneumonia characterized by large numbers of *Nocardia asteroides* (nocardial pneumonia). Three co-workers exposed in the accident died immediately. Hoeffler et al. (1982) reported on the case of a 30-year-old woman who died 3 years after exposure to ammonia during an accident involving a tanker truck carrying anhydrous ammonia (Houston accident). Her injuries resulted in severe immediate respiratory effects, including pulmonary edema. She required mechanically assisted respiration throughout her remaining life. Bronchiectasis was detected 2 years after exposure and confirmed on autopsy. The autopsy examination also showed bronchopneumonia and cor pulmonale (heart disease secondary to pulmonary disease). According to the authors, the bronchiectasis may have been due to bacterial bronchitis or to the chemical injury.

In the Houston accident, the crash of a tanker truck released 17.2 tonnes of pressurized anhydrous ammonia. The chemical cloud extended 1,500 m downwind and was 550 m wide. Five people were killed, 178 were injured, some with permanent disabling injuries (not otherwise described). The fatalities and disabling injuries occurred within about 70 m of the accident (NTSB 1979). The Potchefstroom, South Africa accident involved a pressurized ammonia storage tank that failed and instantaneously released 38 tonnes of anhydrous ammonia into the atmosphere. Eighteen people died and an unknown number were injured (Lonsdale 1975). A visible cloud extended about 300 m wide and about 450 m downwind; all deaths occurred within 200 m of the release point (Pedersen and Selig 1989). Pedersen and Selig used the WHAZAN gas dispersion model, which incorporated meteorological data and physicochemical data for ammonia to predict the concentration isopleths for ammonia released during both the Houston and Potchefstroom accidents. For the Houston accident, a 10,000-ppm isopleth extended 600 m long and 350 m wide, the 5,000-ppm isopleth was

835 m long and 430 m wide, the 2,500-ppm isopleth was 875 m long and 420 m wide, and the 1,200-ppm isopleth was 1,130 m long and 400 m wide. The investigators reported that their model overestimated the distance to zero deaths (200m) by 2.9 times for the Houston accident and by 2.5 times for the Potchefstroom accident. Pederson and Selig estimated the risk due to a few minutes, exposure to ammonia as very high for the general population at 10,000 ppm, as high for risk of fatalities among the general population and as very high for the vulnerable population (elderly people, children, and people with respiratory or heart disorders) at 5,000 ppm, and as some risk to the general population and high risk to the vulnerable population at 2,500 ppm.

Pedersen and Selig estimated the LC<sub>50</sub> for a 30-min exposure to the general population to be 11,500 ppm. They did not report their actual LC<sub>50</sub> estimate for the vulnerable population, but it would be lower than that estimated for the general population.

Mudan and Mitchell (1996) used the HGSYSTEM gas dispersion model to estimate atmospheric ammonia concentrations generated at the time of the ammonia accident in Potchefstroom. They provided upper-bound (wind speed = 1 m/s) and lower-bound (wind speed = 2 m/s) estimates of ammonia concentration based on distance from the release point and the time after release. Instantaneous concentrations were estimated to be in excess of 500,000 ppm (upper bound) within 50 m of the release point. The model predicted rapidly decreasing concentrations, such that, by 1 min after the release, concentrations would fall below 100,000 ppm. Mudan and Mitchell estimated that personnel were exposed to ammonia concentrations exceeding 50,000 ppm for the first 2 min, decreasing to 10,000 ppm during the next 3-4 min. The charts provided by Mudan and Mitchell of the South Africa accident showed that 10 workers were in Zone 1 (50 m of the release point) at the time of release; seven died (100% mortality for workers exposed outside). All survivors in Zone 1 remained sheltered inside buildings and therefore would not have experienced the outside atmospheric ammonia concentrations predicted by the model. Five deaths occurred in Zone 2 (50-100 m). Workers in Zone 2 who were upwind and outside at the time of the release survived, as did those who escaped in an upwind direction. Workers in Zone 2 who were downwind and outside at the time of release or attempted to escape downwind did not survive (except for one worker who escaped downwind; 83% mortality of workers exposed). All Zone 2 victims who died were outside; whereas individuals who were inside buildings survived. Five deaths occurred in Zone 3 (100 to ~200 m). Four victims were found downwind and >150 m from the release point, and another victim was found <150 m from the release point and in a crosswind location. The charts did not show the location or number of any survivors downwind and inside or outside buildings in Zone 3 (i.e., no data were available from the charts to determine if there were individuals who remained outside buildings in Zone 3 and survived). Therefore, the mortality rate cannot be calculated for Zone 3. It appears that within 150 m of the release point, individuals downwind of the ammonia cloud and outside a building were not likely to survive, but individuals downwind and sheltered indoors

or those upwind whether or not they were sheltered indoors were likely to survive. Thus, the lack of data on survivors in the path of the plume precludes estimating ammonia concentrations associated with zero mortality. RAM TRAC (1996) used the results of the HGSYSTEM gas dispersion model to predict 5-min ammonia concentrations of 87,479 ppm for 60% mortality, 73,347 ppm for 26% mortality, and 33,737 ppm for zero mortality for the Potchefstroom accident. RAM TRAC estimated a 5-min LC<sub>50</sub> of 83,322 ppm. See Section 7.1 for details of the evaluation of dose reconstruction models.

Henderson and Haggard (1943) reported that, exposure to ammonia at concentrations >2,500 ppm for durations ≥30 min is dangerous to humans. They noted that concentrations ≥5,000 ppm are rapidly fatal to humans.

## 2.2. Nonlethal Toxicity

### 2.2.1. Experimental Studies, Case Reports, and Anecdotal Data

The available literature detailing the disabling, long-term, or irreversible effects of inhaling ammonia gas or vapor is quite extensive. However, none of the studies contain quantitative exposure data. The acute effects of inhaling high nonlethal concentrations of ammonia include burns to the eyes and oral cavity and damage to the nasopharyngeal and tracheobronchial regions of the respiratory tract. Manifestations of damage include conjunctivitis, corneal burns, visual impairment, pain in the pharynx and chest, cough, dyspnea, hoarseness, aphonia, rales, wheezing, rhonchi, hyperemia and edema of the pharynx and larynx, tracheitis, bronchiolitis, and purulent bronchial secretions (Levy et al. 1964; Walton, 1973; Hatton et al. 1979; Montague and Macneil 1980; Flury et al. 1983; O’Kane 1983). Cyanosis, tachycardia, convulsions, and abnormal electroencephalograms also have been described for some patients (Kass et al. 1972; Walton 1973; Hatton et al. 1979; Montague and Macneil 1980). Pulmonary edema occurred in some patients who survived (Caplin 1941) but is most often seen in fatal cases. A few case studies are described below to document some of the disabling or irreversible injuries seen in individuals who inhaled high concentrations of ammonia. Some of the injuries would probably have resulted in death without rescue and medical treatment. The duration of exposure is reported when known.

Short-term recovery from serious injury due to inhaling ammonia is exhibited by three children and a 17-year-old female exposed to high but unknown concentrations of ammonia in the Houston accident (Hatton et al. 1979). These patients suffered second- or third-degree burns to the body, damage to the eyes, burns to the oral mucosa, upper-airway obstruction (probably due to damage to the laryngeal and tracheobronchial regions), and some pulmonary damage. All four patients recovered within 7-32 days. Nine of 14 patients exposed to an unknown concentration ammonia by inhalation for only a few seconds or few min-

utes showed moderate symptoms of chest abnormalities or airway obstruction and recovered within 6.3 days (average) (Montague and Macneil 1980).

Two young women accidentally exposed to anhydrous ammonia fumes (concentration unknown) for 30 or 90 min continued to show effects more than 2 years after exposure (Kass et al. 1972). One woman was found unconscious 90 min after the accident, and the other woman was exposed when she went outdoors for 30 min after the accident. The accident in which these two women were injured involved a railroad tanker car carrying 33,000 gal of anhydrous ammonia; 8 people died and 70 were injured. A heavy fog kept the ammonia vapors close to the ground for a long period of time after the accident. Damage to the eyes caused marked visual deterioration. Bronchiectasis was detected 2 years after exposure, and pulmonary function tests showed abnormalities indicative of small-airway obstruction. Various tests and examinations showed areas of atelectasis and emphysema in the lungs, thickened alveolar walls with histiocytic infiltration into the alveolar spaces, and mucous and desquamated cells in the bronchiolar lumen. Some of these effects may be secondary to the damage caused by ammonia. The woman exposed for 90 min was carrying her 1-year-old child, who was exposed at the same time. The child became "quite ill" but recovered completely except for a chemical scar on his abdomen (Kass et al. 1972).

In another accident, four patients (three farm workers and one refrigeration technician) who had been struck in the face and upper body with liquid ammonia had damage to their tracheobronchial regions, causing upper-airway obstruction and injury to the respiratory tract persisting for 2 years after the accident (Levy et al. 1964). A man splashed with liquid ammonia during a refrigeration accident showed evidence of peripheral (possibly bronchiolitis) and central airway obstruction 5 years after the accident (Flury et al. 1983). Tubular bronchiectasis was detected 8 years after exposure of a 28-year-old man to a high concentration of anhydrous ammonia in an industrial accident. Twelve years after exposure, the man continued to have a productive cough, frequent bronchial infections, dyspnea upon exertion, and severe airflow obstruction (62% reduction in forced expiratory volume at 1 s, FEV<sub>1</sub>; Leduc et al. 1992). O'Kane (1983) described several patients who had been exposed to ammonia vapor by inhalation for 5 min. One developed necrotizing pneumonia and was "left with chronic infective lung disease", one had persistent hoarseness and a productive cough for several months, and a third was left with a diffusion defect that was 75% of normal. Finally, Shimkin et al. (1954) described a man who developed epidermoid carcinoma 6 months after ammonia was splashed on his upper lip and nose. The authors postulated that the carcinoma was due to a single-exposure chemical trauma that exteriorized a latent cutaneous carcinoma. There was no evidence that ammonia caused the carcinoma.

Nondisabling and reversible effects of inhaling ammonia have been documented in several experimental studies of human subjects exposed to ammonia at various concentrations and durations. These studies are summarized below.

Five or six laboratory workers inhaled the exhaust fumes generated in an exposure chamber for an inhalation study and noted that the disagreeable odor and respiratory distress would prevent a person from voluntarily remaining in an atmosphere containing 170 ppm of ammonia (average concentration, 140-200 ppm) for an appreciable length of time (Weatherby 1952).

Henderson and Haggard (1943) reported that, based on observations of human responses to ammonia, the lowest concentration (or threshold) to cause coughing is 1,720 ppm, the lowest concentration to cause eye irritation is 698 ppm, and the lowest concentration to cause throat irritation is 408 ppm. They reported the least detectable odor to be 53 ppm. Pierce (1994) reported the odor threshold as 5-53 ppm.

McLean et al. (1979) examined the effect of ammonia on nasal airway resistance (NAR) in atopic and nonatopic human subjects. Ammonia (100 ppm at a pressure of 9 newtons/cm<sup>2</sup>) was introduced into each nostril for 5, 10, 15, 20, or 30 seconds (s). NAR was measured every minute for 5 min and then every 2 min for 10 min (total of 10 measurements over a 15-min period) using a pneumotachograph attached to a face mask. The same subjects were used for each successive ammonia exposure, which immediately followed the NAR measurements. The nonatopic subjects were screened based on strict criteria that included a questionnaire, physical examination, spirometry, nasal smear for eosinophils, and a battery of 19 prick and six intracutaneous tests. Nonatopic subjects could have no personal or immediate family history of atopic disease (allergic rhinitis, asthma, or atopic dermatitis), could have no more than 5% eosinophils in their nasal smears, and had to have a negative prick test reaction. Atopic subjects were screened based on a characteristic history of allergic rhinitis and at least one 3+ or 4+ prick test reaction. Some of the atopic subjects had a history of asthma. All subjects had been symptom-free for several weeks before the study, and none were taking medications that would influence skin or mucosal tests. Baseline NAR measurements were made for a 15-min period before introducing the ammonia. Additional tests included introducing 0.1 mL of aerosolized phosphate-buffered saline, 0.1 mL atropine, or 0.1 mL chlorpheniramine maleate into the nostrils, each followed by ammonia for 20 s.

The NAR after ammonia exposure to nonatopic and atopic subjects increased significantly with time of exposure from 5 to 20 s. Only a small further increase was noted for subjects exposed for 30 s compared with 20 s. The percent increase for atopic compared with nonatopic subjects was similar, and there was no difference between the allergic rhinitis subjects with or without a history of asthma. Atropine inhibited the response to ammonia in atopic and nonatopic subjects by up to 89%, whereas chlorpheniramine had no effect on the NAR induced by ammonia. The study's authors noted that the results of atropine and chlorpheniramine administration suggest that ammonia irritancy is mediated primarily by a parasympathetic reflex on the nasal vasculature and not via histamine release (McLean et al. 1979).

The Industrial Bio-Test Laboratories (1973) determined the irritation threshold in 10 human volunteers exposed to ammonia at four different concen-

trations (32, 50, 72, or 143 ppm) for 5 min. Irritation was defined as any annoyance to the nose, throat, eyes, mouth, or chest. The results are summarized in Table 2-3. The subjects showed dose-related responses for dryness of the nose and also eye, throat, nasal, and chest irritation. The severity of the effects was not noted.

MacEwen et al. (1970) studied six human volunteers exposed head only to ammonia at concentrations of 30 and 50 ppm for 10 min. The scale for intensity/description of irritation to the nose and eyes was as follows: 0, no irritation/not detectable; 1, faint/just perceptible, not painful; 2, moderate/moderate irritation; 3, strong/discomforting, painful, but may be endured; and 4, intolerable/exceedingly painful, cannot be endured. The scale for odor intensity/description was as follows: 0, no odor/no detectable odor; 1, very faint/minimum but positively perceptible odor; 2, faint/weak odor, readily perceptible; 3, easily noticeable/moderate intensity; 4, strong/highly penetrating; and 5, very strong/intense. At 30 ppm, two subjects reported irritation as faint (grade = 1) and three as not detectable (grade = 0); one gave no response. Also at 30 ppm, the odor was strong or highly penetrating for three subjects (grade = 4) and easily noticeable or moderate (grade = 3) for two subjects; no response was given by one subject. At 50 ppm, four subjects reported the irritation as moderate (grade = 2), faint or just perceptible (grade = 1) for one, and not detectable (grade = 0) for another. The odor was strong or highly penetrating (grade = 4) for all six subjects inhaling 50 ppm of ammonia. This study showed a concentration-related increase in the intensity of the response to ammonia at concentrations of 30 and 50 ppm.

Silverman et al. (1949) studied seven male subjects exposed to 500 ppm of anhydrous ammonia by means of a nose and mouth mask; six subjects were exposed for 30 min and one for 15 min. The inspired ammonia concentration was calculated, and the expired ammonia concentration was analyzed in grab samples taken every 3 min. The analytical technique consisted of a modified Nessler's reagent using a Klett photoelectric colorimeter. The sensitivity of the technique was 0.5 µg of ammonia. Respiratory rate and minute volume were

**TABLE 2-3** Effect of Ammonia Inhalation on Human Volunteers Exposed for 5 Min

Effects	32 ppm	50 ppm	72 ppm	134 ppm
Dryness of the nose	+ (1) <sup>a</sup>	+ (2)	—	—
Nasal irritation	—	—	+ (2)	+ (7)
Eye irritation	—	—	+ (3)	+ (5)
Lacrimation	—	—	—	+ (5)
Throat irritation	—	—	+ (3)	+ (8)
Chest irritation	—	—	—	+ (1)

<sup>a</sup>Number of volunteers showing a response out of a total of 10 participating.

Source: Data from Industrial Bio-Test Laboratories 1973, as cited in NIOSH 1974.

measured for each subject. Throat irritation was reported by two subjects. Nasal irritation with stuffiness similar to that of a cold or nasal dryness was reported by six subjects. The stuffiness lasted for about 24 h. Only two subjects were able to continue nasal breathing for the full 30 min, the others changing to mouth breathing on account of nasal dryness and irritation. Hypoesthesia (decreased sensitivity) of the skin around the nose and mouth was experienced by all subjects, and excessive lacrimation was reported by two. Hyperventilation (increases in the respiratory rates and minute volumes) occurred in all subjects. Hyperventilation occurred immediately in three subjects, was delayed for 10-30 min in the remaining four, and fluctuated with a 25% decrease at 4- to 7-min intervals. The increase in the minute volume was 141-289%. No coughing was reported; the authors noted that 1,000 ppm caused immediate coughing. This study showed that irritation of the upper respiratory tract and throat occurred in subjects inhaling 500 ppm of anhydrous ammonia for 15-30 min. There was no difference in the effects noted in the subject inhaling ammonia for 15 min and those inhaling ammonia for 30 min.

Verberk (1977) examined the effects of ammonia on respiratory function and recorded the subjective responses of two groups of subjects. One group consisted of eight individuals familiar with the effects of ammonia and who had no previous exposure (expert group, 29-53 years old); the other group consisted of eight university students unfamiliar with the effects of ammonia or with experiments in laboratory situations (nonexpert group, 18-30 years old). The subjects were paid for their participation and were informed that the study involved subjective effects and posed no danger to their health at the concentrations used. The subjects had the opportunity to leave the chamber before the test was completed. Four members of each group were smokers. Each group was exposed to ammonia at concentrations of 50, 80, 110, and 140 ppm for up to 2 h. Subjective responses (e.g., smell, eye irritation, throat irritation, cough) were recorded every 15 min and parameters of respiratory function (vital capacity, forced expiratory volume ( $FEV_{1s}$ ), forced inspiratory volume ( $FIV_{1s}$ )) were measured before exposure and after the 2-h exposure. Subjective responses were rated on a scale of 0-5 (0 = no sensation; 1 = just perceptible; 2 = distinctly perceptible; 3 = nuisance; 4 = offensive; and 5 = unbearable). Chamber concentrations were monitored instantaneously using an infrared spectrometer. There was no effect on respiratory function in either group inhaling any concentration of ammonia.

Table 2-4 summarizes the average and range of responses for both groups. Generally, the expert group scored responses lower than those of the nonexpert group. Four nonexpert subjects exposed to 140 ppm left the exposure chamber between 30 min and 1 h, and none remained in the chamber for the full 2 h. The greatest difference in responses between the expert and nonexpert groups was in general discomfort. The expert group perceived no general discomfort even after exposure to the highest concentration for 2 h, whereas the four nonexpert subjects perceived their general discomfort to range from "distinctly perceptible" to "unbearable" after 1 h. This study showed dose- and duration-response relation-

**TABLE 2-4** Average (Range) Scores of Subjective Responses of Expert and Nonexpert Subjects Exposed to Ammonia<sup>a</sup>

Response	50 ppm		80 ppm		110 ppm		140 ppm <sup>c</sup>	
	Expert	Nonexpert	Expert	Nonexpert	Expert	Nonexpert	Expert	Nonexpert <sup>c</sup>
Smell								
1/2 h	2.0 (1-3) <sup>b</sup>	2.5 (2-3)	2.0 (1-3)	3.0 (2-4.5)	2.0 (2-3)	3.0 (2-4)	2.0 (1-3)	4.0 (2-4.5)
1 h	2.0 (1-3)	2.5 (1-4)	2.0 (1-3)	3.0 (2-4)	2.0 (2-3)	3.0 (2-4)	2.0 (1-3)	4.0 (3.5-4.5)
2 h	2.0 (0.5-3)	3.0 (2-4)	1.5 (0.5-3)	3.0 (2-4)	2.0 (1.5-3)	3.0 (2-4)	2.0 (1-3)	WD <sup>c</sup>
Eye irritation								
1/2 h	1.5 (0-3)	0.8 (0-3)	1.5 (1-2)	1.5 (0-4)	2.5 (1-3)	2.5 (0-4)	3.0 (1.5-3.5)	3.0 (1-4.8)
1 h	1.5 (0-3)	0.8 (0-3)	2.0 (0-3)	1.5 (0-3)	2.5 (2-3.5)	2.5 (0-4)	2.0 (2-3)	3.5 (1-5)
2 h	1.0 (0-2)	1.2 (0-3)	1.5 (0-2)	2.0 (0-4)	2.0 (0.3-3)	2.5 (0-4)	2.5 (1-3)	WD
Throat irritation								
1/2 h	0.4 (0-2)	0.4 (0-1)	0.8 (0-2)	1.0 (0-3)	1.5 (0-3.5)	2.0 (0-4)	1.0 (0-2)	3.7 (3.5-5)
1 h	0.4 (0-3)	0.5 (0-3)	1.0 (0-3)	1.4 (1-3)	1.4 (0-3)	2.5 (1-4)	1.5 (0-2)	4.5 (2-4)
2 h	0.7 (0-3)	1.5 (0.3)	0.8 (0-2)	2.0 (0-4)	1.0 (0-2)	3.0 (2-4)	1.0 (0-3.7)	WD
Urge to cough								
1/2 h	0.2 (0-1.2)	0.2 (0-1)	0.3 (0-1)	0.5 (0-2)	0.8 (0-2)	1.5 (0-2)	0.5 (0-2)	2.0 (0-5)
1 h	0.3 (0-2)	0.2 (0-2)	0.5 (0-2)	1.0 (0-2)	0.5 (0-3.5)	1.7 (0-3)	0.6 (0-2.5)	1.7 (0-3)
2 h	0.3 (0-2)	0.4 (0-2)	0.4 (0-2)	0.3 (0-4)	0.3 (0-2.5)	1.7 (0-4)	0.4 (0-2.3)	WD
General discomfort								
1/2 h	0	0.1 (0-1)	0	1.0 (0-3)	0.2 (0-2)	1.0 (0-3)	0	2.2 (0-4)
1 h	0	0.2 (0-1)	0	1.2 (0-3)	0.2 (0-1)	1.2 (0-3)	0	3.3 (0-4.7)
2 h	0	1.0 (0-2)	0	1.3 (0-3)	0.3 (0-1)	1.5 (0-4)	0	WD
Irritation to chest	Similar to urge to cough, but scores tended to be a little lower.							

<sup>a</sup>Expert subjects: individuals who were familiar with the effects of ammonia and who had no previous exposure; nonexperts students were unfamiliar with the effects of ammonia or with experiments in laboratory situations.

<sup>b</sup>Based on a scale of 1-5: 0 = no sensation; 1 = just perceptible; 2 = distinctly perceptible; 3 = nuisance; 4 = offensive; and 5 = unbearable.

<sup>c</sup>Only four of the nonexpert subjects tolerated the ammonia for 1 h; none of the nonexpert subjects tolerated the ammonia for 2 h.

Source: Adapted from Verberk 1977.

ships for the effects of ammonia, particularly for the nonexpert subjects. This study also showed that general knowledge about the chemical may help alleviate the concern about exposure and the intensity of the symptoms experienced during exposure.

Cole et al. (1977) studied the effects of exercise on 18 servicemen who inhaled ammonia at concentrations of 71, 106, 144, or 235 mg/m<sup>3</sup> (102, 152, 206, or 336 ppm). The subjects were exposed for durations of between 95 and 120 min while cycling under a load of 20 watts increased up to 180 watts in 20-watt increments (based on assumptions of “zero time” and extrapolation from figures of Cole et al.). The same subjects served as their own controls. Measurements of respiratory parameters (respiratory rate, minute volume, tidal volume, and oxygen uptake) and cardiac frequency were taken under control conditions when the subjects inhaled air only and during the experimental conditions when the subjects inhaled ammonia. During exposure to ammonia, the subjects noted only a sensation in the nose and a slight dryness of the mouth. Minute volume was decreased by 8%, 10%, and 6% at 152, 206, and 336 ppm, respectively, compared with control measurements; statistical significance was achieved for all three concentrations. However, no clear dose-related trend was observed relative to the control measurements. The tidal volume was significantly decreased (9 and 8%, respectively) and respiratory frequency was increased (10 and 8% respectively) at 206 and 336 ppm compared with the control values, but there was no clear dose-response relationship. The small changes in tidal volume and respiratory frequency are unlikely to be clinically significant.

Sundblad et al. (2004) studied the acute effects of repeated low-level ammonia exposures of human subjects at rest and performing ergometric exercise. Twelve healthy atopic adults (seven females and five males, 21-28 years old, with a mean age of 25) with no reported present or past symptoms of allergy or airway disease were exposed in a 20-m<sup>3</sup> stainless steel chamber to ammonia at 0, 5, and, 25 ppm for 3 h on three separate occasions separated by at least 7 days in which subjects did not undergo experimental ammonia exposures. Exposure concentrations were monitored by infrared spectrophotometry. During each 3-h exposure period, 1.5 h was spent at seated rest and 1.5 h was spent exercising at 50 watts on a bicycle ergometer; activity was changed every 30 min. At specific times during exposure and 1.5 h postexposure, the subjects rated their level of discomfort related to odor, eyes, and airway symptoms and general symptoms (such as headache, dizziness, nausea, “feeling of intoxication”) on a scale of 0-100. The general symptoms were characterized by Sundblad and co-workers as central nervous system (CNS) effects. Sundblad et al. (2004) performed no neurophysiological measurements or studies showing systemic uptake of ammonia.

Subjective symptom rankings by questionnaire exhibited a dose-response relationship. Based on examination of questionnaire results, Sundblad et al. (2004) noted a tendency of sensory adaptation to “solvent smell” among those exposed to 5 ppm but not those exposed to 25 ppm. Ratings of symptoms related to eye and respiratory irritation and general symptoms were significantly greater in the 25-ppm exposure group than those of controls, while about half of the

symptoms experienced by the 5-ppm exposure group exhibited higher rankings than in the control group. Average rating of irritation and the CNS symptoms did not exceed “rather” (rating of 48). All symptomatic effects were transient.

Sundblad et al. (2004) collected pretrial and posttrial measurements to characterize lung function, methacholine challenge, cell composition in nasal lavage fluids, total and differential peripheral leukocyte counts, complement factor C3b, exhaled nitric oxide, body temperature, and peak expiratory flow. Under the Sundblad et al. experimental protocol, ammonia at 5 or 25 ppm did not induce detectable changes in pulmonary function or total cell concentration in nasal lavage fluid or induce an exposure-related bronchial response to methacholine, an increase in exhaled nitric oxide, an increase in the total or differential leukocyte, or a change in complement factor C3b.

Ferguson et al. (1977) reported that workers in their company in 1972 did not voluntarily use gas masks until ammonia concentrations reached 400 or 500 ppm. They also reported that before 1951 workers were subjected to continuous concentrations ranging from 150 to 200 ppm. To establish the bounds for controlled exposure studies, they conducted two reconnaissance experiments. In the first experiment they reported that four male subjects were able to tolerate “continued exposure” of 130-150 ppm (duration not reported) after exposure to lower concentrations for <2 h. In the second experiment they noted that in the bicarbonate plant, after 30 min of acclimation at 100 ppm, a 30-s exposure at 300 ppm was just barely tolerable.

In the controlled exposure study, Ferguson et al. assessed the effect of ammonia on six (three groups of two) human volunteers (industrial workers) exposed to concentrations of 25, 50, or 100 ppm after exposure to the same concentrations during a 1-week practice period. The subjects were exposed at a sodium bicarbonate plant in areas where concentrations of 25 and 50 ppm were achieved; the subjects were exposed to 100 ppm in an exposure chamber. Ammonia concentrations were monitored each half hour using detector tubes certified by the National Institute for Occupational Safety and Health (NIOSH) that had an overall accuracy of  $\pm 10\%$ . Exposure periods ranged from 2 to 6 h/day for 5 weeks. There was no adverse effect on respiratory function and no increase in the frequency of eye, nose, and throat irritation with increasing concentrations. The only complaints were lacrimation and nasal dryness during brief excursions above 150 ppm. There was no interference with performance of work duties and no effect on pulse rate or respiratory function during exercise (i.e., no effect on physical or mental ability to perform work duties) that was consistent with concentration or duration. Definite redness of the nasal mucosa occurred in one subject exposed to 100 ppm with excursion up to 200 ppm, but the effect cleared by the next morning (i.e., no lasting effects occurred). Four of the six subjects were exposed to different concentrations, making it difficult to establish trends related to exposure concentration or duration.

Erskine et al. (1993) measured the threshold concentration of ammonia required to elicit reflex glottis closure, which is a protective response stimulated by inhaling irritant or noxious vapors at concentrations too low to produce

cough. It is accompanied by a brief pause in inspiration. The investigators measured glottis closure in 102 healthy nonsmoking subjects, ranging from 17 to 96 years old, after single intermittent breaths of ammonia vapor using an inspiratory pneumotachograph. The results showed a strong positive correlation coefficient of .85 between age and the threshold concentration. The younger subjects were more sensitive, with the reflex response occurring at  $571 \pm 41.5$  ppm ( $\pm$  standard error) in subjects 21-30 years old compared with  $1,791 \pm 52$  ppm ( $\pm$  standard error) in subjects 86 to 95 years old. The threshold was about 1,000 ppm for 60-year-old subjects. The data showed that younger people are about three times more sensitive to the induction of this protective mechanism (glottis closure) by ammonia than the elderly.

### 2.2.2. Epidemiologic Studies

Holness et al. (1989) compared the respiratory effects in a group of 58 workers (51 production and six maintenance workers at Allied Chemical Canada, Ltd.) exposed to ammonia during the production of soda ash with 31 control workers from stores and offices. The exposed group had worked in soda ash production for an average of 12.2 years. The workers were assessed at the beginning of a workweek and at the end of the workweek. They were assessed based on a questionnaire, sense of smell, and pulmonary function. The time-weighted average ammonia concentration was  $9.2 \pm 1.4$  ppm (mean  $\pm$  standard deviation) for the exposed workers compared with  $0.3 \pm 0.1$  ppm for a control group assessed over one workweek. The investigators reported essentially no differences in the parameters assessed comparing the first and last days of the workweek and no differences based on level or length of exposure to ammonia. There were no differences between the two groups.

Minor pulmonary function deficits have been observed in swine workers exposed to ammonia, in combination with dust and endotoxin (Reynolds et al. 1996). While ammonia levels as high as 200 ppm have been reported (Carlile 1984), mean exposure levels of 4-7 ppm are more typical for workers (Reynolds et al. 1996; Donham et al. 1995). Confounding due to exposure to multiple agents and lack of information on clinical symptoms limit the usefulness of these data.

### 2.3. Summary

Numerous case studies describing disabling, irreversible, or long-term effects on humans inhaling ammonia at high concentrations were available in the literature. However, measured concentrations were not available for any of these studies.

Dose reconstruction has been conducted using WHAZAN and HG-SYSTEM models to predict atmospheric ammonia concentrations produced dur-

ing the Houston and Potchefstroom accidents. LC<sub>50</sub> values were estimated from results of each model. An evaluation of these models is presented in Section 7.1.

Sensitive individuals include children, elderly people, and people with respiratory or heart disorders. For very brief (<1 min) high-level exposures, decreased sensitivity of reflex glottis closure in elderly people implies a loss of protective reflexes, which could increase the risk of damage to the lower respiratory tract from the effects from inhaled ammonia in the elderly.

Ammonia causes severe irritation and burning to the skin, eyes, oral cavity, and respiratory tract, particularly mucous surfaces immediately upon contact due to the rapid conversion of ammonia to the very caustic ammonium hydroxide. Therefore, acute exposure to very high concentrations of ammonia severely damages the pulmonary region (bronchiolar and alveolar) of the respiratory tract, with permanent injury or death likely, even with prompt medical attention. Pulmonary edema, in particular, signals a poor prognosis for recovery in the short term, and secondary effects such as bronchiectasis, bronchopneumonia, and emphysema have occurred in individuals who survived for several days or sometimes several years. The damage caused by ammonia is progressive down the respiratory tract, starting with irritation of the nasopharyngeal region, extending to the tracheobronchial region, and finally the bronchiolar and alveolar regions.

Humans who have inhaled ammonia at concentrations high enough to experience disabling effects without causing death usually experience severe damage to the eyes, oral cavity, and respiratory tract involving the tracheobronchial region. Severe damage to the eyes can cause permanent visual deterioration or blindness. Damage to the pharynx and/or tracheobronchial regions may cause airway obstruction that could lead to death if medical help is not available. Damage to the lungs (particularly the bronchioles) may be manifested by bronchopneumonia. Chronic effects of acute exposure to ammonia (manifested years after exposure) have included bronchiectasis, bronchiolitis, atelectasis, emphysema, chronic bronchitis, and reduced performance in pulmonary function tests. The long-term effects are considered to be secondary to the initial damage caused by ammonia.

Nondisabling and reversible effects of ammonia are summarized in Table 2-5.

### **3. ANIMAL TOXICITY DATA**

#### **3.1. Acute Lethality**

##### **3.1.1. Rats**

Groups of 10 male CFE rats were exposed to 0, 6,210, 7,820, or 9,840 ppm (0, 4,343, 5,468, or 6,881 mg/m<sup>3</sup>, respectively) of ammonia for 1 h; surviving

**TABLE 2-5 Summary of Nondisabling and Reversible Effects of Inhaled Ammonia in Humans**

Concentration	Duration of Exposure	Effect <sup>a</sup>	Reference
5 ppm	3 h, with rest and exercise for 1.5 h each	Subjective rating of eye discomfort and smell, headache, dizziness, and “feeling of intoxication” significantly greater than of controls; sensory adaptation to odor; no exposure-related change in pulmonary function, increase in nasal cells, no increase in exhaled NO, and no alteration in bronchial response to methacholine.	Sundblad et al. 2004
25 ppm	3 h, with rest and exercise for 1.5 h each	Subjective rating of eye, upper respiratory, and throat irritation, smell, headache, dizziness, and “feeling of intoxication” significantly greater than of controls; no sensory. Adaptation to odor; no exposure-related change in pulmonary function, increase in nasal cells, no increase in inhaled NO, and no alteration in bronchial response to methacholine.	Sundblad et al. 2004
30 ppm	10 min	Odor was moderately intense to highly penetrating; irritation was faint or not detectable.	MacEwen et al. 1970
32 ppm	5 min	Nasal dryness.	Industrial Bio-Test Laboratories 1973
50 ppm	5 min	Nasal dryness.	Industrial Bio-Test Laboratories 1973
50 ppm	10 min	Highly penetrating odor; moderate irritation.	MacEwen et al. 1970
50 ppm	30 min	Moderately intense odor; moderate irritation to eyes and nose; mild irritation to throat and chest; slight urge to cough; slight general discomfort.	Verberk 1977
50 ppm	1 h	Highly intense odor; moderate irritation to eyes, nose, throat, and chest; mild urge to cough; slight general discomfort.	Verberk 1977
50 ppm	2 h	Offensive odor; moderate irritation to eyes, nose, throat, and chest; mild urge to cough; mild general discomfort	Verberk 1977
72 ppm	5 min	Nasal, eye, and throat irritation.	Industrial Bio-Test Laboratories 1973
80 ppm	30 min	Highly intense odor; highly intense eye and nose irritation; moderate throat and chest irritation; mild urge to cough; moderate general discomfort.	Verberk 1977
80 ppm	1 h	Highly intense odor; moderate eye, nose, throat, and chest irritation; mild urge to cough; moderate general discomfort.	Verberk 1977

(Continued)

**TABLE 2-5 Continued**

Concentration	Duration of Exposure	Effect <sup>a</sup>	Reference
80 ppm	2 h	Highly intense odor; highly intense eye, nose, throat, and chest irritation; highly intense urge to cough; and moderate general discomfort.	Verberk, 1977
100 ppm	5-30 s	Significant increase in nasal airway resistance, but atopic subjects, including asthmatics, responded similarly to the nonatopic subjects.	McLean et al. 1979
100 ppm	2-6 h/day, 5 weeks	No adverse effects on respiratory function and no increase in frequency of eye, nose, or throat irritation.	Ferguson et al. 1977
110 ppm	30 min	Highly intense odor; highly intense eye, nose, throat, and chest irritation, mild urge to cough, and moderate general discomfort.	Verberk 1977
110 ppm	1 h	Highly intense odor; highly intense eye, nose, throat, and chest irritation; moderate urge to cough; moderate general discomfort.	Verberk 1977
110 ppm	2 h	Highly intense odor; highly intense eye, nose, throat, chest irritation; urge to cough; general discomfort.	Verberk 1977
140 ppm	30 min	Highly intense odor; unbearable eye, nose, throat, and chest irritation; mild urge to cough; moderate general discomfort.	Verberk 1977
140 ppm	1 h	Highly intense odor; unbearable eye, nose, throat, and chest irritation; moderate urge to cough; moderate general discomfort.	Verberk 1977
140 ppm	2 h	Highly intense odor; unbearable eye and nose irritation; highly intense throat and chest irritation; highly intense urge to cough; unbearable general discomfort.	Verberk 1977
143 ppm	5 min	Nose, eye, throat, and chest irritation; lacrimation.	Industrial Bio-Test Laboratories 1973
500 ppm	15-30 min	Nose and throat irritation; nasal dryness and stuffiness; excessive lacrimation; hyperventilation; unbearable.	Silverman et al. 1949
570 ppm	Single breath	Threshold for reflex glottis closure, 21 to 30-year-old subjects.	Erskine et al. 1993
1,000 ppm	Single breath	Threshold for reflex glottis closure, 60-year-old subjects.	Erskine et al. 1993
1,000 ppm	NR	Immediate urge to cough.	Silverman et al. 1949
1,790 ppm	Single breath	Threshold for reflex glottis closure, 86 to 90-year-old subjects.	Erskine et al. 1993

<sup>a</sup>The categories from Verberk (1977) have been recategorized as follows: just perceptible = slight; distinctly perceptible = mild; nuisance = moderate; offensive = highly intense; unbearable = unbearable.  
 NR = not reported.

animals were observed for 14 days (MacEwen and Vernot 1972). Signs of eye and nasal irritation were seen immediately, followed by labored breathing and gasping. Surviving animals exposed to the low concentration weighed less than controls on day 14, and gross examination showed mottling of the liver and fatty changes at the two highest concentrations. All rats exposed to 6,210 ppm survived, and eight exposed to 7,820 ppm and nine exposed to 9,840 ppm died. The  $LC_{50}$  was 7,338 ppm (95% confidence interval = 6,822-7,893 ppm).

Appelman et al. (1982) calculated  $LC_{50}$  values for 7- to 8-week-old male and female Wistar rats exposed to ammonia by inhalation. Five animals of each sex per group were exposed to ammonia at concentrations ranging from 9,870 to 37,820  $mg/m^3$  (14,114-54,083 ppm) for 10, 20, 40, or 60 min and observed for 14 days. Clinical signs of toxicity during exposure included restlessness, closing of the eyes, signs of eye irritation (particularly for 60-min exposures), eye discharge (after 30 min), wet noses, and nasal discharge. Mouth breathing and signs of dyspnea also were observed; the signs of dyspnea disappeared within 24 h after exposure terminated. Gross findings included hemorrhagic lungs in animals dying early and those killed at termination. The lowest concentrations causing death were 23,389  $mg/m^3$  (33,446 ppm) for a 10-min exposure to males, 18,290  $mg/m^3$  (26,155 ppm) for a 20-min exposure (30% mortality) to males, 12,620  $mg/m^3$  (18,047 ppm) for a 40-min exposure to males, and 9,870  $mg/m^3$  (14,114 ppm) for a 60-min exposure to males and females. The  $LC_{50}$  values and mortality rates for male, female, and male and female rats combined as reported by Appelman et al. (1982) are summarized in Table 2-6. The data showed that the  $LC_{50}$  values were significantly higher in male rats than in females for the 20-, 40-, and 60-min exposures.

Coon et al. (1970) exposed male and female Sprague-Dawley or Long-Evans rats repeatedly or continuously to ammonia for various durations. No clinical signs of toxicity or gross pathologic findings were reported for 15 rats exposed to 222 ppm (155  $mg/m^3$ ) 8 h/day for 6 weeks. No deaths or clinical signs of toxicity were reported for 15 rats similarly exposed to 1,101 ppm (770  $mg/m^3$ ); nonspecific inflammatory changes, which were slightly more severe than in controls, were observed in the lungs. Continuous exposure of 15 rats to 57 ppm (40  $mg/m^3$ ) for 114 days resulted in no clinical signs of toxicity or other clinically significant effects compared with the controls. Continuous exposure of 48 rats to ammonia for 90 days resulted in no clinical signs of toxicity or other effects at 182 ppm (127  $mg/m^3$ ). Mild nasal discharge observed in about 25% of 49 rats was the only clinical sign attributed to the 90-day continuous exposure to 375 ppm (262  $mg/m^3$ ). Mild signs of dyspnea, nasal irritation, and 98% mortality occurred among 51 rats exposed to 651 ppm (455  $mg/m^3$ ) continuously for 65 days (exposure terminated early); histopathologic examinations were not conducted on these animals. Thirteen of 15 rats (87%) died during a 90-day continuous exposure to 672 ppm (470  $mg/m^3$ ). Histopathologic lesions included focal or diffuse interstitial pneumonitis in the lungs of all animals examined and renal tubular calcification, bronchial epithelial calcification, renal tubular epi-

**TABLE 2-6** Acute Lethality Data for Male and Female Rats Exposed to Ammonia

Experimental Concentration (ppm)	Exposure Time (min)	Mortality Rate			LC <sub>50</sub> (ppm)
29,959	10	0/5	0/5	0/10	
33,433		1/5	0/5	1/10	
37,766		5/5	1/5	6/10	37,094 (male)
38,925		5/5	0/5	5/10	44,945 (female)
54,083		5/5	4/5	9/10	40,300 (male and female)
26,155	20	3/5	0/5	3/10	
27,213		1/5	0/5	1/10	
28,814		5/5	2/5	7/10	25,511 (male)
29,201		3/5	3/5	6/10	32,661 (female)
33,176		5/0	4/5	9/10	28,595 (male and female)
18,047	40	2/5	0/5	2/10	
19,176		4/5	1/5	5/10	
22,694		4/5	1/5	5/10	17,532 (male)
23,295		5/5	3/5	8/10	23,724 (female)
24,081		5/5	2/5	7/10	20,300 (male and female)
14,114	60	2/5	1/5	3/10	
14,629		4/5	0/5	4/10	
16,159		5/5	0/5	5/10	14,086 (male)
17,875		5/5	1/5	6/10	19,691 (female)
18,933		5/5	2/5	7/10	16,600 (male and female)

Source: Appelman et al. 1982. Reprinted with permission; copyright 1982, *American Industrial Hygiene Association Journal*.

thelial cell proliferation, myocardial fibrosis, and fatty changes in the liver of several animals. These effects also occurred in control animals, but the severity was greater in the exposed animals.

### 3.1.2. Mice

Silver and McGrath (1948) calculated the LC<sub>50</sub> value for mice exposed to ammonia (6.1-9.0 mg/L or 8,723-12,870 ppm) by inhalation for 10 min and observed for 10 days. The concentrations of ammonia in the exposure chamber were measured analytically. Each group consisted of 20 mice (sex and strain not specified). During exposure the mice closed their eyes, exhibited great excitement initially but soon became quiet, gasped, pawed, scratched their noses, and convulsed before dying. At the lowest concentration of 8,723 ppm, 25% of the animals died, and 80% died at the highest concentration of 12,870 ppm. Overall 90/180 mice died during the second 5-min of exposure and another eight died during the observation period. The other animals surviving exposure recovered rapidly. The LC<sub>50</sub> for the 10-min exposure was 7.06 mg/L (10,096 ppm).

Groups of 10 male CF1 mice were exposed to ammonia at analytically measured concentrations of 0, 3,600, 4,550, or 5,720 ppm (0, 2,520, 3,185, 4,004 mg/m<sup>3</sup>) for 1 h (MacEwen and Vernot 1972). Immediately upon exposure, the animals showed signs of nasal and eye irritation, followed by labored breathing and gasping. Animals surviving the low and intermediate concentrations lost weight during the 14-day observation period. Gross examination of surviving mice showed mild congestion of the liver at the intermediate and high concentrations. Three mice exposed to 4,500 ppm died, and nine exposed to 5,720 ppm died, but none exposed to 3,600 ppm died. The LC<sub>50</sub> was 4,837 ppm (95% confidence interval = 4,409-5,305 ppm).

In a study by Hilado et al. (1977), four Swiss mice per group were exposed to 7,143-28,571 ppm of ammonia for 30 min. Exposure concentrations were calculated rather than measured analytically. One mouse died at 19,048 ppm, two at 21,429 ppm, three at 23,810 ppm, and four each at 26,190 and 28,571 ppm. All deaths occurred during exposure except the death at the lowest concentration, which occurred 1 day after exposure. No deaths occurred after exposure to concentrations of 14,286 ppm or lower. The LC<sub>50</sub> value was reported as 21,000 ppm for the 30-min exposure. In 1978, Hilado et al. reported the LC<sub>50</sub> as 21,430 ppm for the 30-min exposure; the previous value was probably rounded to two significant figures.

Kapeghian et al. (1982) determined the LC<sub>50</sub> value for male albino ICR mice (12/group) exposed to 1,190-4,860 ppm of ammonia for 1 h. Concentrations of ammonia in the exposure chambers were measured analytically. The animals were observed for 14 days following exposure. A control group exposed to air only was included for comparison. Clinical signs, which were noted immediately and lasted 5-10 min, included excitation/escape behavior, rapid vigorous tail revolution, blinking and scratching (eye and nose irritation), and dyspnea. As signs of irritation decreased, the animals became less active and other signs of toxicity were noted, including tremors, ataxia, clonic convulsions, frothing, coma, final tonic extensor seizure, and death. At the higher concentrations, almost all deaths (90%) occurred during the first 15-20 min of exposure and as late as 45 min at the lower concentrations. Additional deaths occurred during the first 3 days following exposure. All deaths occurred at concentrations  $\geq$  3,950 ppm (25 to 100% mortality). The mortality response was 22/24 at 4,860 ppm; 8/12 at 4,490 ppm; 5/12 at 4,220 ppm; 3/12 at 3,950 ppm; and 0/12 at 3,440, 2,130, 1,340, and 1,190 ppm. The LC<sub>50</sub> was 4,230 ppm for the 1-h inhalation exposure to ammonia. Other effects observed during the 14-day observation period included lethargy, dyspnea, weight loss, and a "humped back" appearance. The pathologic lesions occurring in mice that died during exposure included acute vascular congestion, intra-alveolar hemorrhage, disruption of alveolar septal continuity, and acute congestion of hepatic sinusoids and blood vessels. In animals surviving the 14-day observation period, pathologic lesions included mild to moderate pneumonitis (dose-related severity), focal atelectasia in the lungs (4,860 ppm), and degenerative hepatic lesions (dose-related sever-

ity, 3,440 to 4,860 ppm). The author did not discuss specific effects in animals exposed to concentrations less than 3,440 ppm.

Groups of 12 male albino ICR mice were exposed to ammonia at concentrations of 0, 1,350, or 4,380 ppm for 4 h and the effects of ammonia on hexobarbital-induced latency to hypnosis (time to loss of righting reflex) and sleeping time were assessed 1 h after exposure terminated (Kapeghian et al. 1985). All mice exposed to 1,350 ppm survived; three mice exposed to 4,380 ppm died during exposure and one died during hexobarbital hypnosis. Latency to hypnosis was significantly reduced in animals exposed to both concentrations compared with controls exposed to air only. Hexobarbital sleeping time was significantly increased in animals exposed to 4,380 ppm of ammonia. The hexobarbital effects were not attributed directly to exposure to ammonia.

### **3.2. Nonlethal Toxicity**

#### **3.2.1. Rats**

Dalhamn (1956) studied the effect of inhaling ammonia on tracheal ciliary activity in male Wistar rats. Two or three rats per group were exposed to 0, 3, 6.5, 10, 20, 45, or 90 ppm of ammonia for 10 min. No effects were observed in rats exposed to air. In rats exposed to ammonia, ciliary activity ceased in 7-8 min with 3 ppm, 150 s with 6.5 ppm, 20 s with 20 ppm, 10 s with 45 ppm, and 5 s with 90 ppm. Thus, the time required for ciliary activity to cease showed a concentration-response relationship. Within 20-30 s after exposure was terminated, ciliary activity resumed.

The behavioral activity (wheel running) was assessed in three male Long-Evans rats exposed sequentially to the following concentrations of ammonia: 100, 300, 300, or 100 ppm for 6 h for each session with 2 days separating each session (Tepper et al. 1985). The activity of the rats on the running wheel was recorded during exposure and the time between exposures. The rats had previously been exposed to ozone in a similar experiment that was terminated 2 weeks before starting the experiment with ammonia. Controls were not described, but the performance of treated animals was compared to control performances, probably conducted before exposure to ozone. Exposure to 100 ppm of ammonia resulted in an immediate 61% reduction in activity compared with control activity; activity on the wheel ceased almost completely throughout exposure at 300 ppm. After termination of exposure to either 100 or 300 ppm, the activity of the rats steadily increased to 154% and 185%, respectively, compared with that of controls during the first 4 h postexposure.

Groups of eight male rats (CrI:COBS CD[SD]) were exposed to ammonia at concentrations of 15, 32, 310, or 1,157 ppm for 24 h (Schaerdel et al. 1983). No behavioral changes or evidence of irritation to the eyes or mucous membranes were observed. Blood gases ( $pO_2$  and  $pCO_2$ ) and pH were measured at 0, 8, 12, and 24 h; no changes were noted for  $pCO_2$  and pH. Small changes within

the normal range for rats occurred for  $pO_2$ . Groups of seven rats were also exposed continuously to ammonia at concentrations of 0, 4, 24, 44, 165, or 714 ppm for 3 or 7 days. Minimal lesions were seen in the respiratory epithelium of the nasal cavity in animals exposed for 7 days (the authors did not indicate which concentrations of ammonia caused the lesions).

Pinson et al. (1986) showed that respiratory mycoplasmosis is exacerbated by exposure to ammonia. Groups of F344/N rats infected with *Mycoplasma pulmonis* or uninfected were exposed continuously to 100 ppm of ammonia for 3, 5, 7, and 9 days after inoculation to assess the histopathologic effect on the respiratory tract. Ammonia caused hyperplasia and degenerative lesions in the respiratory epithelium of the anterior nasal cavity. Submucosal inflammatory lesions were minimal in uninfected animals exposed to ammonia; these lesions were prominent in infected animals and more severe in infected animals exposed to ammonia. There were inconsistencies in the write-up of this report.

Groups of five female Wistar rats were exposed to gaseous ammonia at concentrations of 0, 25, or 300 ppm for 6 h/day for 5, 10, or 15 days (Manninen et al. 1988). Clinical signs of toxicity were not described. Gross lesions included large hemorrhages on the surfaces of the lungs in several exposed rats (exposure group not reported) and a few control rats, suggesting that the effect may not be treatment related. There were no signs of tracheobronchial or alveolar damage or histopathological effects in the respiratory tract. The liver and kidneys were normal in appearance.

### 3.2.2 Mice

Barrow et al. (1978) calculated  $RD_{50}$  values for ammonia, based on its sensory irritant effects on the upper respiratory tract of the mouse. The  $RD_{50}$  is the concentration expected to elicit a 50% reduction in respiratory rate. Barrow et al. predicted that the  $RD_{50}$  concentration would elicit intense sensory irritation and is expected to be rapidly incapacitating to humans. Groups of four outbred male Swiss Webster mice were exposed to ammonia by inhalation for 30 min. The authors did not report the concentration of ammonia inhaled by the mice, but judging by the graphic representations, the concentrations were 100, 200, 400, and 800 ppm. The maximum depression in respiratory rate was achieved within the initial 2 min of exposure, after which the response diminished. The  $RD_{50}$  was 303 ppm (95% confidence limits = 188-490 ppm) for a 30-min inhalation exposure to ammonia. There was no microscopic examination of the respiratory tract.

In a follow-up study, Buckley et al. (1984) assessed the histopathologic effects of repeated exposures to ammonia at the  $RD_{50}$  concentration of 303 ppm. Groups of 16-24 male Swiss-Webster mice were exposed to 303 ppm of ammonia for 6 h/day for 5 days; an unexposed group served as the control. The respiratory tract was examined in one-half the animals killed immediately after terminating exposure and in the other half killed 3 days later. The authors did not

describe any clinical signs of toxicity. Histopathological findings, which were confined to the respiratory epithelium of the nasal cavity, included minimal exfoliation, erosion, ulceration and necrosis; moderate inflammatory changes; and slight squamous metaplasia. No lesions were seen in the tracheobronchial or pulmonary regions.

In a similar study, Zissu (1995) exposed groups of 10 male Swiss OF<sub>1</sub> mice to ammonia at analytically measured concentrations of  $0.3 \times \text{RD}_{50}$  (78.0 ppm),  $\text{RD}_{50}$  (257 ppm), or  $3 \times \text{RD}_{50}$  (711 ppm) for 6 h/day for 4, 9, or 14 days. The three target concentrations were 90.9, 303, and 909 ppm. Control mice were exposed to filtered air. The entire respiratory tract was examined microscopically. No clinical signs of toxicity were noted for mice exposed to ammonia. Pathologic lesions including rhinitis with metaplasia and necrosis were seen only in the respiratory epithelium of the nasal cavity of mice inhaling 711 ppm ( $3 \times \text{RD}_{50}$ ); the severity of the lesions increased with duration of exposure, ranging from moderate on day 4, to severe on day 9, and very severe on day 14. No lesions were seen in the controls or in mice inhaling the lower concentrations of ammonia. In contrast to the study conducted by Buckley et al. (1984), this study showed no lesions in the nasal cavity of mice exposed to 257 ppm, which is near the  $\text{RD}_{50}$  of 303 ppm.

Behavioral activity (wheel running) was assessed in 6 male Swiss mice exposed sequentially to ammonia at 100, 300, 300, or 100 ppm for 6 h each session with 2 days separating each session (Tepper et al. 1985). The activity of the mice on the running wheel was recorded during each 6-h exposure and for 2 days after each exposure. These mice had been previously exposed to ozone in a similar experiment terminated 2 weeks before starting the experiment using ammonia. Controls were not described, but the performance of treated animals was compared to control performances, probably conducted before exposure to ozone. At 100 ppm, activity showed an initial increase during the first hour, followed by a marked decrease during the third and fourth hours, and an increase exceeding control activity during the fifth and sixth hours. At 300 ppm, activity was suppressed throughout exposure; it returned to control levels after exposure was terminated. The results suggest that the mice adapted to inhaling 100 ppm of ammonia but not to 300 ppm. The authors attributed the decreased activity to the sensory irritant property of ammonia.

### **3.2.3. Cats**

Four groups of five stray mixed-breed cats were fitted with cuffed endotracheal tubes and subjected to a battery of pulmonary function tests (baseline results) followed by exposure to 1,000 ppm of ammonia gas for 10 min to evaluate the effect of ammonia on pulmonary function and lung pathology. Two unexposed cats were housed with the experimental cats for pathologic comparison (Dodd and Gross 1980). On days 1, 7, 21, and 35 following exposure, a group of cats was given pulmonary function tests, killed, and examined for gross

and microscopic lesions in the lungs. Signs of toxicity included poor general condition, severe dyspnea, anorexia, dehydration, bronchial breath sounds, sonorous and sibilant rhonchi, and coarse rales. Pulmonary function tests showed evidence of airway damage throughout the experiment and central lung damage on day 21. Gross examination of the lungs showed congestion, hemorrhage, edema, and evidence of interstitial emphysema and collapse. Bronchopneumonia, which caused the death of one animal, was commonly seen after day 7. Microscopic examination showed necrosis and sloughing of the bronchial epithelium accompanied by acute inflammation on day 1; no notable findings occurred in the bronchiolar or alveolar regions. Healing of the mucosal epithelium of the bronchi was noted on day 7, and varying degrees of bronchitis, bronchiolitis, bronchopneumonia, and bulbous emphysema were seen on days 21 and 35. The authors attributed the effects on days 21 and 35 to opportunistic bacteria or viruses. They suggested that the effects of ammonia are biphasic, consisting of an acute phase, which could cause death, and a secondary phase, which could cause debilitating chronic respiratory dysfunction.

#### 3.2.4. Other Species

Boyd et al. (1944) exposed groups of healthy rabbits to ammonia at 10,010 ppm (range 5,005 to 12,441 ppm) [ $7,000 \text{ mg/m}^3$ , range 3,500-8,700  $\text{mg/m}^3$ ] for 1 h before or after intratracheal cannulation, which was inserted to collect respiratory tracheal fluid. The mean survival time was 33 h for rabbits exposed before cannulation and 18 h for rabbits exposed after cannulation. Signs of toxicity included marked excitation during the early stages of exposure followed by a "curare-like paralysis." The major effects of exposure occurred in the respiratory tract at both concentrations, the tracheobronchial and pulmonary regions of animals exposed to ammonia after cannulation and the pulmonary region of animals exposed before cannulation. Microscopically, the trachea and bronchi appeared normal in rabbits exposed before cannulation but were severely damaged in animals exposed after cannulation. Bronchiolar (damage to epithelial lining) and alveolar effects (congestion, edema, atelectasis, hemorrhage, and emphysema) were similar in both groups.

Groups of three rabbits, 15 guinea pigs, two dogs, and three monkeys were exposed to ammonia 8 h/day for 6 weeks at concentrations of 222 or 1,101 ppm (155 or 770  $\text{mg/m}^3$ ; Coon et al. 1970). No clinical signs of toxicity or other clinically significant effects occurred in animals exposed to 222 ppm except for focal pneumonitis in one monkey. The only effects observed at 1,101 ppm were mild to moderate lacrimation and dyspnea in the dogs and rabbits during the first week of exposure only and nonspecific inflammatory changes in the lungs of guinea pigs. The same number of animals of each species was exposed continuously to 57 or 672 ppm (40 or 470  $\text{mg/m}^3$ ) for 90 days; no clinical signs of toxicity or other clinically significant effects were observed at 57 ppm. At 672 ppm, marked eye irritation (heavy lacrimation) and nasal discharge were seen in dogs

and erythema, discharge, and corneal opacity were seen in the rabbits. Hemorrhagic lesions occurred in the lungs of one dog and moderate lung congestion in two rabbits. Focal or diffuse interstitial pneumonitis was seen in all animals; renal tubular calcification, bronchial epithelial calcification, renal tubular epithelial cell proliferation, myocardial fibrosis, and fatty changes in the liver were observed in several animals of each species. Similar lesions were seen in control animals but were more severe in the treated animals. Four guinea pigs died during the experiment (Coon et al. 1970).

### 3.3. Summary

The LC<sub>50</sub> values for mice and rats are presented in Table 2-7. The LC<sub>50</sub> for rats ranged from 7,338 and 16,600 ppm for 60-min exposures to 40,300 ppm for a 10-min exposure. The LC<sub>50</sub> for mice ranged from 4,230 ppm for a 60-min exposure to 10,096 ppm for a 10-min exposure. The lowest experimental concentrations associated with lethality are summarized in Table 2-8.

Rats exposed to lethal concentrations of ammonia showed signs of dyspnea and irritation to the eyes and nose and hemorrhage in the lungs (Appelman et al. 1982). Mice exposed to lethal concentrations of ammonia showed signs of irritation to the eyes and nose, labored breathing, and gasping, along with tremors, ataxia, convulsions, and seizures; pathologic lesions occurred in the alveoli (Silver and McGrath 1948; MacEwen and Vernot 1972; Kapeghian et al. 1982).

Nondisabling reversible effects in laboratory animals were mild after single exposures and transient after repeated exposures (subchronic duration), suggesting that adaptation occurred. Rats showed a decrease in tracheal ciliary activity during exposure to 3-90 ppm for 10 min (Dalhamn 1956), a decrease in motor activity (wheel running) during exposure to 100 ppm for 6 h, and a complete cessation of motor activity during exposure to 300 ppm for 6 h (Tepper et al. 1985). Mice exposed to the same concentrations of ammonia showed responses similar to those of the rats. Another study in rats exposed to concentrations of ammonia ranging from 15 to 1,157 ppm for 24 h did not show any behavioral changes or irritation to the eyes or mucous membranes; only minimal effects on the respiratory epithelium of the upper respiratory tract were seen after continuous exposure to concentrations up to 714 ppm for several days (Schaerdel et al. 1983). A 50% reduction in the respiration rate (RD<sub>50</sub>) was noted in mice exposed to about 300 ppm for 30 min (Barrow et al. 1978). Repeated exposures of the mice to the RD<sub>50</sub> for 6 h/day for 3 or 7 days did not cause pathologic lesions in the respiratory epithelium (Buckley et al. 1984), but exposure to approximately three times the RD<sub>50</sub> (711 ppm) resulted in slight to moderate exfoliation, erosion, ulceration, and necrosis of the respiratory epithelium of the nasal cavity; no lower respiratory tract lesions were produced (Zissu 1995). The RD<sub>50</sub> is considered to be incapacitating to humans (Barrow et al. 1978). There was no evidence of pulmonary lesions in mice or rats exposed to a single nonlethal concentration of ammonia.

**TABLE 2-7** Comparison of Acute Lethality (LC<sub>50</sub>) Data in Different Species

Species	LC <sub>50</sub>		Exposure Time (min)	Reference
	mg/m <sup>3</sup>	ppm		
Rat	28,130	40,300	10	Appelman et al. 1982
Mouse	7,060	10,096	10	Silver and McGrath 1948
Rat	19,960	28,595	20	Appelman et al. 1982
Mouse	14,986	21,430	30	Hilado et al. 1978
Rat	14,170	20,300	40	Appelman et al. 1982
Rat	5,131	7,338	60	MacEwen and Vernot 1972
Rat	11,592	16,600	60	Appelman et al. 1982
Mouse	3,383	4,837	60	MacEwen and Vernot 1972
Mouse	2,858	4,230	60	Kapeghian et al. 1982

**TABLE 2-8** Lowest Experimental Concentrations Causing Death

Species	Concentration (ppm)	Exposure Time (min)	% Mortality	Reference
Mouse	8,723	10	25	Silver and McGrath 1948
Mouse	19,048	30	25	Hilado et al. 1977
Mouse	3,950	60	25	Kapeghian et al. 1982
Mouse	4,550	60	30	MacEwen and Vernot 1972
Mouse	4,380	240 <sup>a</sup>	25	Kapeghian et al. 1985
Rat	33,433	10	10	Appelman et al. 1982
Rat	26,155	20	30	Appelman et al. 1982
Rat	18,047	40	20	Appelman et al. 1982
Rat	14,114	60	30	Appelman et al. 1982
Cat	1,000	10	5	Dodd and Gross 1980

<sup>a</sup>No observation period after exposure.

Signs of eye and respiratory irritation were observed in several species exposed continuously or repeatedly to ammonia for 6 weeks to 114 days (Coon et al. 1970). Except for nonspecific inflammation of the lungs at 1,101 ppm, repeated daily exposures to rats of 57 ppm for 114 days or 222 or 1,101 ppm for 6 weeks (8 h/day) produced no effects. Almost all rats died after continuous exposure to 651 or 672 ppm for 65 days. Repeated exposures to 1,101 ppm for 6 weeks (8 h/day) produced transient dyspnea and lacrimation in dogs and rabbits, whereas continuous exposure to 672 ppm for 90 days resulted in signs of irritation to the eyes and nose and pathologic lesions in the lungs of dogs and rabbits and pneumonitis in several species (dog, rabbit, guinea pig, and monkey). Studies on repeated exposures showed that mice are more sensitive than other species; for example, mice exposed to 771 ppm for only a few days showed pathologic effects, whereas other species required higher concentrations or longer exposure durations to produce pathologic or clinical effects (Coon et al. 1970).

## 4. SPECIAL CONSIDERATIONS

### 4.1. Metabolism, Disposition, and Kinetics

Ammonia is a product of amino acid and protein metabolism; therefore, it is found naturally in the body. The normal concentration of ammonia in the blood of humans is about 1  $\mu\text{g}/\text{mL}$ . The liver rapidly detoxifies ammonia to urea in order to maintain the isotonic system (Visek 1972; Pierce 1994).

The concentration of ammonia in blood remains stable (not altered significantly) after inhalation exposure of humans to very high concentrations of ammonia gas, indicating a lack of appreciable absorption from the respiratory tract or rapid detoxification. Leduc et al. (1992) reported normal concentrations of ammonia in the blood of a 28-year-old man exposed to an unknown concentration of ammonia gas that was sufficient to cause severe tracheobronchial injury. Swotinsky and Chase (1990) presented no supporting data but stated that individuals with impaired liver function could have elevated levels of ammonia in blood after inhalation exposure.

Silverman et al. (1949) reported no changes in blood or urine ammonia, urea, or nonprotein nitrogen in seven human subjects exposed to ammonia at concentrations of 350-500 ppm for 30 min. The concentration of ammonia in expired air remained stable at 350-400 ppm after 10-27 min of exposure, suggesting an equilibrium with the concentration in inhaled air. Within 3-8 min following exposure, the concentration of ammonia in expired air decreased to preexposure levels. The calculations of Silverman et al. indicated that, if all the retained ammonia was absorbed into the blood, there would have been no significant change in blood or urine urea, ammonia, or nonprotein nitrogen.

Animal studies have shown, however, that blood ammonia levels may be altered following inhalation exposure. Schaerdel et al. (1983) measured ammonia levels in the blood of rats 8, 12, and 24 h after inhalation exposures to 15, 32, 310, or 1,157 ppm of ammonia for 24 h. The values were corrected by pre-exposure concentrations (control). The blood ammonia concentrations 8 and 12 h after exposure to 15 and 32 ppm and 24 h after exposure to 15 ppm were slightly below those of the controls. The concentrations of ammonia in the blood of rats exposed to 310 and 1,157 ppm exceeded control levels and showed a peak at 8 h and time-related decreases at 12 and 24 h postexposure. Mayan and Merilan (1976) found no significant increase in the blood ammonia levels in male Holstein calves after exposure to 50 or 100 ppm of ammonia for 2.5 h compared with the preexposure levels. Blood urea nitrogen and pH were not significantly altered after exposure to ammonia. Adult female rabbits exposed to 50 or 100 ppm of ammonia for 2.5-3 h showed a significant increase in blood urea nitrogen at 100 ppm and no significant increase in blood pH (Mayan and Merilan 1972).

During exposure, ammonia is efficiently retained (scrubbed) in the nasopharyngeal region of the respiratory tract, thus protecting the lower regions from damage. However, the work by Silverman et al. (1949) indicated that scrubbing

of ammonia in the nasopharyngeal area is concentration and time dependent. Landahl and Herrmann (1950) showed that 91-93% of ammonia [concentrations = 40, 200, or 300 mg/m<sup>3</sup> (57, 286, or 429 ppm); flow rate = 18 L/min] inhaled by human subjects was retained in the respiratory tract during a single inspiration. At the same flow rate, 83% of inhaled ammonia was retained in the nose.

Mongrel dogs exposed to 150-500 mg/m<sup>3</sup> (215-715 ppm) of ammonia vapor retained 74-83% of the inhaled ammonia in the entire respiratory tract; 76-80% of inhaled ammonia can be retained in the upper respiratory tract (Egle 1973). The duration of exposure was not reported. Ventilatory rate and tidal volume had no effect on retention. Other experiments showed 78-80% retention in the lower respiratory tract and 88% retention in the upper respiratory tract when mechanical devices were used to bypass the upper and lower respiratory tracts.

#### **4.2. Mechanism of Toxicity**

Ammonia is an irritant gas that produces effects immediately on contact with moist mucous membranes of the eyes, mouth, and respiratory tract via the formation of ammonium hydroxide (a corrosive alkali) or the production of heat (Wong 1995). Because of its irritant properties, individuals coming into contact with ammonia vapor (or gas) will try to escape as quickly as possible (Swotinsky and Chase 1990). The odor threshold for ammonia is lower than its irritancy effect and serves as a warning of its presence.

#### **4.3. Structure-Activity Relationship**

Ammonia is an alkaline substance, and its corrosiveness is not different from that of other corrosive agents such as calcium, sodium, potassium hydroxide, and calcium oxide. Aerosols or vapors and fumes are very caustic on contact with moist mucous membranes, causing injury of the respiratory tract and eyes (Pierce 1994).

#### **4.4. Other Relevant Information**

##### **4.4.1. Odor**

The odor threshold for ammonia is between 5 and 53 ppm (Pierce 1994), suggesting that it has adequate warning properties. Ferguson et al. (1977) reported the odor threshold for ammonia in the presence of mixed odors as 10-20 ppm. The odor of ammonia at 30 ppm described as moderately intense by 2/6 subjects and highly penetrating by 3/6, indicating that the odor threshold was clearly exceeded at 30 ppm (MacEwen et al. 1970). A group of nonexpert and

expert subjects judged the odor of 50 ppm of ammonia to be just perceptible to nuisance during the first 30 min of exposure and just perceptible to offensive after 2 h.

Ferguson et al. (1977) conducted a study showing adaptation to concentrations up to 150 ppm of ammonia, with excursions up to 200 ppm, in individuals acclimated to 25-100 ppm for 1 week. More details of this study are described in Section 2.2.1.

#### **4.4.2. Species Variability**

ten Berge et al. (1986) found that mice are usually more sensitive (to irritants) than other mammals. The most direct comparison of mice and rats to inhalation exposure to ammonia can be found in Table 2-7 of this chapter. These data show that the mouse is 2.7 to 4 times more sensitive to inhalation exposure to ammonia than the rat.

#### **4.4.3. Susceptible Populations**

Erskine et al. (1993) showed that the glottis of elderly people (86-90 years old) is less responsive to inhalation exposure to ammonia than younger people (21-30 years old); the two age groups differed by a factor of 3. McLean et al. (1979) showed that nonatopic and atopic subjects, some of whom had a history of asthma, responded similarly in a nasal airway resistance (NAR) test to 100 ppm of ammonia introduced into each nostril under pressure for up to 30 s. The increased NAR was attributed to parasympathetic reflex and not to histamine release. Ammonia is water soluble and efficiently scrubbed in the nasopharyngeal regions; ammonia would not reach the tracheobronchial and pulmonary regions of the respiratory tract until the scrubbing action has been saturated. It is unlikely that concentrations detected only by odor or irritation to the nasal cavity or eyes would reach the tracheobronchial and pulmonary regions and have a differential effect on asthmatic individuals.

#### **4.4.4. Concentration-Exposure Duration Relationship**

Appelman et al. (1982) used multiple linear weighted regression to show the general correlation between concentration, time, and mortality expressed as probit. They derived the following equation:

$$\text{Probit} = a \ln c + b \ln t - q,$$

where a, b, and q are the regression parameters; c is the concentration (mg/m<sup>3</sup> or ppm); and t is the time of exposure. The values for regression parameters for the

combined sexes were as follows:  $a = 4.62$ ,  $b = 2.30$ , and  $q = 47.8$ . The quotient for  $b/a$  is equal to  $n$ . Converting the above equation to

$$\text{Probit} = 2.30 \ln [C^{2.02} \times t] - 47.8$$

shows that the relationship of any concentration and time corresponding to a mortality rate can be expressed as  $C^n \times t = k$ , where  $n = 2.02$ . ten Berge et al. (1986) reported an  $n$  value of 2 and confidence intervals of 1.6 and 2.4 for ammonia. ten Berge et al. (1986) also noted that the value of the exponent  $n$  should be derived empirically.

## **5. DATA ANALYSIS FOR AEGL-1**

### **5.1. Human Data Relevant to AEGL-1**

Human data relevant for deriving the AEGL-1 value are summarized in Section 2.3, Table 2-5. Faint or no detectable irritation was reported for exposure to 30 ppm for 10 min (MacEwen et al. 1970), and moderate irritation was reported for exposure to 50 ppm for 10 min to 2 h (MacEwen et al. 1970; Verberk 1977). Moderate irritation also was reported for exposure to 80 ppm for up to 1 h. No adverse effect on respiratory function has been reported for exposure to ammonia at concentrations of 140 ppm for 2 h or up to 500 ppm for 30 min (Verberk 1977; Silverman et al. 1949).

### **5.2. Animal Data Relevant to AEGL-1**

Animal studies were available, but none was judged to be adequate for deriving AEGL-1 values in view of the available human data.

### **5.3. Derivation of AEGL-1**

Humans experience either faint or no irritation after exposure to ammonia at 30 ppm for 10 min (MacEwen et al. 1970); therefore, 30 ppm was used to derive AEGL-1 values. An interspecies uncertainty factor is not applied to these data because the AEGL value is based on human data. An intraspecies uncertainty factor of 1 was selected because ammonia is efficiently scrubbed in the upper respiratory tract, and if irritation occurs, it would be confined to the nasal cavity (and possibly the eyes). Nonatopic and atopic subjects, including asthmatics, responded similarly in a nasal airway resistance test when 100 ppm of ammonia was introduced into each nostril for up to 30 s (McLean et al. 1979); therefore, asthmatic individuals are not expected to respond differently than nonasthmatic individuals. Exercising subjects showed only a clinically nonsig-

nificant decrease in pulmonary function after exposure to higher concentrations of ammonia (Cole et al. 1977); therefore, exercise is not expected to cause an appreciable difference in effects experienced during exposure to AEGL-1 concentrations. The same value is proposed for 5, 30, 60, 240, and 480 min, because any effects that occur are not expected to become more severe with duration of exposure because adaptation occurs during prolonged exposure. AEGL-1 values are summarized in Table 2-9. The AEGL-1 value of 30 ppm for all time points is supported by observations that humans reported similar intensities of response after exposure to 50 ppm for 10 min to 2 h (MacEwen et al. 1970; Verberk 1977).

## 6. DATA ANALYSIS FOR AEGL-2

### 6.1. Human Data Relevant to AEGL-2

Data detailing disabling, irreversible, or long-term effects of ammonia were discussed in Section 2.2.1. The immediate response of individuals exposed to severe irritating concentrations of ammonia is to escape. Therefore, only those people who are incapacitated and unable to escape or those who are not rescued by others would remain in an atmosphere containing highly irritating concentrations of ammonia. They would be in danger with prolonged continuous exposure. The case studies on irreversible or long-term effects of ammonia did not report exposure concentrations and cannot be used to derive AEGL values. Several studies showing reversible irritation in humans had quantitative exposure data judged suitable for deriving AEGL-2 levels. These studies are summarized in Table 2-10. The subjects in the Verberk (1977) study were exposed to concentrations ranging from 50 to 140 ppm for durations ranging up to 2 h, and this study established exposure concentrations and durations of exposure considered to be offensive and unbearable but reversible. Other studies provide additional data to support to the Verberk study. Silverman et al. (1949) exposed subjects to 500 ppm of ammonia for 30 min by means of a half mask; there was no direct contact of the eyes with the ammonia. Ferguson et al. (1977) reported no adverse effects on respiratory function in human volunteers exposed for 2-6 h/day for 5 days to ammonia levels as high as 100 ppm.

There are difficulties in determining the ammonia concentrations associated with irreversible effects for the longer exposure times (4 or 8 h). Reversible

**TABLE 2-9** AEGL-1 Values for Ammonia

5 min	10 min	30 min	1 h	4 h	8 h
30 ppm (21 mg/m <sup>3</sup> )					

**TABLE 2-10** Nonlethal Effects of Ammonia on Humans and Experimental Animals

Species	Concentration (ppm)	Exposure Time (min)	Effect	Reference
Human	50	10	Moderate irritation (NOS).	MacEwen et al. 1970
Human	110	120	Irritation: eyes, nose, throat, chest.	Verberk 1977
Human	140	30	Irritation: eyes, nose, throat, chest; urge to cough.	Verberk 1977
Human	140	120	Nuisance irritation: eyes, throat; urge to cough.	Verberk 1977
Human	143	5	Irritation: eyes, mouth, nose, throat, chest.	Ind. Bio.-Test Lab. 1973
Human	571	One breath	Threshold for glottis closure in young males.	Erskine et al. 1993
Human	500	30	Only 2 of 7 subjects tolerated ammonia via nose breathing; irritation effects: nose and throat; lacrimation, hyperventilation, decreased respiratory function.	Silverman et al. 1949
Mouse	303	30	RD <sub>50</sub> (50% depression in respiratory rate)	Barrow et al. 1978

<sup>a</sup>Based on  $C^2 \times t = k$ .

Abbreviations: NA, not applicable; NOS, not otherwise specified.

effects may become irreversible and irreversible effects may become lethal due to delays in medical treatment as well as to continued exposure. Furthermore, exposure concentrations were not measured for the cases in which severe but reversible damage occurred in the respiratory tract. Therefore, AEGL-2 levels for ammonia can be determined from studies reporting “unbearable” upper respiratory tract irritation, which could potentially impair the ability to escape, rather than the threshold for irreversible or long-term effects. The unbearable concentrations are much lower than those that would be associated with the threshold for irreversible damage to the respiratory tract.

## 6.2. Animal Data Relevant to AEGL-2

The RD<sub>50</sub> (30-min exposure) of 303 ppm for the mouse (Barrow et al. 1978), which is predicted to cause intense sensory irritation and rapid incapacitation in humans, produced histopathological lesions in the nasal cavity but not

in the tracheobronchial or pulmonary regions in mice exposed repeatedly for 5 days (Buckley et al. 1984). Tepper et al. (1985) showed that mice exposed to 300 ppm ceased motor activity (wheel running) during the entire 6-h exposure period. These mice had prior ozone exposure that may have affected the outcome of the study.

### 6.3. Derivation of AEGL-2

The AEGL-2 values were based on “offensive” irritation to the eyes and respiratory tract experienced by nonexpert human subjects (unfamiliar with the effects of ammonia or with laboratory studies) exposed to 110 ppm of ammonia for 2 h (Verberk 1977). The responses of the nonexpert subjects ranged from “no sensation” to “offensive” for eye irritation, cough, or discomfort and from “just perceptible” or “distinctly perceptible” to “offensive” for throat irritation. No residual or irreversible effects were reported after termination of exposure, and pulmonary function was not affected by exposure. At the next higher concentration of 140 ppm, some subjects reported the effects to be unbearable and left the chamber between 30 min and 1 h; none remained for the full 2 h. Some irritation to the eyes, nose, throat, and chest along with a disagreeable odor are expected at the AEGL-2 level. An interspecies uncertainty factor is not applied to these data because the AEGL values are based on human data. An intraspecies uncertainty factor of 1 was selected because ammonia is a contact irritant, it is efficiently scrubbed in the upper respiratory tract, and any perceived irritation is not expected to be greater than that of the most sensitive nonexpert subject. The range of responses for this group is considered comparable to the range of responses that would be encountered in the general population, including asthmatics. Investigations have shown a link between nasal symptoms or allergic rhinitis and asthma, with rhinitis preceding the development of asthma (Corren 1997), and studies have shown that atopic subjects, including asthmatics, and nonatopic subjects respond similarly to a brief nasal exposure to ammonia (McLean et al. 1979). Exposure to exercising subjects showed only clinically nonsignificant changes in pulmonary function during exposure to ammonia at concentrations up to 336 ppm (Cole et al. 1977). In addition, a child experienced less severe effects than an adult exposed to very high concentrations of ammonia (Kass et al. 1972).

Time scaling across the pertinent timeframes was based on the ten Berge et al. (1986) equation ( $C^n \times t = k$ , where  $C$  = concentration,  $n = 2$ , and  $k$  is a constant). The value of  $n$  was derived from mouse and rat lethality data and was reported by Appelman et al. (1982) and ten Berge et al. (1986). The value of 110 ppm was adopted as the 4- and 8-h values, because the maximum severity rating for irritation in the Verberk (1977) study changed very little between 30 min and 2 h and is not expected to change for exposures up to 8 h. The 30-min value was also adopted as the 10-min AEGL-2 value because time scaling would yield a

10-min value (380 ppm) that might impair escape. The AEGL-2 values are summarized in Table 2-11.

The AEGL values are supported by other studies showing that exposures up to 100 ppm were tolerated by human subjects for 2-6 h without causing serious effects (Ferguson et al. 1977). The data of Cole et al. (1977) and Silverman et al. (1949) showed no serious irreversible effects at 336 or 500 ppm, respectively.

## 7. DATA ANALYSIS FOR AEGL-3

### 7.1. Human Data Relevant to AEGL-3

Although numerous case studies describing lethal and potentially life-threatening exposures to ammonia resulting from various accidental releases were found in the literature, the lack of definitive information on actual exposure concentrations limits the usefulness of these studies for establishing AEGL-3 values. Substantial uncertainties are associated with the values derived from the gas dispersion models (WHAZAN and HGSYSTEM). In both cases, estimates for atmospheric ammonia concentrations were used as surrogates for exposure concentration. For the South Africa ammonia accident, the HGSYSTEM dispersion model did not address exposure estimates for the survivors sheltered inside buildings or the people located upwind from the release. This fact alone renders any analysis derived from the WHAZAN or RAM TRAC, which includes individuals sheltered inside buildings, inadequate for estimating human survival levels. The HGSYSTEM model of the South Africa accident may be unable to address releases from multiple sources, unable to model a delayed transport scenario or puff expansion in calm wind followed by wind transport, and is limited by the complex meteorological conditions (Mazzola 1996). In a more detailed analysis of the HGSYSTEM model and dose reconstruction models in general, Mazzola (1997) noted that (1) the absence of real-time meteorological data during and subsequent to the release would significantly limit the confidence in using HGSYSTEM modeling results; (2) the HGSYSTEM may be unable to accurately simulate the complex thermodynamics of anhydrous ammonia releases; (3) the HGSYSTEM is unable to address indoor concentrations; and (4) the Benign Bubble hypothesis cannot be proven in the absence of three-dimensional wind field data. Mazzola also noted other sources of uncertainties in the HGSYSTEM model of the Potchefstroom, South Africa, ammonia accident as reported by Mudan and Mitchell (1996); as the levels of uncertainty

**TABLE 2-11** AEGL-2 Values for Ammonia

10 min	30 min	1 h	4 h	8 h
220 ppm (154 mg/m <sup>3</sup> )	220 ppm (154 mg/m <sup>3</sup> )	160 ppm (112 mg/m <sup>3</sup> )	110 ppm (77 mg/m <sup>3</sup> )	110 ppm (77 mg/m <sup>3</sup> )

accumulate and become very large, confidence in the final results diminishes. Therefore, atmospheric ammonia concentrations generated by the HGSYSTEM model cannot serve as a surrogate for exposure and should not be used to derive AEGL values.

Because of the inability to estimate the response variable, the inability to estimate concentrations to individuals sheltered inside buildings, and the uncertainties associated with accident dose reconstruction as surrogates for exposure, animal data are preferred for deriving AEGL-3 values. Although there is an inherent weakness in extrapolating from experimental animal concentrations to human exposure, animal studies are strengthened by having measured exposure concentrations and known response data. Therefore, an approach using experimental animal data, where exposure estimates are more reliable, is recommended for deriving AEGL-3 values.

## **7.2. Animal Data Relevant to AEGL-3**

Data from the rat studies reported by Appelman et al. (1982) and MacEwen and Vernot (1972) and the mouse studies reported by Silver and McGrath (1948), MacEwen and Vernot (1972), and Kapeghian et al. (1982) were considered relevant to deriving AEGL-3 values. The rat study by Appelman et al. and the mouse studies by Kapeghian et al. and MacEwen and Vernot were well conducted. However, the results of the Appelman et al. study were based on four different exposure durations, whereas only one exposure duration was used in the mouse studies by Kapeghian et al. and MacEwen and Vernot. ten Berge et al. (1986) noted that mice are more sensitive to respiratory irritants than other mammalian species. The two mouse studies, however, produced similar  $LC_{50}$  values (4,230 and 4,837 ppm), which increases the confidence in using the mouse data to derive the AEGL-3 values. In addition, probit analysis of the rat data reported by MacEwen and Vernot (1972) produced an  $LC_{50}$  value of 7,338 ppm for a 60-min exposure; this value is less than one-half the  $LC_{50}$  of 16,600 ppm derived by Appelman et al. The discrepancy in the two studies increases the uncertainty of using the rat data to derive AEGL-3 values. A study in the cat provided the lowest lethal concentration of 1,000 ppm (Dodd and Gross 1980). Lower respiratory tract lesions produced in cats exposed to ammonia are similar to those described for humans. However, the cats were exposed using a cuffed endotracheal tube, which bypassed the nasopharyngeal region where a significant amount of scrubbing occurs. This method of exposure could produce more severe tracheobronchial lesions than would occur from nose breathing. It should be noted that the cat study used only one ammonia concentration and one exposure duration; it was not designed to evaluate exposure-related effects. Because of inconsistencies in the results of the rat studies and the exposure method used for cat the study, the mouse studies are considered the most suitable for deriving AEGL-3 values.

### 7.3. Derivation of AEGL-3

LC<sub>01</sub> values derived from the mouse and rat studies are presented in Table 2-12. AEGL-3 values are derived using the data for mice reported by Kapeghian et al. (1982) and MacEwen and Vernot (1972). The 60-min LC<sub>01</sub> derived by the probit analysis of Kapeghian et al. is 3,317 ± 195 ppm (± standard error), and the 60-min LC<sub>01</sub> derived by probit analysis of the MacEwen and Vernot data is 3,374 ± 376 ppm. The LC<sub>01</sub> values from the two mouse studies are similar and both have small standard errors. These values compare closely with the 2,932 ppm 60-min LC<sub>01</sub> derived from use of regression coefficients from the combined mouse datasets of Kapeghian et al. (1982) and Silver and McGrath (1948) as presented by ten Berge et al. (1986) (see Table 2-12). For comparison, LC<sub>01</sub> values using the rat data reported by Appelman et al. (1982) and MacEwen and Vernot (1972) also are presented. The Benchmark Dose approach was applied to the Kapeghian et al. and MacEwen and Vernot mouse data; the resulting BMDL<sub>05</sub> values derived from the probit model are 3,278 and 3,219 ppm, respectively.

The mouse is unusually sensitive to exposure to respiratory irritants, including ammonia (ten Berge et al. 1986); therefore, an interspecies uncertainty factor of 1 was applied to the LC<sub>01</sub> for the mouse. An uncertainty factor of 3 was applied to account for intraspecies variability because concentrations of ammonia that are life threatening cause severe tracheobronchial and pulmonary damage and these effects are not expected to be more severe in asthmatics than in nonasthmatics (McLean et al. 1979), more severe in children than adults (Kass et al. 1972), or more severe in exercising than in nonexercising individuals (Cole et al. 1977; see rationale for AEGL-2), but tracheobronchial and pulmonary effects may occur at a lower concentration in the elderly. Investigations showed that reflex glottis closure (protective mechanism) is 3-fold less sensitive in the elderly than in young subjects (Erskine et al. 1993); this mechanism may be

**TABLE 2-12** LC<sub>01</sub> Estimates for Ammonia Derived from Animal Data

Exposure Time (min)	Concentration (ppm)					
	Mouse <sup>a</sup>	Mouse <sup>b</sup>	Mouse <sup>c</sup>	Mouse <sup>d</sup>	Rat <sup>a</sup>	Rat <sup>b</sup>
5	9,800	11,688	11,487	6,031	34,356	17,899
30	4,104	4,772	4,690	2,462	14,134	7,307
60	2,932	3,374	3,317	1,741	10,024	5,167
240	1,494	1,687	1,658	871	5,042	2,584
480	1,067	1,193	1,172	616	3,575	1,827

<sup>a</sup>Concentrations derived using Appelman et al. (1982) regression coefficients  $b_0 = 47.8$ ,  $b_1 = 4.64$ , and  $b_2 = 2.30$  for the rat and ten Berge et al. (1986) regression coefficients  $b_0 = 54.5$ ,  $b_1 = 5.95$ , and  $b_2 = 2.89$  for the mouse.

<sup>b</sup>Derived from data reported by MacEwen and Vernot 1972; n = 2.

<sup>c</sup>Derived from data reported by Kapeghian et al. 1982; n = 2.

<sup>d</sup>Derived from data reported by Silver and McGrath 1948; n = 2.

applicable only when concentrations of ammonia exceed 570 ppm. A larger interspecies or intraspecies uncertainty factor would lower the 30-min AEGL-3 value to approximately 500 ppm, which was tolerated by humans without lethal or long-term consequences (Silverman et al. 1949). Therefore, applying a total uncertainty factor of 3 to the LC<sub>01</sub> values of 3,317 or 3,374 ppm results in an AEGL-3 value of 1,100 ppm for the 1-h duration. Ten Berge's equation was used to extrapolate to the relevant exposure durations. The value of *n* was calculated from the regression coefficients (*b*<sub>1</sub>/*b*<sub>2</sub>) for mouse data reported by ten Berge et al. (1986). The AEGL-3 values for 10, 30, 60, 240, and 480 min are presented in Table 2-13.

No verified lethal concentrations for ammonia in humans were found in the available literature. However, Silverman et al. (1949) reported that 1,000 ppm induced an immediate urge to cough. Legters (1980) noted that coughing may indicate that the adsorptive (scrubbing) capacity of the upper respiratory tract has been exceeded and that ammonia is penetrating the lower respiratory passages. Data presented in Section 2.1 show that death in humans exposed to ammonia is associated with damage to the lower respiratory tract, and data presented in Section 2.2.1 showed effects caused by ammonia on the lower respiratory tract that would be lethal without prompt medical attention. Therefore, concentrations of ammonia that exceed the scrubbing capacity of the upper respiratory tract and cause coughing, which indicates lower respiratory effects, have potentially serious effects. Although no experimental studies were available for exposures to ammonia for durations longer than 1 h, there is a need to derive AEGL-3 values for 4- and 8-h exposures. Kass et al. (1972) showed that the ammonia cloud formed after an accident does not always dissipate rapidly. In the accident with the railroad car, a heavy fog kept the ammonia cloud close to the ground for a prolonged period of time.

The AEGL-3 value for 8 h is supported by studies in rats, rabbits, guinea pigs, dogs, and monkeys showing that daily 8-h exposures to 1,101 ppm for 6 weeks caused no deaths (Coon et al. 1970). The only effects observed were non-specific inflammation (rats and guinea pigs), lacrimation (dogs and rabbits), and dyspnea (dogs and rabbits).

## 8. SUMMARY OF AEGLs

### 8.1. AEGL Values and Toxicity End Points

The AEGL values are summarized in Table 2-14. Ammonia is irritating upon immediate contact with mucous surfaces of the eyes, mouth, and respiratory tract. The following factors were taken into account in proposing the AEGL values. Inhaling low concentrations of ammonia causes mild irritation to the eyes, nose, and throat, which is reversible upon termination of exposure. Individuals will attempt to escape immediately from atmospheres containing ammo-

**TABLE 2-13** AEGL-3 Values for Ammonia

10 min	30 min	1 h	4 h	8 h
2,700 ppm (1,888 mgm <sup>3</sup> )	1,600 ppm (1,119 mgm <sup>3</sup> )	1,100 ppm (769 mgm <sup>3</sup> )	550 ppm (385 mgm <sup>3</sup> )	390 ppm (273 mgm <sup>3</sup> )

**TABLE 2-14** AEGL Values for Ammonia

Classification	10 min	30 min	1 h	4 h	8 h	End Point (Primary References)
AEGL-1 (nondisabling)	220 ppm (154 mgm <sup>3</sup> )	30 ppm (21 mgm <sup>3</sup> )	30 ppm (21 mgm <sup>3</sup> )	30 ppm (21 mgm <sup>3</sup> )	30 ppm (21 mgm <sup>3</sup> )	Mild irritation (MacEwen et al. 1970)
AEGL-2 (disabling)	220 ppm (154 mgm <sup>3</sup> )	220 ppm (154 mgm <sup>3</sup> )	160 ppm (112 mgm <sup>3</sup> )	110 ppm (77 mgm <sup>3</sup> )	110 ppm (77 mgm <sup>3</sup> )	Irritation: eyes and respiratory tract, urge to cough (Verberk 1977)
AEGL-3 (lethal)	2,700 ppm (1,888 mgm <sup>3</sup> )	1,600 ppm (1,119 mgm <sup>3</sup> )	1,100 ppm (769 mgm <sup>3</sup> )	550 ppm (385 mgm <sup>3</sup> )	390 ppm (273 mgm <sup>3</sup> )	Threshold for lethality (LC <sub>01</sub> ) (Kapeghian et al. 1982; MacEwen and Vernot 1972)

nia at concentrations considered highly irritating or intolerable. Reflex glottis closure and nasopharyngeal scrubbing may protect the lower respiratory tract from potential injury during brief exposures. When the scrubbing capacity of the nasopharyngeal region is exceeded, the potential for damage to the lower regions of the respiratory tract increases. Most deaths occur when damage causes pulmonary edema or airway obstruction. However, recovery from airway obstruction is usually assured with medical treatment, whereas pulmonary edema may lead to death even with medical treatment.

## 8.2. Comparison of AEGLs with Other Standards and Criteria

Table 2-15 summarizes standards and guidelines established by various agencies and organizations. The AEGL values are similar to the values recommended by other organizations and agencies. The 1-h ERPG-3 (750 ppm) is slightly less than the proposed AEGL-3 value of 1,100 ppm, the ERPG-2 value (150 ppm) is slightly less than the AEGL-2 value of 110 ppm, and ERPG-1 value (25 ppm) is the same as the AEGL-1 value. NIOSH's IDLH is slightly

**TABLE 2-15** Extant Standards and Guidelines for Ammonia

Guideline	10 min	30 min	1 h	4 h	8 h
AEGL-1	30 ppm	30 ppm	30 ppm	30 ppm	30 ppm
AEGL-2	220 ppm	220 ppm	160 ppm	110 ppm	110 ppm
AEGL-3	2,700 ppm	1,600 ppm	1,100 ppm	550 ppm	390 ppm
ERPG-1 (AIHA) <sup>a</sup>			25 ppm		
ERPG-2 (AIHA)			150 ppm		
ERPG-3 (AIHA)			750 ppm		
EEGL (NRC) <sup>b</sup>			100 ppm		100 ppm (24 h)
PEL-TWA (OSHA) <sup>c</sup>					50 ppm
IDLH (NIOSH) <sup>d</sup>		300 ppm			
REL-TWA (NIOSH) <sup>e</sup>					25 ppm
REL-STEL (NIOSH) <sup>f</sup>	35 ppm (15 min)				
TLV-TWA (ACGIH) <sup>g</sup>					25
TLV-STEL (ACGIH) <sup>h</sup>	35 ppm (15 min)				
MAK (Germany) <sup>i</sup>					20
MAK Peak Limit (Germany) <sup>j</sup>					
OELV (Sweden) <sup>l</sup> (Dutch)	50 ppm (15 min)				25 ppm
SMAC <sup>m</sup>			20 ppm		14 ppm (24 h)

<sup>a</sup>ERPG (emergency response planning guideline, American Industrial Hygiene Association) (AIHA 2000). The ERPG-1 is the maximum airborne concentration below which it is believed nearly all individuals could be exposed for up to 1 h without experiencing other than mild, transient adverse health effects or without perceiving a clearly defined objectionable odor. The ERPG-1 for ammonia is based on a concentration associated with a mild odor perception or mild irritation. The ERPG-2 is the maximum airborne concentration below which it is believed nearly all individuals could be exposed for up to 1 h without experiencing or developing irreversible or other serious health effects or symptoms that could impair an individual's ability to take protective action. At the ERPG-2 level, ammonia will likely have a strong odor and cause some eye and upper respiratory irritation in susceptible populations, but serious effects are unlikely. The ERPG-3 is the maximum airborne concentration below which it is believed nearly all individuals could be exposed for up to 1 h without experiencing or developing life-threatening health effects. The ERPG-3 for ammonia is based on the median lethal concentrations of 7,340-16,600 ppm for the rat and 4,230-4,840 ppm for the mouse. This concentration may cause respiratory distress and severe eye and nasal irritation.

<sup>b</sup>EEGL (Emergency exposure guidance level, National Research Council) (NRC 1987). The EEGL is the concentration of contaminants that can cause discomfort or other evidence of irritation or intoxication in or around the workplace but avoids death, other se-

(Continued)

**TABLE 2-15** Continued

vere acute effects, and long-term or chronic injury. The EEGL for ammonia is based on effects experienced by subjects exposed to it at 140 ppm for up to 2 h.

<sup>c</sup>PEL-TWA (permissible exposure limit–time-weighted average, Occupational Health and Safety Administration) (OSHA 1999) is defined analogous to the ACGIH TLV-TWA but is for exposures of no more than 10 h/day, 40 h/week.

<sup>d</sup>IDLH (immediately dangerous to life and health, National Institute of Occupational Safety and Health) (NIOSH 1997) represents the maximum concentration from which one could escape within 30 min without any escape-impairing symptoms or any irreversible health effects. The IDLH for ammonia is based on acute toxicity data in humans.

<sup>e</sup>REL-TWA (recommended exposure limit–time-weighted average, National Institute of Occupational Safety and Health) (NIOSH 1997) is defined analogous to the ACGIH TLV-TWA.

<sup>f</sup>REL-STEL (recommended exposure limit–short-term exposure limit) (NIOSH 1997) is defined analogous to the ACGIH TLV-STEL.

<sup>g</sup>TLV-TWA (American Conference of Governmental Industrial Hygienists, Threshold Limit Value–time-weighted average) (ACGIH 2001) is the time-weighted average concentration for a normal 8-h workday and a 40-h workweek, to which nearly all workers may be repeatedly exposed, day after day, without adverse effect.

<sup>h</sup>TLV-STEL (Threshold Limit Value–short-term exposure limit) (ACGIH 2001) is defined as a 15-min TWA exposure, which should not be exceeded at any time during the workday even if the 8-h TWA is within the TLV-TWA. Exposures above the TLV-TWA up to the STEL should not be longer than 15 min and should not occur more than four times per day. There should be at least 60 min between successive exposures in this range.

<sup>i</sup>MAK (maximale arbeitsplatzkonzentration [maximum workplace concentration]) (Deutsche Forschungsgemeinschaft [German Research Association] 2000) is defined analogous to the ACGIH TLV-TWA.

<sup>j</sup>MAK spitzbegrenzung (peak limit [give category]) (Deutsche Forschungsgemeinschaft [German Research Association] 2000) constitutes the maximum average concentration to which workers can be exposed for a period up to 30 min with no more than two exposure periods per work shift; total exposure may not exceed 8-h MAK.

<sup>k</sup>MAC (maximaal aanvaarde concentratie [maximal accepted concentration]) (SDU Uitgevers [under the auspices of the Ministry of Social Affairs and Employment], The Hague, The Netherlands 2000) is defined analogous to the ACGIH TLV-TWA.

<sup>l</sup>OELV (occupational exposure limit value) (Swedish National Board of Occupational Safety and Health 1996) is the maximum acceptable average concentration (time-weighted average) of an air contaminant in respiratory air. An occupational exposure limit value is either a level limit value (one working day) or a ceiling limit value (15 min or some other reference time period).

<sup>m</sup>SMACs (spacecraft maximum allowable concentrations) (NRC 2000) provide guidance on chemical exposures during normal operations of spacecraft as well as emergency situations. Short-term (1-24 h) SMACs refer to concentrations of airborne substances (such as a gas, vapor, or aerosol) that will not compromise the performance of specific tasks by astronauts during emergency conditions or cause serious or permanent toxic effects. Such exposures may cause reversible effects such as mild skin or eye irritation but are not expected to impair judgment or interfere with proper responses to emergencies. The 1- and 24-h SMACs are based on concentrations that would cause only slight mucosal irritation (Wong 1995).

higher than the value for the AEGL-2 30-min exposure. Mahlum and Sasser (1991) determined maximum exposure levels for operators in nuclear reactor control rooms. The recommended 2-min exposure limit was 300 ppm, which would allow a person to perform their task, don protective clothing, and suffer no long-lasting effects.

### 8.3. Data Adequacy and Research Needs

A large body of data was available for deriving AEGL values for ammonia. The studies on lethal or irreversible effects in humans did not have quantitative exposure estimates. However, human studies on upper respiratory tract irritation with quantitative exposure were available. In the human studies available, subjects were exposed to ammonia at concentrations that ranged from odor detection levels to concentrations causing “unbearable” irritation to the respiratory tract and eyes. Human studies using concentrations of ammonia higher than those reported in this document have the potential for causing more severe irritation and are not necessary for further documenting of exposure-response relationships in humans. The available human data were considered adequate for deriving AEGL-1 and -2 values. Lethality data were available for two animal species, and these data were considered adequate for deriving AEGL-3 values. The only data deficiency of note was the lack of lethal data for rodents for exposure periods longer than 1 h.

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## APPENDIX A

### Derivation of AEGL-1 Values

Key study:	MacEwen et al. 1970
Toxicity end point:	Faint or irritation (humans)
Time scaling:	None
Uncertainty factors:	Interspecies: NA Intraspecies: 1
Calculations:	
10-min: AEGL-1:	$30 \text{ ppm}/\text{UF} = 30 \text{ ppm}/\text{L} = 30 \text{ ppm}$
30-min, 1-, 4-, and 8-h:	AEGL-1: Same as AEGL-1: 30 ppm

### Derivation of AEGL-2 Values

Key study:	Verberk 1977
Toxicity end point:	Irritation: eyes and upper respiratory tract in humans
Time scaling:	$C^n \times t = k$ ; $n = 2$ (ten Berge et al. 1986)
Uncertainty factors:	1 for intraspecies variability; not applicable for interspecies sensitivity
Calculations:	
Point of departure:	110 ppm for 2 h
10-min AEGL:	Same as the 30-min value = 220 ppm
30-min AEGL-2:	$C^n \times t = k$ ; $C = 110 \text{ ppm}$ , $t = 120 \text{ min}$ , $n = 2$ $C = (k/t)^{1/2} = (1.45 \times 10^6 \text{ ppm}\cdot\text{min}/30 \text{ min})^{1/2}$ $C = 220 \text{ ppm}$
1-h AEGL-2:	$C = (k/t)^{1/2} = (1.45 \times 10^6 \text{ ppm}\cdot\text{min}/30 \text{ min})^{1/2}$ $C = 160 \text{ ppm}$

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4-h AEGL-2: C = 110 ppm, same as the POD

8-h AEGL-2: C = 110 ppm, same as the POD

**Derivation of AEGL-3 Values**

Key study: Kapeghian et al. 1982;  
MacEwen and Vernot 1972

Toxicity end point: Lethality: the LC<sub>50</sub> for the two sets of mouse data were extrapolated to an LC<sub>01</sub>

Time scaling: C<sup>n</sup> × t = k; n = 2 (ten Berge et al. 1986)

Uncertainty factors: Three for intraspecies variability; one for interspecies sensitivity

Calculations:

1-h AEGL-3: C = 3,317 ppm/3 (uncertainty factor) = 1,106 ppm  
C = 3,374 ppm/3 (uncertainty factor) = 1,125 ppm

Kapeghian et al. 1982 C<sup>n</sup> × t = k; C = 1,106 ppm, t = 60 min, n = 2,  
k = 7.335 × 10<sup>7</sup> ppm•min  
C = (k/t)<sup>1/2</sup> = (7.335 × 10<sup>7</sup> ppm•min/60 min)<sup>1/2</sup>  
C = 1,106 ppm = 1,100 ppm

MacEwen and Vernot 1972 C<sup>n</sup> × t = k; C = 1,125 ppm, t = 60 min, n = 2,  
k = 7.59 × 10<sup>7</sup> ppm•min  
C = (k/t)<sup>1/2</sup> = (7.59 × 10<sup>7</sup> ppm•min/60 min)<sup>1/2</sup>  
C = 1,125 ppm = 1,100 ppm

10-min AEGL -3: C = (k/t)<sup>1/2</sup> = (7.335 × 10<sup>7</sup> ppm•min/10 min)<sup>1/2</sup>  
C = 2,708 ppm = 2,700 ppm  
C = (k/t)<sup>1/2</sup> = (7.59 × 10<sup>7</sup> ppm•min/10 min)<sup>1/2</sup>  
C = 2,755 ppm = 2,700 ppm

30-min AEGL-3: C = (k/t)<sup>1/2</sup> = (7.335 × 10<sup>7</sup> ppm•min/30 min)<sup>1/2</sup>  
C = 1,564 ppm = 1,600 ppm  
C = (k/t)<sup>1/2</sup> = (7.59 × 10<sup>7</sup> ppm•min/30 min)<sup>1/2</sup>  
C = 1,591 ppm = 1,600 ppm

4-h AEGL-3:  $C = (k/t)^{1/2} = (7.335 \times 10^7 \text{ ppm}\cdot\text{min}/240 \text{ min})^{1/2}$   
 $C = 553 \text{ ppm} = 550 \text{ ppm}$   
 $C = (k/t)^{1/2} = (7.59 \times 10^7 \text{ ppm}\cdot\text{min}/240 \text{ min})^{1/2}$   
 $C = 562 \text{ ppm} = 560 \text{ ppm}$

8-h AEGL-3:  $C = (k/t)^{1/2} = (7.335 \times 10^7 \text{ ppm}\cdot\text{min}/480 \text{ min})^{1/2}$   
 $C = 391 \text{ ppm} = 390 \text{ ppm}$   
 $C = (k/t)^{1/2} = (7.59 \times 10^7 \text{ ppm}\cdot\text{min}/480 \text{ min})^{1/2}$   
 $C = 398 \text{ ppm} = 400 \text{ ppm}$

**APPENDIX B**

**Acute Exposure Guideline Levels for Ammonia**

**Derivation Summary for Ammonia AEGLS**

**AEGL-1 VALUES**

10 min	30 min	1 h	4 h	8 h
30 ppm	30 ppm	30 ppm	30 ppm	30 ppm
Reference: MacEwen, J.D.; J. Theodore, and E. H. Vernot. 1970. Human exposure to EEL concentrations of monomethylhydrazine, AMRL-TR-70-102, Paper No. 23. In: Proc. 1st Ann. Conf. Environ. Toxicol., September 9-11, 1970, Wright-Patterson AFB, OH. Pp. 355-363.				
Test species/Strain/Sex/Number: Humans.				
Exposure route/Concentrations/Durations: Inhalation.				
Effects: 30 ppm for 10 min: 2/6 subjects reported faint irritation; 3/6 reported no irritation; 1/6 provided no response.				
End point/Concentration/Rationale: Faint irritation in human subjects exposed to 30 ppm of ammonia for 10 min. The responses by all subjects exposed to 30 ppm of ammonia were consistent with the definition of AEGL-1 or below the definition of AEGL-1.				
Uncertainty factors/Rationale:				
Total uncertainty factor: 1.				
Interspecies: Not applicable.				
Intraspecies: 1; Ammonia is a contact irritant and is efficiently scrubbed in the upper respiratory tract, particularly at the low AEGL-1 concentration; therefore, members of the population are not expected to respond differently to effects confined to the upper respiratory tract. Atopics, including asthmatics, and nonatopics responded similarly to a brief nasal exposure to ammonia. Exercising subjects showed only a clinically nonsignificant decrease in pulmonary function after exposure to ammonia.				

*(Continued)*

**AEGL-1 VALUES** Continued

10 min	30 min	1 h	4 h	8 h
30 ppm				

Modifying factor: 1.

Animal to human dosimetric adjustment: Not applicable.

Time scaling: The severity of upper respiratory tract irritation is not expected to increase with duration of exposure to low concentrations of ammonia; therefore, the same value is applied to all AEGL-1 exposure duration.

Data adequacy: Upper respiratory tract irritation at 30 ppm and above is well documented in the literature. Therefore, sufficient data were available to document the irritation threshold.

**AEGL-2 VALUES**

10 min	30 min	1 h	4 h	8 h
220 ppm	220 ppm	160 ppm	110 ppm	110 ppm

Reference: Verberk, M.M. 1977. Effects of ammonia on volunteers. *Int. Arch. Occup. Environ. Health* 39:73-81.

Test species/Strain/Sex/Number: Humans, mixed sex; 8 expert and 8 nonexpert subjects.

Exposure route/Concentrations/Durations: Inhalation; 50, 80, 110, or 140 ppm for durations up to 2 h.

Effects: 50 ppm: just perceptible to offensive odor; no sensation to nuisance eye, nose, and throat irritation; no sensation to distinctly perceptible urge to cough, chest irritation, or general discomfort.

80 ppm: just perceptible to offensive odor; no sensation to offensive eye, nose, throat, and chest irritation and urge to cough; no sensation to nuisance general discomfort;

110 ppm: distinctly perceptible to offensive odor; no sensation to offensive eye, nose, throat, and chest irritation, urge to cough, or general discomfort;

140 ppm: just perceptible to offensive odor; just perceptible to unbearable eye irritation; no sensation to offensive nose, throat, and chest irritation, urge to cough, or general discomfort;

severity ratings: 0 = no sensation, 1 = just perceptible, 2 = distinctly perceptible, 3 = nuisance, 4 = offensive, and 5 = unbearable.

End point/Concentration/Rationale: 110 ppm for 2 h; respiratory tract and eye irritation and urge to cough ranged from “no sensation” to “offensive” during the 2-h exposure of the nonexpert subjects. The AEGL-2 derivation was based on the response (offensive irritation) of the most sensitive nonexpert subjects. The responses changed very little between 30 min and 2 h. The nonexperts considered the effects to be near the maximum response (offensive), whereas the expert responses were always of a lesser degree.

(Continued)

**AEGL-2 VALUES** Continued

10 min	30 min	1 h	4 h	8 h
220 ppm	220 ppm	160 ppm	110 ppm	110 ppm

Uncertainty factors/Rationale:

Total uncertainty factor: 1.

Interspecies: Not applicable.

Intraspecies: 1; Ammonia is a contact irritant and is efficiently scrubbed in the upper respiratory tract, and any perceived irritation experienced by the general public including sensitive individuals at low AEGL-2 concentrations is not expected to be greater than that of the most sensitive nonexpert subject. Atopics, including asthmatics, and nonatopics responded similarly to a brief nasal exposure to ammonia; a child experienced less severe effects than that of an adult exposed to high concentrations of ammonia; and exercising subjects showed only a nonclinically significant decrease in pulmonary function after exposure to ammonia.

Modifying factor: 1; POD was from a controlled exposure study on human subjects.

Animal to human dosimetric adjustment: Not applicable.

Time scaling:  $C^n \times t = k$ , where  $n = 2$  based on an analysis of empirical mouse and rat lethality data in which the times of exposure ranged from 10 to 60 min (ten Berge et al. 1986). Values for 4 and 8 h are the same as the POD because the responses of the subjects did not change considerably between 30 min and 2 h and are not expected to change for exposures up to 8 h. The 10-min AEGL-2 is the same as the 30-min AEGL-2 because the time-scaled value of 380 ppm might impair escape.

Data adequacy: The AEGL-2 values were based on a study using human subjects exposed to ammonia for 2 h; the responses of the subjects ranged from “no sensation” to “offensive,” which is expected to be comparable to the range of responses in the general public, including sensitive individuals. Case reports of long-term or irreversible effects in humans with exposure estimates were not available in the literature.

**AEGL-3 VALUES**

10 min	30 min	1 h	4 h	8 h
2,700 ppm	1,600 ppm	1,100 ppm	550 ppm	390 ppm

References: MacEwen, J.D., and E.H. Vernot. 1972. Toxic Hazards Research Unit Annual Technical Report. SysteMed Report No. W-72003, AMRL-TR-72-62. Sponsor: Aerospace Medical Research Laboratory, Wright-Patterson AFB, OH. (I);

Kapeghian, J.C., H.H. Mincer, and A.B. Hones et al. 1982. Acute inhalation toxicity of ammonia in mice. Bull. Environ. Contam. Toxicol. 29:371-378. (II)

Test species/Strain/Number: CF1 or ICR male mice, 10 or 12 per group.

(Continued)

AEGL-3 VALUES Continued

10 min	30 min	1 h	4 h	8 h
2,700 ppm	1,600 ppm	1,100 ppm	550 ppm	390 ppm

Exposure route/Concentrations/Durations:

Inhalation: 0, 3,600, 4,550, or 5,700 ppm for 1 h (I).

Inhalation: 0; 1,190; 1,340; 2,130; 3,400; 3,950; 4,220; 4,860 ppm for 1 h (II).

Effects:

(I): Clinical signs: nasal and eye irritation, labored breathing, gasping, convulsions, and low body weight gain.

Mortality: 3,600 ppm (0/10), 4,500 ppm (3/10), and 5,720 ppm (9/10); LC<sub>01</sub>: 3,374 ppm.

(II): Clinical signs: eye and nasal irritation, hypoactivity, labored breathing, ataxia, convulsions, weight loss.

(III): Mortality: ≤3,440 ppm (0/12), 3,950 ppm (3/12), 4,220 ppm (5/12), 4,490 ppm (8/12), and 4,860 ppm (12/12); LC<sub>01</sub>: 3317 ppm.

End point/Concentration/Rationale: Lethality; LC<sub>01</sub> = 3,374 ppm (I) and 3,317 ppm (II) for 1 h are the estimated thresholds for lethality derived by probit analysis of the data. Both numbers when divided by an uncertainty factor of 3 give the same result when the AEGL value is expressed to two significant figures.

Uncertainty factors/Rationale:

Total uncertainty factor: 3

Interspecies: 1, The mouse was unusually sensitive to ammonia compared with other mammalian species. An UF of 3 would yield a 30 min AEGL-3 value below a level that humans can tolerate (500 ppm) for 30 min.

Intraspecies: 3, Life-threatening concentrations of ammonia cause severe tracheobronchial and pulmonary effects and these effects, are not expected to be more severe in asthmatics than in nonasthmatic individuals, more severe in children than in adults, or more severe in exercising than resting individuals, but tracheobronchial and pulmonary effects may occur at a lower concentration in the elderly than in young adults. Reflex glottis closure (protective mechanism) is 3-fold less sensitive in the elderly than in young subjects; this mechanism may only be applicable when concentrations of ammonia exceed 570 ppm.

Modifying factor: 1.

Animal to human dosimetric adjustment: 1.

Time scaling:  $C^n \times t = k$  where  $n = 2$  based on an empirical analysis of mouse and rat lethality data in which the durations of exposure ranged from 10 to 60 min (ten Berge et al. 1986).

Data adequacy: No quantitative exposure data were available for humans who died from exposure to ammonia. Lethality data were available for two animal species—mice and rats. The AEGL-3 values were based on two mouse studies that were in close agreement, although they were conducted 12 years apart by two different laboratories.

APPENDIX C

CATEGORY PLOT FOR AMMONIA

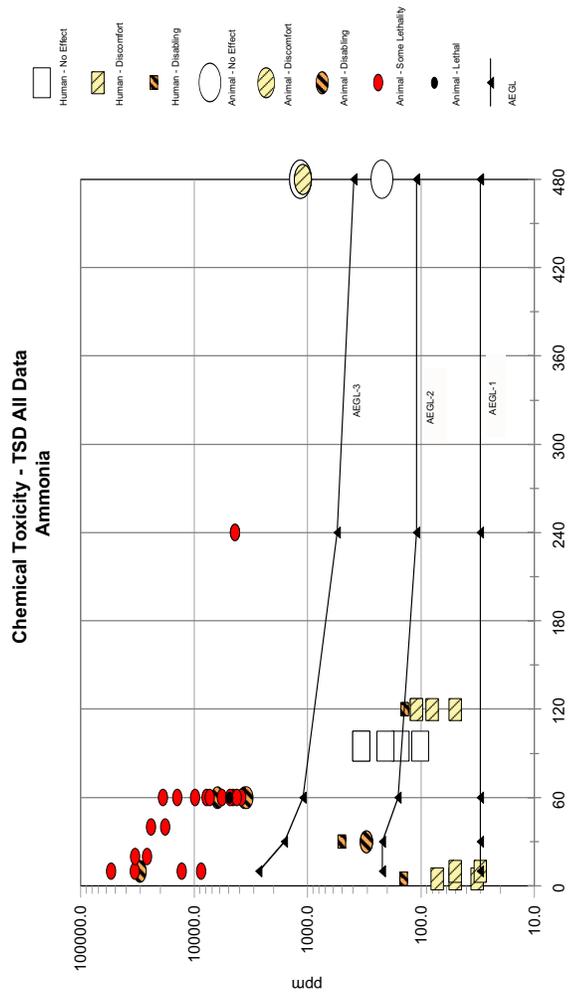


FIGURE 2-1 Chemical toxicity TSD all data—ammonia.

**Center for Disease Control**

**(CDC)**

**&**

**National Institute for Occupational Safety and Health**

**(NIOSH)**



May 1994

## Documentation for Immediately Dangerous To Life or Health Concentrations (IDLHs)

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### Ammonia

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**CAS number:** 7664-41-7

**NIOSH REL:** 25 ppm (18 mg/m<sup>3</sup>) TWA, 35 ppm (27 mg/m<sup>3</sup>) STEL

**Current OSHA PEL:** 50 ppm (35 mg/m<sup>3</sup>) TWA

**1989 OSHA PEL:** 35 ppm (27 mg/m<sup>3</sup>) STEL

**1993-1994 ACGIH TLV:** 25 ppm (17 mg/m<sup>3</sup>) TWA, 35 ppm (24 mg/m<sup>3</sup>) STEL

**Description of substance:** Colorless gas with a pungent, suffocating odor.

**LEL:** 15% (10% LEL, 15,000 ppm)

**Original (SCP) IDLH:** 500 ppm

**Basis for original (SCP) IDLH:** The chosen IDLH is based on the statement by AIHA [1971] that 300 to 500 ppm for 30 to 60 minutes have been reported as a maximum short exposure tolerance [Henderson and Haggard 1943]. AIHA [1971] also reported that 5,000 to 10,000 ppm are reported to be fatal [Mulder and Van der Zahm 1967] and exposures for 30 minutes to 2,500 to 6,000 ppm are considered dangerous to life [Smyth 1956].

**Existing short-term exposure:**

1988 American Industrial Hygiene Association (AIHA) Emergency Response Planning Guidelines (ERPGs)

- ERPG-1: 25 ppm
- ERPG-2: 200 ppm
- ERPG-3: 1,000 ppm

National Research Council [NRC 1987] Emergency Exposure Guidance Levels (EEGLs)

- 1-hour EEGL: 100 ppm
- 24-hour EEGL: 100 ppm

U.S. Navy Standards [U.S. Bureau of Ships 1962] Maximum allowable concentrations (MACs):

- Continuous exposure (60 days): 25 ppm
- 1 hour: 400 ppm

**ACUTE TOXICITY DATA**

**Lethal concentration data:**

Species	Reference	LC50 (ppm)	LCLo (ppm)	Time	Adjusted 0.5-hr LC (CF)	Derived Value
Rat	Alarie 1981	40,300	-----	10 min	23,374 ppm (0.58)	2,337 ppm
Rat	Alarie 1981	28,595	-----	20 min	23,448 ppm (0.82)	2,335 ppm
Rat	Alarie 1981	20,300	-----	40 min	23,345 ppm (1.15)	2,335 ppm
Rat	Alarie 1981	11,590	-----	1 hr	16,342 ppm (1.41)	1,634 ppm
Rat	Back et al. 1972	7,338	-----	1 hr	10,347 ppm (1.41)	1,035 ppm
Mouse	Back et al. 1972	4,837	-----	1 hr	6,820 ppm (1.41)	682 ppm
Rabbit	Boyd et al. 1944	9,859	-----	1 hr	13,901 ppm (1.41)	1,309 ppm
Cat	Boyd et al. 1944	9,859	-----	1 hr	13,901 ppm (1.41)	1,309 ppm
Rat	Deichmann and Gerarde 1969	2,000	-----	4 hr	5,660 ppm (2.83)	566 ppm
Mammal	Flury 1928	-----	5,000	5 min	2,050 ppm (0.41)	205 ppm
Mouse	Kapeghian et al. 1982	4,230	-----	1 hr	5,964 ppm (1.41)	596 ppm
Human	Tab Biol Per 1933	-----	5,000	5 min	2,050 ppm (0.41)	205 ppm

\*Note: Conversion factor (CF) was determined with "n" = 2.0 [ten Berge et al. 1986].

**Other animal data:** RD50 (mouse), 303 ppm [Appelman et al. 1982].

**Other human data:** The maximum short exposure tolerance has been reported as being 300 to 500 ppm for 0.5 to 1 hour [Henderson and Haggard 1943]. A change in respiration rate and moderate to severe irritation has been reported in 7 subjects exposed to 500 ppm for 30 minutes [Silverman et al. 1946].

**Revised IDLH: 300 ppm**  
 Basis for revised IDLH: The revised IDLH for ammonia is 300 ppm based on acute inhalation toxicity data in humans [Henderson and Haggard 1943; Silverman et al. 1946].

**REFERENCES:**

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## **APPENDIX D**

Key References for Fluoride Toxicity Values

**Agency for Toxic Substances and Disease Registry**  
**(ATSDR)**

## APPENDIX A. ATSDR MINIMAL RISK LEVEL AND WORKSHEETS

The Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA) [42 U.S.C. 9601 et seq.], as amended by the Superfund Amendments and Reauthorization Act (SARA) [Pub. L. 99–499], requires that the Agency for Toxic Substances and Disease Registry (ATSDR) develop jointly with the U.S. Environmental Protection Agency (EPA), in order of priority, a list of hazardous substances most commonly found at facilities on the CERCLA National Priorities List (NPL); prepare toxicological profiles for each substance included on the priority list of hazardous substances; and assure the initiation of a research program to fill identified data needs associated with the substances.

The toxicological profiles include an examination, summary, and interpretation of available toxicological information and epidemiologic evaluations of a hazardous substance. During the development of toxicological profiles, Minimal Risk Levels (MRLs) are derived when reliable and sufficient data exist to identify the target organ(s) of effect or the most sensitive health effect(s) for a specific duration for a given route of exposure. An MRL is an estimate of the daily human exposure to a hazardous substance that is likely to be without appreciable risk of adverse noncancer health effects over a specified duration of exposure. MRLs are based on noncancer health effects only and are not based on a consideration of cancer effects. These substance-specific estimates, which are intended to serve as screening levels, are used by ATSDR health assessors to identify contaminants and potential health effects that may be of concern at hazardous waste sites. It is important to note that MRLs are not intended to define clean-up or action levels.

MRLs are derived for hazardous substances using the no-observed-adverse-effect level/uncertainty factor approach. They are below levels that might cause adverse health effects in the people most sensitive to such chemical-induced effects. MRLs are derived for acute (1–14 days), intermediate (15–364 days), and chronic (365 days and longer) durations and for the oral and inhalation routes of exposure. Currently, MRLs for the dermal route of exposure are not derived because ATSDR has not yet identified a method suitable for this route of exposure. MRLs are generally based on the most sensitive chemical-induced end point considered to be of relevance to humans. Serious health effects (such as irreparable damage to the liver or kidneys, or birth defects) are not used as a basis for establishing MRLs. Exposure to a level above the MRL does not mean that adverse health effects will occur.

MRLs are intended only to serve as a screening tool to help public health professionals decide where to look more closely. They may also be viewed as a mechanism to identify those hazardous waste sites that

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are not expected to cause adverse health effects. Most MRLs contain a degree of uncertainty because of the lack of precise toxicological information on the people who might be most sensitive (e.g., infants, elderly, nutritionally or immunologically compromised) to the effects of hazardous substances. ATSDR uses a conservative (i.e., protective) approach to address this uncertainty consistent with the public health principle of prevention. Although human data are preferred, MRLs often must be based on animal studies because relevant human studies are lacking. In the absence of evidence to the contrary, ATSDR assumes that humans are more sensitive to the effects of hazardous substance than animals and that certain persons may be particularly sensitive. Thus, the resulting MRL may be as much as a hundredfold below levels that have been shown to be nontoxic in laboratory animals.

Proposed MRLs undergo a rigorous review process: Health Effects/MRL Workgroup reviews within the Division of Toxicology, expert panel peer reviews, and agencywide MRL Workgroup reviews, with participation from other federal agencies and comments from the public. They are subject to change as new information becomes available concomitant with updating the toxicological profiles. Thus, MRLs in the most recent toxicological profiles supersede previously published levels. For additional information regarding MRLs, please contact the Division of Toxicology, Agency for Toxic Substances and Disease Registry, 1600 Clifton Road, Mailstop E-29, Atlanta, Georgia 30333.

## APPENDIX A

**MINIMAL RISK LEVEL (MRL) WORKSHEET**

Chemical Name: Hydrogen Fluoride  
CAS Number: 7664-39-3  
Date: December 1, 2003  
Profile Status: Final  
Route:  Inhalation  Oral  
Duration:  Acute  Intermediate  Chronic  
Key to Figure: 6  
Species: Humans

Minimal Risk Level: 0.02  mg/kg/day  ppm

Reference: Lund K, Ekstrand J, Poe J, et al. 1997. Exposure to hydrogen fluoride: an experimental study in humans of concentrations of fluoride in plasma, symptoms, and lung function. *Occup Environ Med* 54:32-37.

Lund K, Refsnes M, Sandstrøm T, et al. 1999. Increased CD3 positive cells in bronchoalveolar lavage fluid after hydrogen fluoride inhalation. *Scand J Work Environ Health* 25:326-334.

Experimental design (human study details or strain, number of animals per exposure/control groups, sex, dose administration details): Groups of 7-9 healthy, nonsmoking males (21-44 years of age) were exposed to 0.2-0.6, 0.7-2.4, or 2.5-5.2 mg/m<sup>3</sup> hydrogen fluoride for 1 hour. For the last 15 minutes of the exposure, the subjects performed an ergometric test at a fixed work load of 75W. Bronchoalveolar lavage (BAL) was performed 3 weeks prior to exposure and 24 hours after exposure. Lung function tests were performed immediately before exposure, every 15 minutes during exposure, at exposure termination, 30 minutes after exposure, and 1, 2, 3, and 4 hours after exposure. Symptom surveys were completed before exposure initiation, after 30 minutes of exposure, at exposure termination, and 4 and 24 hours after exposure. Eye, upper airway (nose and throat), and lower airway symptoms were scored based on a 5 point scale with 5 being the most severe.

The midpoint of the range of concentrations was used to calculate ppm levels: 0.4 mg hydrogen fluoride/m<sup>3</sup> x 24.45/20 x 19/20 = 0.5 ppm fluoride; 1.7 mg/m<sup>3</sup> = 1.9 ppm, 3.9 mg/m<sup>3</sup> = 4.5 ppm

Effects noted in study and corresponding concentrations: No significant exposure-related alterations in lung function (FEV1 or FVC) were observed and no significant correlations between plasma fluoride concentrations and FVC or FEV1 were found. Increases (as compared to scores prior to exposure) in upper airway symptom scores were observed in the low (p=0.06) and high (p=0.02) concentration groups and for all concentrations combined (p<0.001); similarly, total symptom scores were significantly (p<0.04) increased in the low and high concentration groups and all groups combined. The severity of the upper airway score was low (scores of 1-3) in the low exposure group. All subjects reported a change in the upper airway symptom score in the high concentration group; four subjects scored the symptoms as low and three scored them as high. A significant increase in eye symptom score was also observed in all groups combined, but not for individual exposure level groups. The effect of hydrogen fluoride exposure was assessed by comparing the before and after exposure BAL fluid. Significant increases in the percentage of CD3-positive cells were found in the bronchial portion of the mid- and high-dose group and in the bronchoalveolar portion of the high-dose group. A significant increase in the percentage of lymphocytes in the bronchial and bronchoalveolar portions in the mid-concentration group was observed. A significant correlation between the individual changes in the percentage of CD3-positive cells and the

## APPENDIX A

changes in the percentage of lymphocytes from the bronchoalveolar portion was also observed. Significant increases in myeloperoxidase and interleukin-6 levels were found in the high dose group.

Concentration and end point used for MRL derivation: The MRL is based on a minimal LOAEL of 0.5 ppm fluoride as hydrogen fluoride for upper respiratory tract irritation.

[ ] NOAEL [X] LOAEL

Uncertainty Factors used in MRL derivation:

[X]	3 for use of a minimal LOAEL
[ ]	3 for extrapolation from animals to humans with dosimetric adjustments
[X]	10 for human variability

Was a conversion factor used from ppm in food or water to a mg/body weight dose? No

If an inhalation study in animals, list conversion factors used in determining human equivalent concentration:

Was a conversion used from intermittent to continuous exposure? No. Data on nasal irritation from the Largent (1960) report, the Lund et al. (2002) study, and the intermediate-duration study by Largent (1960) provide suggestive evidence that the severity of nasal irritation does not increase with increasing exposure duration. These three studies identified similar LOAEL values for different exposure durations: 3.22 ppm 6 hours/day for 10 days (Largent 1960), 3.8 ppm 1 hour/day for 1 day (Lund et al. 2002), and 2.98 ppm 6 hours/day, 6 days/week for 15–50 days. Thus, time scaling was not used to derive the acute MRL.

Other additional studies or pertinent information that lend support to this MRL: The respiratory tract appears to be the primary target of hydrogen fluoride toxicity. Upper respiratory tract irritation and inflammation and lower respiratory tract inflammation have been observed in several human studies. Nasal irritation was reported by one subject exposed to 3.22 ppm fluoride as hydrogen fluoride 6 hours/day for 10 days (Largent 1960). Very mild to moderate upper respiratory symptoms were reported by healthy men exposed to 0.5 ppm fluoride as hydrogen fluoride for 1 hour (Lund et al. 1997). At higher concentrations, 4.2–4.5 ppm fluoride as hydrogen fluoride for 1 hour, more severe symptoms of upper respiratory irritation were noted (Lund et al. 1997, 2002). In subjects exposed to 4.2 ppm for 1 hour, analysis of nasal lavage fluid provided suggestive evidence that hydrogen fluoride induces an inflammatory response in the nasal cavity (Lund et al. 2002). Similarly, bronchoalveolar lavage fluid analysis revealed suggestive evidence of bronchial inflammation in another study of subjects exposed to 1.9 ppm fluoride as hydrogen fluoride for 1 hour (Lund et al. 1999); no alterations were observed at 0.5 ppm. Respiratory effects have also been reported in rats acutely exposed to hydrogen fluoride. Mild nasal irritation was observed during 60-minute exposure to 120 ppm fluoride (Rosenholtz et al. 1963), and respiratory distress was observed at 2,310, 1,339, 1,308, and 465 ppm fluoride for 5, 15, 30, or 60 minutes, respectively (Rosenholtz et al. 1963). Midtracheal necrosis was reported in rats exposed to 902 or 1,509 ppm fluoride as hydrogen fluoride for 2 or 10 minutes using a mouth breathing model with a tracheal cannula (Dalbey et al. 1998a, 1998b). These effects were not observed when the tracheal cannula was not used.

The Lund et al. (1997, 1999) study was selected as the basis of the acute-duration inhalation MRL for hydrogen fluoride. As reported in the 1997 publication, a trend ( $p=0.06$ ) toward increased upper respiratory tract symptom score, as compared to pre-exposure symptom scores, was observed at the lowest concentration tested (0.5 ppm). A significant increase in the total symptom score was also

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observed at this concentration. No significant alterations in symptom scores were observed at the mid concentration (1.9 ppm), and increases in upper respiratory and total symptom scores were observed at the high concentration (4.5 ppm). Suggestive evidence of bronchial inflammation was also observed at  $\geq 1.9$  ppm fluoride (Lund et al. 1999), although no alterations in lower respiratory tract symptoms (Lund et al. 1997) or lung function (Lund et al. 1997) were observed at any of the tested concentrations.

Agency Contact (Chemical Manager): Carolyn A. Tylenda, D.M.D., Ph.D., Dennis Jones, D.V.M.

## APPENDIX A

**MINIMAL RISK LEVEL (MRL) WORKSHEET**

Chemical Name: Fluorine  
CAS Number: 7782-41-4  
Date: December 1, 2003  
Profile Status: Final  
Route:  Inhalation  Oral  
Duration:  Acute  Intermediate  Chronic  
Key to Figure: 6  
Species: Humans

Minimal Risk Level: 0.01  mg/kg/day  ppm

Reference: Keplinger ML, Suissa LW. 1968. Toxicity of fluorine short-term inhalation. Am Ind Hyg Assoc J 29(1):10-18.

Experimental design (human study details or strain, number of animals per exposure/control groups, sex, dose administration details): Five volunteers (aged 19–50 years; gender not specified) were exposed to various concentrations of fluorine: 10 ppm for 3, 5, or 15 minutes; 23 ppm for 5 minutes, 50 ppm for 3 minutes, 67 ppm for 1 minute, 78 ppm for 1 minute, and 100 ppm for 0.5 or 1 minute. The fluorine was administered via a mask that covered the eyes and nose; the subjects could remove the mask from their face and could breathe fresh air via their mouth. No information was provided on the amount of time between exposures or whether all subjects were exposed to all concentrations.

Effects noted in study and corresponding concentrations: No nasal or eye irritation was noted by subjects exposed to 10 ppm for 3, 5, or 15 minutes; it was also noted that the 15-minute exposure did not result in respiratory tract irritation. Eye irritation was observed at  $\geq 23$  ppm; nose irritation at  $\geq 50$  ppm, and skin irritation at  $\geq 78$  ppm. The severity of the irritation was concentration related. Exposure to 100 ppm was considered very irritating and the subjects did not inhale during the exposure period. No incidence data were reported.

Concentration and end point used for MRL derivation: The MRL is based on a NOAEL of 10 ppm and LOAEL of 23 ppm fluorine for irritation in humans.

NOAEL  LOAEL

Uncertainty Factors used in MRL derivation:

- 10 for use of a LOAEL
- 10 for extrapolation from animals to humans
- 10 for human variability

Was a conversion factor used from ppm in food or water to a mg/body weight dose? No

If an inhalation study in animals, list conversion factors used in determining human equivalent concentration: NA

## APPENDIX A

Was a conversion used from intermittent to continuous exposure? Yes. The 15-minute exposure duration was adjusted for a continuous 24-hour exposure using the following equation:

$$10 \text{ ppm} \times 0.25 \text{ hours}/24 \text{ hours} = 0.1 \text{ ppm}$$

The study authors noted that exposure to 10 ppm for 3–5 minutes every 15 minutes over a 2- or 3-day period resulted slight irritation to the eyes and skin, but no other subjective effects (no additional details on this study were provided). These data are suggestive that the toxicity of fluorine may be dependent on concentration and duration of exposure. Thus, it is appropriate to adjust for continuous exposure.

Other additional studies or pertinent information that lend support to this MRL: Respiratory effects have also been observed in, rats, mice, guinea pigs, rabbits, and dogs exposed to fluorine for 1–60 minutes (Keplinger and Suissa 1968). The observed effects include diffuse lung congestion, dyspnea, irritation, and alveolar necrosis and hemorrhage. The severity of the lung congestion was concentration-related and no species differences were found.

Agency Contact (Chemical Manager): Carolyn A. Tylenda, D.M.D., Ph.D., Dennis Jones, D.V.M.



**Environmental Protection Agency**

**(RfD)**



## Integrated Risk Information System

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# Fluorine (soluble fluoride) (CASRN 7782-41-4)

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**0053**

### Fluorine (soluble fluoride); CASRN 7782-41-4

Human health assessment information on a chemical substance is included in the IRIS database only after a comprehensive review of toxicity data, as outlined in the [IRIS assessment development process](#). Sections I (Health Hazard Assessments for Noncarcinogenic Effects) and II (Carcinogenicity Assessment for Lifetime Exposure) present the conclusions that were reached during the assessment development process. Supporting information and explanations of the methods used to derive the values given in IRIS are provided in the [guidance documents located on the IRIS website](#).

STATUS OF DATA FOR Fluorine (soluble fluoride)

**File First On-Line 01/31/1987**

Category (section)	Status	Last Revised
Oral RfD Assessment (I.A.)	on-line	06/01/1989
Inhalation RfC Assessment (I.B.)	no data	
Carcinogenicity Assessment (II.)	no data	

## **\_I. Chronic Health Hazard Assessments for Noncarcinogenic Effects**

### **\_I.A. Reference Dose for Chronic Oral Exposure (RfD)**

Substance Name — Fluorine (soluble fluoride)

CASRN — 7782-41-4

Primary Synonym — Fluoride

Last Revised — 06/01/1989

The oral Reference Dose (RfD) is based on the assumption that thresholds exist for certain toxic effects such as cellular necrosis. It is expressed in units of mg/kg-day. In general, the RfD is an estimate (with uncertainty spanning perhaps an order of magnitude) of a daily exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime. Please refer to the Background Document for an elaboration of these concepts. RfDs can also be derived for the noncarcinogenic health effects of substances that are also carcinogens. Therefore, it is essential to refer to other sources of information concerning the

carcinogenicity of this substance. If the U.S. EPA has evaluated this substance for potential human carcinogenicity, a summary of that evaluation will be contained in Section II of this file.

### \_\_\_I.A.1. Oral RfD Summary

Critical Effect	Experimental Doses*	UF	MF	RfD
Objectionable dental fluorosis, a cosmetic effect	NOAEL: 1 ppm (converted 0.06 mg/kg/day  LOAEL: 2 ppm	1	1	6E-2 mg/kg/day
Epidemiologic Study in Children				
Hodge, 1950, cited in Underwood, 1977				

\*Conversion Factors: see text

### \_\_\_I.A.2. Principal and Supporting Studies (Oral RfD)

Hodge, H.C. 1950. The concentration of fluorides in drinking water to give the point of minimum caries with maximum safety. J. Am. Dent. Assoc. 40: 436. Cited in: Underwood, E.J. 1977. Trace Elements in Human and Animal Nutrition. Academic Press, NY.

Fluoride-related compounds are used in the prevention of dental caries. Extensive human epidemiologic studies with large populations have been carried out over the last 40 years. The NOAEL (1 ppm) and LOAEL (2 ppm) in drinking water are defined within a narrow dose range.

Hodge (1950) studied children consuming fluoride in their drinking water. Fluoride levels of 0-14 ppm were investigated. Dental mottling was the parameter of interest. Fluoride levels of 2-10 ppm produced a linear dose- response curve (increasing mottling with increasing dose). Fluoride levels of 0.1-1.0 ppm produced no observable effect. An assumption of 20 kg bw and 1 L/day water consumption for children was used, since the children studied were 12-14 years old. It is further assumed that a 20-kg child consumes 0.01 mg of fluoride/kg bw/day in the diet (50 FR 20164). Thus, a total intake would be approximately 0.06 mg/kg/day.

### \_\_\_I.A.3. Uncertainty and Modifying Factors (Oral RfD)

UF — Uncertainty factors were not deemed necessary since the NOAEL is that of the critical effect (i.e., dental fluorosis) in a sensitive population of humans (i.e., children) for a length of exposure that encompasses both the critical effect and the sensitive population.

MF — None

### \_\_\_I.A.4. Additional Studies/Comments (Oral RfD)

Dental fluorosis results from excess exposure to fluoride during the age of calcification of the teeth (up to about 8 years of age for anterior teeth). Dental fluorosis in its mild form is characterized by white opaque areas covering 50% of a given tooth; in its severe form, dental fluorosis is characterized by brown to black stains and pitting (50 FR 20164). There is considerable controversy over whether objectionable dental fluorosis (moderate and severe) is a toxic and/or adverse health effect. However, the U.S. EPA has determined that objectionable dental fluorosis is a cosmetic effect

and not a toxic and/or adverse health effect (50 FR 47142). Numerous epidemiologic studies have been conducted in the U.S. concerning the relationship between dental fluorosis and fluoride levels in drinking water (50 FR 20164). Based on these studies, the NOAEL for objectionable dental fluorosis is approximately 1.0 ppm fluoride in drinking water. Assuming that a child weighs 20 kg, drinks 1.0 L of water/day and ingests fluoride at 0.01 mg/kg/day in the diet (50 FR 20164), a NOAEL of 1 ppm fluoride in drinking water corresponds to 0.06 mg/kg/day. Since data are available for the only susceptible population (children), an uncertainty factor of 1 is appropriate.

It has been estimated that the development of crippling skeletal fluorosis in man requires the consumption of 20 mg or more of fluoride/person/day over a 20-year period, i.e., 0.28 mg/kg/day (U.S. EPA, 1985). While the NOEL for crippling skeletal fluorosis in humans is unknown, a safe level of fluoride exposure can be determined. No cases of crippling skeletal fluorosis have been observed in the United States associated with the consumption of 2 L of water/day containing 4 ppm fluoride (50 FR 20614). Assuming a 70 kg adult ingests 0.01 mg fluoride/day in the diet and consumes 8 mg fluoride/day in drinking water (2 L/day containing 4 ppm fluoride), this would correspond to a total intake of 0.12 mg/kg/day. Thus, 0.12 mg fluoride/kg/day is a safe exposure level for this more severe endpoint in adults.

#### **\_\_I.A.5. Confidence in the Oral RfD**

Study — High  
Database — High  
RfD — High

Confidence in both the study and the database is high because the large number of studies conducted in children all support the chosen NOAEL. Confidence in the RfD is high because little uncertainty remains in the toxicity database.

#### **\_\_I.A.6. EPA Documentation and Review of the Oral RfD**

Source Document — U.S. EPA. 1985. Federal Register, Vol. 50, p. 20164, 47142.

ECAO-Cincinnati Internal Review, July 1985.

Other EPA Documentation — None

Agency Work Group Review — 08/05/1985, 02/05/1986, 02/26/1986

Verification Date — 02/26/1985

Screening-Level Literature Review Findings — A screening-level review conducted by an EPA contractor of the more recent toxicology literature pertinent to the RfD for Fluorine (soluble fluoride) conducted in November 2001 identified one or more significant new studies. IRIS users may request the references for those studies from the IRIS Hotline at [hotline.iris@epa.gov](mailto:hotline.iris@epa.gov) or (202)566-1676.

#### **\_\_I.A.7. EPA Contacts (Oral RfD)**

Please contact the IRIS Hotline for all questions concerning this assessment or IRIS, in general, at (202)566-1676 (phone), (202)566-1749 (FAX) or [hotline.iris@epa.gov](mailto:hotline.iris@epa.gov) (internet address).

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**\_I.B. Reference Concentration for Chronic Inhalation Exposure (RfC)**

Substance Name — Fluorine (soluble fluoride)

CASRN — 7782-41-4

Primary Synonym — Fluoride

Not available at this time.

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**\_II. Carcinogenicity Assessment for Lifetime Exposure**

Substance Name — Fluorine (soluble fluoride)

CASRN — 7782-41-4

Primary Synonym — Fluoride

This substance/agent has not undergone a complete evaluation and determination under US EPA's IRIS program for evidence of human carcinogenic potential.

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**\_III. [reserved]**

**\_IV. [reserved]**

**\_V. [reserved]**

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**\_VI. Bibliography**

Substance Name — Fluorine (soluble fluoride)

CASRN — 7782-41-4

Primary Synonym — Fluoride

Last Revised — 08/01/1989

**\_VI.A. Oral RfD References**

Hodge, H.C. 1950. The concentration of fluorides in drinking water to give the point of minimum caries with maximum safety. J. Am. Dent. Assoc. 40: 436.

Underwood, E.J. 1977. Trace elements in human and animal nutrition. Academic Press, New York. p. 347-369.

U.S. EPA. 1985. Federal Register. Vol. 50, p. 20164, 47142.

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**\_VI.B. Inhalation RfC References**

None

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**\_VI.C. Carcinogenicity Assessment References**

None

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**\_VII. Revision History**

Substance Name — Fluorine (soluble fluoride)

CASRN — 7782-41-4

Primary Synonym — Fluoride

<b>Date</b>	<b>Section</b>	<b>Description</b>
03/31/1987	I.A.6.	Documentation corrected
06/30/1988	I.A.7.	Contacts switched
04/01/1989	V.	Supplementary data on-line
06/01/1989	I.A.6.	Work group review dates corrected
08/01/1989	VI.	Bibliography on-line
01/01/1992	I.A.7.	Secondary contact changed
01/01/1992	IV.	Regulatory actions updated
08/01/1995	I.A.6.	EPA's RfD/RfC and CRAVE workgroups were discontinued in May, 1995. Chemical substance reviews that were not completed by September 1995 were taken out of IRIS review. The IRIS Pilot Program replaced the workgroup functions beginning in September, 1995.
04/01/1997	III., IV., V.	Drinking Water Health Advisories, EPA Regulatory Actions, and Supplementary Data were removed from IRIS on or before April 1997. IRIS users were directed to the appropriate EPA Program Offices for this information.
12/03/2002	I.A.6.	Screening-Level Literature Review Findings message has been added.

**\_VIII. Synonyms**

Substance Name — Fluorine (soluble fluoride)

CASRN — 7782-41-4

Primary Synonym — Fluoride

Last Revised — 01/31/1987

7782-41-4  
 Fluoride  
 Fluoride ion  
 Fluoride ion(1-)  
 Fluorine  
 Fluorine, ion  
 Hydrofluoric acid, ion(1-)  
 Perfluoride

**California Environmental Protection Agency**  
**Office of Environmental Health Hazard Assessment**  
**(OEHHA)**

## CHRONIC TOXICITY SUMMARY

**FLUORIDES *including*  
HYDROGEN FLUORIDE**

*(hydrofluoric acid (aqueous solution); hydrogen fluoride (as a gas);  
fluoride salts (particulates or in solution))*

**CAS Registry Number: 7664-39-3**

**I. Chronic Toxicity Summary**

<i>Inhalation reference exposure level</i>	<b>14 <math>\mu\text{g HF/m}^3</math> (17 ppb); 13 <math>\mu\text{g F/m}^3</math></b>
<i>Oral reference exposure level</i>	<b>0.04 mg/kg-day</b>
<i>Critical effect(s)</i>	Skeletal fluorosis
<i>Hazard index target(s)</i>	Bone and teeth; respiratory system

**II. Physical and Chemical Properties of HF (HSDB, 1995; CRC, 1994)**

<i>Description</i>	Colorless gas (HF), or as particulates
<i>Molecular formula</i>	HF
<i>Molecular weight</i>	20.0 g/mol
<i>Density</i>	0.83 g/L @ 25°C
<i>Boiling point</i>	19.54°C
<i>Melting point</i>	-83.1°C
<i>Vapor pressure</i>	400 torr @ 2.5°C
<i>Solubility</i>	Soluble in water and alcohol
<i>Conversion factor</i>	1 ppm = 0.83 mg/m <sup>3</sup> @ 25°C

**III. Major Uses or Sources**

Hydrofluoric acid (HF) is a colorless, fuming liquid with a sharp, penetrating odor (Fairhall, 1949). This acid is used in the glass etching, electronic, microelectronic, and petroleum refining and chemical industries (Bertolini, 1992). These industries use HF in the manufacture of such things as computer chips (an important industry in California), phosphate fertilizer, metal cans, plastics, refrigerant chemicals (fluorocarbons), inorganic chemicals, soaps and detergents, high-octane gasoline, and aircraft parts (Wohlslagel *et al.*, 1976; Wing *et al.*, 1991). HF is also used in commercial rust removal products. Another high profile use of HF in California has been as a catalyst in petroleum alkylation to make high-octane gasoline. HF is also a product of combustion of any F containing materials; as such, it is produced during structural fires.

Sodium fluoride has been used as a topical and ingested anticaries agent due to its ability to harden tooth enamel during development. The optimal doses are not well established, but have been suggested to be approximately 0.080 mg/kg/day for 7 to 9 month old infants decreasing to 0.034 mg/kg/day at 13 years of age (Shulman *et al.*, 1995). A dose of 1.0 mg F ingested per day was reported to reduce dental caries 43%, and to be associated with a greatly increased rate of minor tooth mottling which caused no esthetic damage (Van Nieuwenhuysen and D'Hoore, 1992). Many communities in California routinely add fluoride to the drinking water. The California Department of Health Services has adopted regulations that establish standards for the addition of F (CDHS, 2002). Any public water system using fluoridation must maintain F levels within the range established for its climate. The ranges vary according to average air temperatures, since people in cooler climates typically drink less water per day than people in warmer climates. Thus, in cooler areas, more F is required to provide the same dental benefit. For 2001-2002, F levels in San Francisco municipal water ranged from 0.65 to 1.1 ppm, while in Los Angeles the range was 0.44 to 0.83 ppm (CDHS, 2002).

The annual statewide industrial emissions from facilities reporting under the Air Toxics Hot Spots Act in California based on the most recent inventory were estimated to be 48,221 pounds of fluorides and compounds, and 62,670 pounds of hydrogen fluoride (CARB, 2000).

#### IV. Effects of Human Exposure

The chronic exposure to fluorides, including HF, and the incidence of minimal osseous changes were studied in the workplace by Derryberry *et al.* (1963). In this study, the 8-hour time-weighted average fluoride exposure was calculated for the employment period of each of 74 male workers (30 Caucasian, 44 African-American). The overall average fluoride exposure in these workers was measured as a time-weighted average of 2.81 mg F/m<sup>3</sup>. In comparison, the 17 workers within this group who had evidence of minimally increased bone density had an average fluoride exposure of 3.38 mg F/m<sup>3</sup>. The other workers were exposed to an average measured concentration of 2.64 mg F/m<sup>3</sup>. In addition, urinary fluoride levels were greater in the 17 individuals with greatest exposure compared to the remaining 57 workers (average = 5.18 mg F/L vs. 4.53 mg F/L). No differences between exposed and unexposed individuals were observed for gastrointestinal, cardiovascular, or hematologic systems, or in a physical exam. A statistically significant ( $p < 0.05$ ) increase in the incidence of acute respiratory disease as determined from past medical histories was observed in fluoride-exposed individuals (19/74 vs. 8/67 in controls); radiographic examination revealed a difference of lesser significance ( $p < 0.10$ ) for pulmonary changes (11/74 vs. 4/67). No pulmonary function tests were reported.

An analysis of these data by OEHHA (see derivation section below) showed a statistically significant relationship between air fluoride and the minimal bone density increases. The raw data from the Derryberry *et al.* (1963) study are shown in Table 1. A Pearson correlation matrix of the variables measured in the Derryberry *et al.* study indicated that bone density was best correlated with mean air fluoride level, and to a lesser extent with the age of the individual. A log-logistic regression using the log air fluoride concentration as the independent variable showed a significant ( $p < 0.033$ ) relationship between increasing air fluoride concentrations and probability of skeletal fluorosis. The parameters for the regression were  $\beta_0 = -2.3468$  (std. error

= 0.6462), and  $\beta_1 = 1.1736$  (std error = 0.5508); the odds ratio for the occurrence of skeletal fluorosis was 3.24. Years of exposure were not correlated with increased bone-density, according to a Pearson Correlation procedure ( $p = 0.63$ ). Bone density has been shown to decrease with age after the age of 40 among normal, non-fluoride-exposed males (Runge *et al.*, 1979). As expected, age was very highly correlated with years exposed ( $p < 0.00001$ ). Therefore including years exposed in the dose-metric likely introduces a confounding variable (see discussion in Section VI.). In addition, Runge *et al.* (1979) found no association between years exposed and mineral content or bone width among 245 aluminum smelter workers exposed to 2.75 or 3.2 mg F/m<sup>3</sup>. For these reasons, years exposed were not used as the dose-metric for bone-density in this analysis.

Although a threshold was not readily apparent from the logistic regression model, grouping the 74 individuals by air fluoride exposure level into quintiles of 15 each with one group of 14, allowed for a comparison of group mean responses (Table 2). The 14 employees exposed to a time-weighted average concentration of 1.07 mg F/m<sup>3</sup> did not exhibit bone density changes. An analysis of the grouped responses using a binomial distribution showed a probability of  $p = 0.008$  for obtaining 4/15 increased bone density observations in the 2.34 mg/m<sup>3</sup> group, and a probability of  $p = 0.047$  for obtaining 3/15 positive observations in the 1.89 mg F/m<sup>3</sup> group. The 1.89 mg F/m<sup>3</sup> group was therefore considered a LOAEL for chronic skeletal fluorosis, and the 1.07 mg/m<sup>3</sup> group was considered a NOAEL. The above probabilities assume that a chance occurrence is, at most, 1 in 18 of skeletal fluorosis or other cause leading to an abnormally dense x-ray in the general population. Since osteosclerosis is a rare condition that is associated with several types of hematological malignancies such as myeloid leukemia, the actual incidence of conditions leading to osteosclerosis is far below 1 in 18. This lends strong support to the consideration of 1.89 mg/m<sup>3</sup> as a LOAEL for skeletal fluorosis.

**Table 1.** Data on worker exposure to fluoride from Derryberry *et al.* (1963)

Observation #	ID	Bone density	Years exposed	Urine max F (mg F/L)	Urine min F (mg F/L)	Mean urinary F (mg F/L)	Age (years)	Air fluoride (mg/m <sup>3</sup> )	OEHHA exposure grouping
1	119	normal	18.5	43.0	2.8	14.7	58	8.16	5
2	0	normal	8.4	24.7	5.3	9.6	42	3.19	4
3	41	normal	15.8	35.0	2.5	9.1	35	3.29	4
4	147	minimally increased	9.6	17.1	2.1	8.9	60	5.98	5
5	120	normal	16.7	20.5	3.4	8.6	55	3.29	4
6	54	minimally increased	17.0	44.0	4.0	8.6	56	7.73	5
7	148	normal	10.5	14.0	3.7	8.4	41	8.32	5
8	314	minimally increased	14.4	22.7	1.7	8.3	56	3.24	4
9	29	normal	17.0	18.2	2.5	7.7	50	2.60	3
10	14	normal	14.3	19.4	2.1	6.3	46	2.33	3
11	115	normal	15.2	18.5	1.4	6.3	38	2.11	3
12	10	minimally increased	10.3	22.0	2.3	6.1	38	2.72	4
13	4	minimally increased	7.1	7.7	2.0	5.7	54	3.22	4
14	51	normal	14.9	42.0	0.8	5.6	46	3.18	4
15	94	normal	16.2	15.4	3.3	5.5	56	5.12	5
16	217	normal	7.1	7.1	2.6	5.3	42	2.54	3
17	281	minimally increased	7.8	8.6	1.1	5.2	36	3.79	4
18	114	normal	10.4	13.2	2.8	5.2	38	7.66	5
19	7	normal	7.8	9.1	2.2	5.1	43	2.91	4
20	308	normal	11.9	6.7	3.5	5.1	44	1.89	2
21	301	minimally increased	15.2	9.5	2.5	5	36	2.56	3
22	72	normal	25.9	13.7	2.1	4.9	55	5.55	5
23	241	minimally increased	17.0	10.0	1.9	4.9	46	4.48	5
24	345	normal	10.5	7.1	2.0	4.9	47	1.49	1
25	26	normal	16.4	12.2	0.5	4.7	39	2.41	3
26	231	minimally increased	16.3	8.2	2.8	4.6	62	1.88	2
27	2	normal	24.7	8.9	2.1	4.6	46	3.53	4
28	295	normal	14.5	10.7	0.9	4.6	44	2.07	3
29	1	normal	8.9	5.9	2.4	4.5	30	1.92	2
30	203	minimally increased	18.2	6.8	1.6	4.4	43	2.66	3
31	63	normal	16.2	7.4	2.0	4.3	55	3.90	5
32	5	normal	4.5	11.5	1.9	4.3	43	1.12	1
33	460	normal	12.5	6.1	1.6	4.3	60	2.13	3

Observation #	ID	Bone density	Years exposed	Urine max F (mg F/L)	Urine min F (mg F/L)	Mean urinary F (mg F/L)	Age (years)	Air fluoride (mg F/m <sup>3</sup> )	OEHHA exposure grouping
34	249	minimally increased	15.0	8.0	1.8	4.3	39	2.95	4
35	3	normal	7.6	14.5	2.1	4.3	31	3.90	5
36	322	normal	9.3	6.3	2.0	4.3	35	4.23	5
37	8	minimally increased	24.8	5.9	3.0	4.2	55	2.50	3
38	3	normal	15.2	12.2	2.1	4.2	42	1.14	1
39	309	normal	12.1	5.5	2.4	4.1	42	1.94	2
40	36	normal	9.1	13.2	0.8	4.1	33	1.94	2
41	45	normal	11.3	14.0	2.2	4.1	33	3.84	4
42	70	normal	17.9	8.0	1.0	3.9	44	4.00	5
43	250	minimally increased	9.8	6.7	1.5	3.9	35	1.78	2
44	38	normal	16.9	5.9	1.0	3.9	35	2.10	3
45	200	minimally increased	14.0	7.0	2.8	3.8	66	3.92	5
46	183	normal	9.8	4.9	2.2	3.7	48	1.67	2
47	32	normal	12.5	6.6	0.9	3.7	47	2.21	3
48	25	normal	13.6	5.5	1.5	3.7	44	1.86	2
49	21	normal	13.9	9.1	0.4	3.7	50	1.98	2
50	304	normal	13.4	5.0	2.1	3.7	36	2.62	3
51	132	normal	10.9	5.1	2.4	3.6	39	1.81	2
52	6	minimally increased	8.4	4.8	0.9	3.6	35	3.85	5
53	244	normal	16.6	7.1	1.4	3.6	62	2.87	4
54	30	normal	14.0	14.0	0.9	3.6	43	1.56	1
55	88	minimally increased	15.5	4.9	1.7	3.5	66	2.06	2
56	227	normal	16.6	5.7	1.0	3.5	41	1.18	1
57	271	normal	17.7	4.1	3.0	3.4	60	1.82	2
58	19	normal	13.9	10.0	1.8	3.4	41	1.32	1
59	190	normal	9.3	7.7	1.9	3.3	36	1.95	2
60	258	normal	17.8	5.6	1.6	3.2	58	0.87	1
61	278	normal	10.0	7.0	0.3	3.2	34	1.93	2
62	331	normal	12.8	5.6	1.5	3.1	34	1.23	1
63	91	normal	25.3	7.9	0.2	3.1	63	3.49	4
64	342	normal	18.5	6.0	1.3	3	40	2.73	4
65	261	normal	18.1	5.3	0.9	2.9	52	4.41	5
66	291	normal	13.5	4.5	1.5	2.8	34	2.14	3
67	149	normal	11.3	4.5	2.1	2.8	34	0.76	1
68	2	normal	24.7	4.5	1.5	2.7	51	1.15	1
69	4	normal	16.8	5.7	1.2	2.7	56	0.71	1
70	109	normal	8.3	5.1	0.8	2.7	36	1.89	2
71	242	normal	18.1	4.1	1.2	2.5	49	1.26	1

Observation #	ID	Bone density	Years exposed	Urine max F (mg F/L)	Urine min F (mg F/L)	Mean urinary F (mg F/L)	Age (years)	Air fluoride (mg F/m <sup>3</sup> )	OEHHA exposure grouping
72	179	normal	18.9	3.9	1.0	2.4	46	0.50	1
73	325	minimally increased	11.8	5.0	0.5	2.2	40	2.10	3
74	159	normal	18.9	5.0	0.7	2.1	45	0.67	1

**Table 2.** Grouped mean exposure

Exposure group	Mean age ± SD	Mean air level mg F/m <sup>3</sup> ± SD	Number of responses	Probability of difference from group 1*
1	45.0 ± 7.0	1.07 ± 0.32	0/14**	Not Applicable
2	43.9 ± 11.2	1.89 ± 0.09	3/15***	0.047
3	43.0 ± 7.6	2.34 ± 0.23	4/15	0.008
4	45.9 ± 9.8	3.22 ± 0.35	5/15	0.001
5	48.5 ± 10.7	5.41 ± 1.72	5/15	0.001

\* Probability of obtaining result assuming a chance occurrence of abnormally dense x-ray of, at most, 1 in 18 individuals, using a binomial distribution (Systat for Windows v.5.05, 1994).

\*\* NOAEL

\*\*\* LOAEL ( $p < 0.05$ )

Largent *et al.* (1951) found a significant increase in bone density in the lower thoracic spine, with calcification extending into the lateral ligaments of 3 workers exposed for 17, 14, and 10 years to HF (concentrations not estimated).

A group of 74 men, who were occupationally exposed to unspecified concentrations of HF for an average of 2.7 years, reported occasions of upper respiratory irritation (Evans, 1940). Repeated chest X-rays over a 5-year period did not reveal any visible evidence of lung changes. The death rate of these workers from pneumonia and other pulmonary infections was the same as that of unexposed plant employees.

There are various reports of asthma and related respiratory effects in pot room workers in the primary aluminum smelting industry. Exposure to fluoride (among other materials such as sulfur trioxide and polycyclic aromatic hydrocarbons) was measured as a possible index of exposures related to this condition (Seixas *et al.*, 2000). However multiple exposures to respiratory irritants and other compounds which may affect immune response appear to be common in this work environment making it difficult to quantitatively relate the respiratory symptoms to inhaled HF or fluorides.

Workers in a warehouse containing HF retorts experienced transitory hyperemia of the skin on their face and hands (Dale and McCauley, 1948). Twenty four of the 40 workers had definite changes in the thickness and number of trabeculae in the upper and lower jaw.

Examinations of 107 pot room workers in two aluminum plants with airborne fluorides revealed 22 subjects with limited motion of the dorsolumbar spine, compared with none in a control group of 108 workers with no history of exposure to fluorides (Kaltreider *et al.*, 1972). In one plant, 76 of 79 workers had increased bone density as measured by roentgenogram, with diagnosis of slight to moderate fluorosis. Moderate and marked fluorosis was observed after 15 years employment. The 8-hour time-weighted average fluoride content in these workplaces was 2.4 to 6.0 mg/m<sup>3</sup>. Balazova (1971) measured significant fluoride uptake and distribution in children living near an aluminum smelter but reported no incidence of fluorosis.

No studies regarding the chronic irritant or respiratory effects of pure HF exposure in humans were available.

Fluoride ion produced by various fluorocarbons has been associated with toxicity to human kidney collecting duct cells leading to sodium and water disturbances (Cittanova *et al.*, 1996).

Oral supplementation of greater than 0.1 mg F/kg body weight daily has been associated with enamel fluorosis in young children (Forsman, 1977).

The Agency for Toxic Substances and Disease Registry (ATSDR, 2001) recently reviewed fluorides since they are found at hazardous waste sites which are candidates for remediation. The focus of this document was on oral exposure studies as that is the main concern for waste site remediation.

## V. Effects of Chronic Exposures to Animals

Stokinger (1949) studied the subchronic effects of HF inhalation in several animal species. Animals (dogs, rabbits, rats, guinea pigs, and mice; 1 to 6 per group) were exposed to 0, 7.2 mg/m<sup>3</sup>, or 25.1 mg/m<sup>3</sup> 6 hours/day, 6 days/week, for 30 days. Mortality, body weight, blood coagulation mechanisms, and gross pathology were measured. Exposure to 25.1 mg/m<sup>3</sup> HF for 30 days resulted in degenerative testicular changes and ulceration of the scrotum in all 4 dogs and hemorrhage and edema in the lungs of 3 dogs. Pulmonary hemorrhage was also seen in 20 of 30 rats, and 4 of 10 rabbits. Renal cortical degeneration was observed in 27 of 30 rats. All of the rats and mice at the 25.1 mg/m<sup>3</sup> concentration died. No mortality was observed in the other species tested. Blood fibrinogen levels were significantly increased in dogs, rats, and rabbits exposed to 25.1 mg/m<sup>3</sup>. Exposure to 7.2 mg/m<sup>3</sup> HF resulted in pulmonary hemorrhage in 1 out of 5 dogs. No other significant effects were observed at the lower concentration.

Shusheela and Kumar (1991) administered male rabbits 10 mg NaF/kg-bw per day orally for 18 months (7 rabbits) or 29 months (3 rabbits), then studied the testis, epididymis, and vas deferens microscopically. After 29 months of F administration, the spermatogenic cells in the seminiferous tubules had degenerated and lacked spermatozoa. After both 18 and 29 months, cilia were lost from the epithelial cells lining the ductuli efferentes of the caput epididymidis. Stereocilia on the epithelial cells lining the vas deferens were also lost. In some regions of epithelia, the cell boundaries were not clear, and even appeared to be peeled off. Mucus droplets were abundant in the vas deferens of controls, but none were present in F treated rabbits.

Spermatogenesis ceased sometime between 18 and 29 months. The authors concluded that ingestion of a high concentration of F has adverse effects (including infertility) on the male rabbit reproductive system.

Ghosh *et al.* (2002) investigated the effects of NaF on steroidogenic and gametogenic activities in rat testes. Male Wistar rats were given 20 mg/kg/day NaF by gavage for 29 days. F treatment resulted in significantly lower relative wet weight of the testis, prostate, and seminal vesicle, decreased testicular delta(5),3beta-hydroxysteroid dehydrogenase (HSD) and 17beta-HSD activities, and significant lowering in plasma levels of testosterone. Epididymal sperm count was decreased significantly in F-treated rabbits and there were fewer mature luminal spermatozoa. Indicators of oxidative stress due to F included increased conjugated dienes in the testis, epididymis, and epididymal sperm pellet, and decreases of peroxidase and catalase in the sperm pellet. Thus F, at a dose encountered in drinking water in contaminated areas (at least of India), exerts an adverse effect on the male rat reproductive system. These effects on rats and rabbits (and dogs; see above) may be relevant to anecdotal reports of reproductive system malfunction in human chronic fluorosis.

Parameter	Control (n=6)	NaF (n=6)	p value
Body weight, final (g)	127.00±3.75	122.00±5.10	
Testis, relative weight (%)	1.522±0.034	1.923±0.081	< 0.05
Prostate, relative weight	0.297±0.043	0.148±0.014	< 0.05
Seminal vesicles, rel. weight	0.448±0.025	0.174±0.027	< 0.05
Testicular delta(5),3beta HSD	~28 <sup>a</sup>	~24 <sup>a</sup>	< 0.05 <sup>b</sup>
Testicular 17betaHSD	~29 <sup>a</sup>	~24 <sup>a</sup>	< 0.05 <sup>b</sup>
Plasma testosterone (ng/ml)	~2 <sup>a</sup>	~1 <sup>a</sup>	< 0.05 <sup>b</sup>
Epididymal sperm count (10 <sup>6</sup> /ml)	7.02±0.17	3.70±0.57	< 0.05

<sup>a</sup> approximate values based on reading Figures 2 and 3 of paper; <sup>b</sup> p values of authors

Long *et al.* (2002) used ligand binding and Western blotting to study neuronal nicotinic acetylcholine receptors (nAChRs) in the brains of male and female Wistar rats ingesting 0.5 ppm (controls), 30 ppm, or 100 ppm F in their drinking water for 7 months. (All received 4 ppm F in their diet.) The brains of rats exposed to 100 ppm had significantly less binding sites for [<sup>3</sup>H]epibatidine, an analgesic agonist, but no change occurred at 30 ppm. Binding sites for [<sup>125</sup>I]alpha-bungarotoxin, a competitive antagonist, were significantly decreased in the brains of rats exposed to both levels. The brain levels of the nAChR alpha4 subunit protein was significantly lowered by exposure to 100 ppm F. Alpha7 subunit protein was significantly decreased by both levels of F. No significant changes were seen in levels of the beta2 subunit protein. These nicotinic receptors have roles in learning and memory. Some of the effects were also seen in rat PC cells cultured for 48 h in up to 50 ppm F (Chen *et al.*, 2003). The results may help to explain anecdotal reports of nervous system symptoms in human chronic fluorosis (Waldbott, 1978).

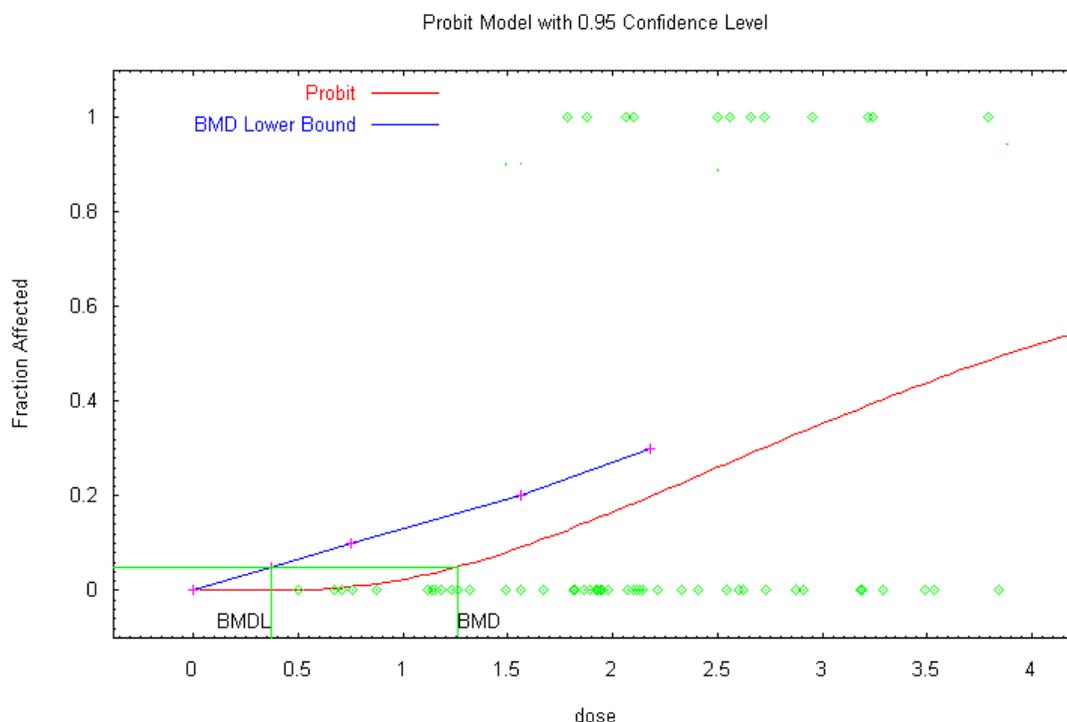
NTP (1990) exposed F344/N rats and B6C3F1 mice of both sexes for two years to 0, 25, 100, and 175 ppm sodium fluoride (NaF) in their drinking water. NaF caused a dose dependent whitish discoloration of the teeth in both rats and mice. Male rats had an increased incidence of

tooth deformities and attrition. NaF increased the dysplasia of dentine in both rats and mice. At the highest dose (175 ppm), osteosclerosis of long bones was increased in female rats. There was also equivocal evidence of carcinogenic activity of NaF in male rats based on four osteosarcomas in dosed animals (Bucher *et al.*, 1991). Other organ systems showed no dose-dependent effects.

## VI. Derivation of Chronic Reference Exposure Level (REL)

<i>Study</i>	Derryberry <i>et al.</i> (1963)
<i>Study population</i>	74 fertilizer plant workers (67 unexposed control subjects)
<i>Exposure method</i>	Occupational
<i>Critical effects</i>	Increased bone density (skeletal fluorosis)
<i>LOAEL</i>	1.89 mg F/m <sup>3</sup> (1.98 mg HF/m <sup>3</sup> )
<i>NOAEL</i>	1.07 mg F/m <sup>3</sup> (1.13 mg HF/m <sup>3</sup> )
<i>BMC<sub>05</sub></i>	0.37 mg F/m <sup>3</sup> (0.39 mg HF/m <sup>3</sup> )
<i>Exposure continuity</i>	8 hours/day, 5 days/week
<i>Exposure duration</i>	14.1 years (range = 4.5 to 25.9 years)
<i>Average exposure concentration</i>	0.14 mg HF/m <sup>3</sup> (0.39 x 10/20 x 5/7) or 0.13 mg F/m <sup>3</sup> (0.37 x 10/20 x 5/7)
<i>Human equivalent concentration</i>	0.14 mg HF/m <sup>3</sup> or 0.13 mg F/m <sup>3</sup>
<i>LOAEL uncertainty factor</i>	1
<i>Subchronic uncertainty factor</i>	1
<i>Interspecies uncertainty factor</i>	1
<i>Intraspecies uncertainty factor</i>	10
<i>Cumulative uncertainty factor</i>	10
<i>Inhalation reference exposure level for F or HF</i>	0.013 mg F/m <sup>3</sup> (13 µg /m <sup>3</sup> ; 0.016 ppm; 16 ppb) or 0.014 mg HF/m <sup>3</sup> (14 µg /m <sup>3</sup> ; 0.017 ppm; 17 ppb)

OEHHA's analysis of the data in Derryberry *et al.* (1963) indicates a LOAEL of 1.89 mg/m<sup>3</sup>, and a NOAEL of 1.07 mg/m<sup>3</sup>. A benchmark concentration (BMC<sub>05</sub>) of 0.37 mg/m<sup>3</sup> was derived by fitting the probit model to the log dose in the U.S. EPA's BMDS (version 1.3) software, for the individual mean air exposure data and incidence data in Table 1 above. Individuals in the highest dose group (group 5 in Table 2) were not included in the model, since none of the models fit this range of exposures well. Several other models produced reasonable fits to the data, but the probit model with log-transformed dose was selected since it produced a good fit not only by statistical criteria ( $p = 0.71$ ) but also, as determined by inspection, it fit the low dose curve shape better than other models. This model also has the advantage of biological plausibility, in that, since lower doses of fluoride have a beneficial or nutritional effect, a threshold type of response for adverse effects is clearly expected. A graphical representation of the fit is shown in Figure 1. Adjusting for exposure continuity and utilizing an intraspecies uncertainty factor of 10 (UF<sub>H</sub>) results in a REL for F of 13 µg/m<sup>3</sup>.

**Figure 1.**

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Changes in bone density in association with fluoride exposure have been observed in several studies, and appear to be the most sensitive health effect for chronic exposure. The minimally increased bone density in the Derryberry study was significantly ( $p < 0.04$ , Fisher's Exact Test) associated with "other osseous changes," which reportedly included disc lesions, arthritis, and calcified ligaments. An increase in pulmonary changes in the workers with high bone density was marginally significant ( $p < 0.06$ ) and included emphysema, fibrosis, and healed tuberculous lesions. Although dental fluorosis is a sensitive endpoint in many fluoride studies, the dental examinations of exposed workers in this study showed healthier teeth than in controls. The increased bone density observed was considered as indicating that adverse effects had occurred, based on the adverse effects associated with the increased density in the study, and on other research showing that increased bone density caused by fluoride exposure (75 mg sodium fluoride per day for four years) also leads to decreased bone strength and increased fragility (Riggs *et al.*, 1990). Symptoms of abdominal pain, backache, restricted joint movement, and respiratory symptoms have been associated with airborne fluoride exposures and bone density increases in industrial settings (Zhiliang *et al.*, 1987).

The absorption of particulate and gaseous fluorides is reported to be similar (Collings *et al.*, 1951). Therefore, it would be expected that the effects on bone density would be similar regardless of the form of fluoride.

As noted in the study description, Derryberry *et al.* (1963) did not find a good correlation between years of exposure to fluoride and bone density change. OEHHA reexamined the original individual data and confirmed that the presence of bone density changes showed a better correlation with mean air fluoride concentration than with years of exposure, or with the product of the individual values of mean air fluoride concentration and years of exposure. However, the product of exposure concentration and time did show a consistent pattern of cumulative incidence suggesting a dose-response relationship for this parameter. An attempt to derive a benchmark value by fitting the probit model to the log of (exposure duration\*concentration) and response (presence or absence of bone density change) did not result in an acceptable fit, so a BMDL<sub>05</sub> could not be reported. However a maximum likelihood estimate of the benchmark (BMD<sub>05</sub>) was found to be 6.04 (mg F\*years/m<sup>3</sup>), with exclusion of the three highest values that appeared to be outliers to the main distribution. If this value is divided by the mean exposure duration for the data set of 14.1 years, a benchmark exposure concentration of 0.43 mg F/m<sup>3</sup> is obtained. While this value is evidently less reliable than that obtained by fitting the mean exposure concentration, it is consistent with it, suggesting that, although other confounding factors related to age or duration prevent the demonstration of a relationship between the exposure/time integral and response in this data set, such a relationship probably does exist, as would be expected.

## VII. Data Strengths and Limitations for Development of the REL

The major strengths of the key study for fluoride are the observation of health effects in a large group of workers exposed over many years, the availability of individual exposure estimates for each worker, and the identification of a NOAEL. The primary uncertainty in the study is the lack of a comprehensive health effects examination. Another source for concern is the potentially greater susceptibility of children to the effects of inhaled fluorides, considering the rapid bone growth in early years.

### Derivation of Chronic Oral REL

In addition to being inhaled, airborne fluoride salts in particulate form can settle onto crops and soil and enter the body by ingestion. Thus an oral chronic reference exposure level (REL) for fluoride is also required in order to conduct a health risk assessment under the Air Toxics Hot Spots Act. California has developed a Public Health Goal (PHG) of 1 ppm (1,000 ppb) fluoride in drinking water (OEHHA, 1997). This level is intended to be an approximate year-round average. Thus it has properties similar to a chronic oral REL. (The PHG assumed that drinking water was the only source of fluoride since it was based on comparing communities with and without added fluoridation.)

<i>Study</i>	Dean, 1942; U.S. Public Health Service, 1991; National Research Council, 1993
<i>Study population</i>	Inhabitants of several U.S. cities
<i>Exposure method</i>	Drinking water
<i>Critical effects</i>	Dental fluorosis
<i>LOAEL</i>	2 ppm
<i>NOAEL</i>	1 ppm = 0.04 mg/kg-day*
<i>Exposure continuity</i>	Continuous
<i>Exposure duration</i>	Long-term
<i>Average experimental exposure</i>	1 ppm = 0.04 mg/kg-day
<i>LOAEL uncertainty factor</i>	1
<i>Subchronic uncertainty factor</i>	1
<i>Interspecies uncertainty factor</i>	1
<i>Intraspecies uncertainty factor</i>	1 (studies included children)
<i>Cumulative uncertainty factor</i>	1
<i>Oral reference exposure level</i>	0.04 mg/kg-day

\* based on the assumption that an 18 kg child drinks 720 ml of water per day (OEHHA, 2000).

The PHG is based on a no-observed adverse-effect-level (NOAEL) of 1 mg/L for dental fluorosis in children (equivalent to 720 µg/day from drinking water for an 18 kg child drinking 40 ml/kg body weight/day of water). Moderate to severe dental fluorosis is rare when the drinking water fluoride level is near 1 mg/L, but begins to become significant at concentrations close to 2 mg/L. Since the study involved long term exposure to humans including children, a sensitive population, the cumulative uncertainty factor was 1. If one were to do a route-to-route extrapolation from this oral REL using the specific parameters for an 18 kg child breathing 4.2 m<sup>3</sup>/day, an equivalent inhalation REL would be about 170 µg/m<sup>3</sup>. Thus, the inhalation REL of 13 µg/m<sup>3</sup> based on the adult occupational data is likely to be protective of children.

### VIII. Potential for Differential Impacts on Children's Health

The critical effect for inhalation exposures is skeletal fluorosis. Since infants' and children's skeletons are developing, they may be more sensitive to this effect. This applies with particular importance to the teeth, and it is established that excessive exposure to fluoride during the period of tooth development in infancy and childhood causes dental fluorosis (Dean, 1942; U.S. Public Health Service, 1991; NRC, 1993). The oral REL and the California PHG for fluoride in drinking water are based on dental fluorosis. Although the inhalation chronic REL proposed is based on a study in adults, the inhalation chronic REL (see section VI) is lower than that implied by the oral REL and PHG. Since the oral REL and PHG are based on exposures throughout life, including the pre-natal period, infancy, and childhood, it is reasonable to conclude that the proposed inhalation REL is generally protective of infants and children, barring some unknown difference in toxicity between the two routes of exposure. The ratio of the intake at the PHG level in drinking water is closer to the effect level than the default intraspecies uncertainty factor of 10; this is to be expected since children are a sensitive subpopulation for the dental fluorosis effect.

Extensive interindividual variation in total fluoride intake ( $930.7 \pm 391.5 \mu\text{g/day}$ ) was recently documented for a small group ( $n = 11$ ) of healthy German children ages 3 to 6 years (Haftenberger *et al.*, 2001). Similar interindividual variation has also been reported for slightly younger children in Connersville ( $n = 14$ ) and Indianapolis, Indiana ( $n = 29$ ) and in San Juan, Puerto Rico ( $n = 11$ ) (Rojas-Sanchez *et al.*, 1999). Consideration should therefore be given to populations with exceptionally high fluoride intake due to locally elevated concentrations in drinking water, since some of these populations are already close to adverse effect levels of fluoride intake, and certain individuals in California experience dental fluorosis. For these individuals, even exposure to fluorides at the oral and/or inhalation RELs, which are acceptable in isolation, might be deleterious. The table below compares the data of Haftenberger *et al.* (2001) with recent estimates of F intake ranges in California (OEHHA, 1997).

Fluoride Intake (mg/day)

F in drinking water (mg/L)	F from drinking water	F from food	F from toothpaste	F from mouthwash	F from a supplement	Total F
Children (OEHHA)						
<0.3	0.1 - 0.3	0.1 - 0.5	0.2 - 1.2	0.1 - 0.5	0.5	1.0 - 3.0
0.7 - 1.2	0.7 - 1.2		0.2 - 1.2	0.1 - 0.5	0	1.1 - 4.6
Haftenberger						
0.25	(see food)	0.20±0.12	0.27±0.18	No data	0 - 1.0	0.93±0.39
Adults (OEHHA)						
<0.3	0.2 - 0.6	0.3 - 1.0	0.02 - 0.15	0.2 - 1.0	0	0.7 - 2.8
0.7 - 1.2	1.4 - 2.4	0.3 - 3.4	0.02 - 0.15	0.2 - 1.0	0	1.9 - 7.0

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**Acute Exposure Guideline Level  
(AEGLe)**

## 5

# Fluorine<sup>1</sup>

## Acute Exposure Guideline Levels

### PREFACE

Under the authority of the Federal Advisory Committee Act (FACA) P.L. 92-463 of 1972, the National Advisory Committee for Acute Exposure Guideline Levels for Hazardous Substances (NAC/AEGL Committee) has been established to identify, review and interpret relevant toxicologic and other scientific data and develop AEGLs for high priority, acutely toxic chemicals.

AEGLs represent threshold exposure limits for the general public and are applicable to emergency exposure periods ranging from 10 mins (min) to 8 hours (h). Three levels—AEGL-1, AEGL-2 and AEGL-3—are developed for each of five exposure periods (10 and 30 min, 1 h, 4 h, and 8 h) and are distinguished by varying degrees of severity of toxic effects. The three AEGLs are defined as follows:

AEGL-1 is the airborne concentration (expressed as parts per million or milligrams per cubic meter [ppm or mg/m<sup>3</sup>]) of a substance above which it is predicted that the general population, including susceptible individuals, could experience notable discomfort, irritation, or certain asymptomatic, non-sensory

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<sup>1</sup>This document was prepared by the AEGL Development Team composed of Sylvia Talmage (Oak Ridge National Laboratory) and Chemical Manager Ernest V. Falke (National Advisory Committee [NAC] on Acute Exposure Guideline Levels for Hazardous Substances). The NAC reviewed and revised the document and AEGLs as deemed necessary. Both the document and the AEGL values were then reviewed by the National Research Council (NRC) Subcommittee on Acute Exposure Guideline Levels. The NRC subcommittee concludes that the AEGLs developed in this document are scientifically valid conclusions based on the data reviewed by the NRC and are consistent with the NRC guidelines reports (NRC 1993; NRC 2001).

effects. However, the effects are not disabling and are transient and reversible upon cessation of exposure.

AEGL-2 is the airborne concentration (expressed as ppm or mg/m<sup>3</sup>) of a substance above which it is predicted that the general population, including susceptible individuals, could experience irreversible or other serious, long-lasting adverse health effects or an impaired ability to escape.

AEGL-3 is the airborne concentration (expressed as ppm or mg/m<sup>3</sup>) of a substance above which it is predicted that the general population, including susceptible individuals, could experience life-threatening health effects or death.

Airborne concentrations below the AEGL-1 represent exposure levels that could produce mild and progressively increasing but transient and non disabling odor, taste, and sensory irritation or certain asymptomatic, non-sensory effects. With increasing airborne concentrations above each AEGL, there is a progressive increase in the likelihood of occurrence and the severity of effects described for each corresponding AEGL. Although the AEGL values represent threshold levels for the general public, including susceptible subpopulations, such as infants, children, the elderly, persons with asthma, and those with other illnesses, it is recognized that individuals, subject to idiosyncratic responses, could experience the effects described at concentrations below the corresponding AEGL.

### SUMMARY

Fluorine is a reactive, highly irritating and corrosive gas used in the nuclear energy industry, as an oxidizer of liquid rocket fuels, and in the manufacture of various fluorides and fluorocarbons. Fluorine is a severe irritant to the eyes, mucous membranes, lungs, and skin; the eyes and the respiratory tract are the target organ and tissues of an acute inhalation exposure. Death is due to pulmonary edema. Data on irritant effects in humans and lethal and sublethal effects in five species of mammals (dog, rat, mouse, guinea pig, and rabbit) were available for development of AEGL values.

Regression analyses of the concentration-exposure durations (for the fixed end point of mortality) for all of the animal species reported in the key study (Keplinger and Suissa 1968) determined that the relationship between concentration and time is  $C^n \times t = k$ , where  $n =$  approximately 2 (actual value of  $n$  for the most sensitive species in irritation and lethality studies, the mouse, is 1.77). This concentration exposure duration relationship was applied to both the AEGL-2 and AEGL-3 levels because the irritant and corrosive action of fluorine on the respiratory tissues differs by only a matter of degree for these AEGL levels: (1) respiratory irritation with edema resulting in mild, reversible lung congestion, and (2) severe respiratory irritation resulting in severe lung congestion. Death results from acute pulmonary edema and consequent respiratory failure. Although the data base for fluorine is small, the data from the key study, aug-

mented with data from several other studies, were considered adequate for derivation of the three AEGL classifications for five time periods.

The AEGL-1 was based on the observation that adult volunteers could tolerate exposure to 10 ppm for 15 min without irritant effects (Keplinger and Suissa 1968). Although this value is below the definition of an AEGL-1 (slight irritation), it provides the longest controlled exposure duration for which no irritation in humans was reported. An intraspecies uncertainty factor of 3 was applied because fluorine is highly corrosive to the tissues of the respiratory tract and effects are not expected to vary greatly among individuals, including susceptible individuals (NRC 2001). Although no data on asthmatics were found, the uncertainty factor of 3 was considered adequate to protect this sensitive subpopulation because the value was a NOAEL and because shorter-term, repeated exposures produced no substantially greater effects in healthy individuals. The value is supported by a second study in which volunteers "tolerated" exposure to 10 ppm for an undefined period of time (Belles 1965). A modifying factor of 2 was applied based on a limited data base and short exposure durations. The resulting value of 1.7 ppm was used across all AEGL-1 exposure durations because, at mildly irritating concentrations, adaptation to slight sensory irritation occurs. As noted, this value is supported by limited workplace monitoring data: workers exposed to fluorine at average yearly concentrations up to 1.2 ppm (range, 0.0-17 ppm) over a four-year period reported fewer incidences of respiratory complaints or diseases than a similar group of nonexposed workers (Lyon 1962). The workers are assumed to encompass a small range of sensitivity; the additional intraspecies uncertainty factor of 3 was considered sufficient to protect sensitive individuals.

Mild lung congestion was selected as the threshold for irreversible, long-lasting effects as defined by the AEGL-2. The AEGL-2 was based on an animal study in which mild lung congestion was observed in mice at 67 ppm for 30 min and 30 ppm for 60 min (Keplinger and Suissa 1968). Effects were slightly less serious in three other species. Although concentrations causing irritant effects or lethality in three other species for the same time periods suggested similar species sensitivity, the mouse data, because of slightly lower values, were chosen as the basis for developing the AEGL-2 and AEGL-3. Similar sensitivity was observed among all species in the key study; therefore, an interspecies uncertainty factor of 1 was applied to address interspecies variability. Fluorine is a highly corrosive gas that reacts directly with the tissues of the respiratory tract, with no pharmacokinetic component involved in the toxicity; therefore, there is likely to be little difference among individuals in response to fluorine at concentrations that define the AEGL-2. The 30- and 60-min values for the mouse were divided by an intraspecies uncertainty factor of 3 to protect sensitive individuals, since effects are not likely to differ greatly among individuals, and by a modifying factor of 2, based on a limited data base. The 30-min value was time scaled to the 10-min AEGL-2, and the 60-min value was time scaled to the 4-h AEGL-2 value. Time scaling was based on the  $C^{1.77} \times t = k$  relationship. The value of  $n$  was derived from regression analysis of the mouse lethality data in the key

study. The 8-h-AEGL-2 value was set equal to the 4-h value because at low concentrations the hygroscopic fluorine would react with and/or be scrubbed by the nasal passages, and because at mildly irritating concentrations, adaptation to sensory irritation occurs. The 10- and 30-min AEGL-2 values are supported by studies in which human volunteers found short-term exposures to 15-25 ppm irritating to the eyes, nose, and throat (Rickey 1959; Keplinger and Suissa 1968).

The AEGL-3 values were derived from the highest exposures that resulted in no deaths in five species over 4 exposure durations (13 tests) for up to 45 days post exposure, but did produce severe lung congestion in the mouse (Keplinger and Suissa 1968). Severe lung congestion in the sensitive mouse was considered the threshold for lethality as defined by the AEGL-3. For the mouse, the 60-min highest non-lethal value was 75 ppm. This value is one-half of the 60-min  $LC_{50}$  value for the mouse. Because of the similar species sensitivity in the key study, based on both irritant effects and lethality, an interspecies uncertainty factor of 1 was considered sufficient to account for interspecies variability. The values were divided by an uncertainty factor of 3 to protect sensitive individuals (fluorine is a highly reactive, corrosive gas whose effect on respiratory tract tissues is not expected to differ greatly among individuals) and by a modifying factor of 2, based on a limited data base. Using the 60-min value of 75 ppm, AEGL-3 values for the other exposure times were calculated based on the  $C^{1.77} \times t = k$  relationship. The value of  $n$  was derived from regression analysis of the mouse lethality data in the key study. The 8-h value was set equal to the 4-h value because fluorine would react with or be scrubbed by the nasal passages at these fairly low time-scaled concentrations. The safety of setting the 8-h value equal to the 4-h value is supported by another study in which a 7-h experimental exposure concentration of 100 ppm that resulted in an overall 60% mortality for four species (Eriksen 1945; Stokinger 1949) is higher than the extrapolated 7-h  $LC_{50}$  values for the mouse (50 ppm) and rat (65 ppm) based on the Keplinger and Suissa (1968) study. The calculated values are listed in Table 5-1.

## 1. INTRODUCTION

Fluorine belongs to the halogen group of elements; these elements do not occur in the elemental state in nature. When formed experimentally, fluorine is a pale yellow, diatomic gas ( $F_2$ ) with a choking, irritating odor. Fluorine is used in the nuclear energy industry to produce gaseous uranium hexafluoride, as an oxidizer of liquid rocket fuels, and in the manufacture of various fluorides and fluorocarbons (Teitelbaum 2001).

Chemically, fluorine is the most electronegative of the halogens and is the most powerful oxidizing agent known (Teitelbaum 2001). It reacts vigorously with most oxidizable substances at room temperature, frequently with ignition. It also combines with most other elements to form fluorides. Reaction with water results in decomposition of the water and formation of hydrofluoric acid, oxygen

(di)fluoride, hydrogen peroxide, oxygen, and ozone (O’Neil et al. 2001). Other relevant chemical and physical properties are listed in Table 5-2.

Fluorine is produced in an enclosed system of fluorine-generating cells. Anhydrous hydrogen fluoride, the basic starting material is mixed with potassium fluoride-hydrogen fluoride to form potassium bifluoride (KHF<sub>2</sub>) which contains various concentrations of free hydrogen fluoride. Fluorine is produced by the electrolysis of anhydrous potassium bifluoride. Commercial fluorine plants operate in the United States, Canada, France, Germany, Italy, Japan, the United Kingdom, and South Africa. In 2003, the total commercial production capacity of fluorine in these countries was estimated at approximately 20,000 tons/year. Production data were unavailable for Russia and China. At most sites, elemental fluorine is used captively for the production of inorganic fluorides. The primary use of elemental fluorine is in the manufacture of uranium hexafluoride (Shia 2003).

In the U.S., fluorine is packaged and shipped under pressure (415 psi) in steel cylinders conforming to Department of Transportation specifications. The size of cylinders containing pure fluorine is limited to 2.7 kg; cylinders containing mixtures of 10-20% fluorine in nitrogen can contain up to 500 kg fluorine (Shia 2003).

## 2. HUMAN TOXICITY DATA

### 2.1. Acute Lethality

No reports of lethal effects from acute inhalation exposure to fluorine were identified. At low concentrations, fluorine is extremely irritating to the nose and eyes.

**TABLE 5-1** Summary of AEGL Values for Fluorine

Classification	10-min	30-min	1-h	4-h	8-h	End Point (Reference)
AEGL-1 <sup>a,b</sup> (Nondisabling)	1.7 ppm (2.6 mg/m <sup>3</sup> )	No irritant effects - humans (Keplinger and Suissa 1968)				
AEGL-2 <sup>c</sup> (Disabling)	20 ppm (31 mg/m <sup>3</sup> )	11 ppm (17 mg/m <sup>3</sup> )	5.0 ppm (7.8 mg/m <sup>3</sup> )	2.3 ppm (3.6 mg/m <sup>3</sup> )	2.3 ppm (3.6 mg/m <sup>3</sup> )	Mild lung congestion - mice (Keplinger and Suissa 1968)
AEGL-3 (Lethal)	36 ppm (56 mg/m <sup>3</sup> )	19 ppm (29 mg/m <sup>3</sup> )	13 ppm (20 mg/m <sup>3</sup> )	5.7 ppm (8.8 mg/m <sup>3</sup> )	5.7 ppm (8.8 mg/m <sup>3</sup> )	Severe lung congestion - mice (Keplinger and Suissa 1968)

<sup>a</sup>The characteristic, pungent odor of fluorine will be noticeable at this concentration.

<sup>b</sup>The same value was used across all time periods because, at mildly irritating concentrations, adaptation to sensory irritation occurs.

<sup>c</sup>30-min and 1-h values are based on separate data points.

**TABLE 5-2** Chemical and Physical Data for Fluorine

Parameter	Data	Reference
Chemical Name	Fluorine	ATSDR 2003
Synonyms	Bifluoriden, fluor, fluorine-19, fluoro	HSDB 2005
CAS Registry No.	7782-41-4	HSDB 2005
Chemical formula	F <sub>2</sub>	O'Neil et al. 2001
Molecular weight	37.99	O'Neil et al. 2001
Physical state	Pale, yellowish green gas	O'Neil et al. 2001
Melting/boiling point	-219.61°C /-188.13°C	O'Neil et al. 2001
Density	1.695 g/cm <sup>3</sup> (air = 1.29)	Lewis 1993
Solubility	No data; reacts with water	O'Neil et al. 2001
Vapor pressure	1 mm Hg at -223°C >10 atm at 20°C	HSDB 2005 Teitelbaum 2001
Flammability	Nonflammable; powerful oxidizing agent	AAR 1987
Conversion factors	1 ppm = 0.64 mg/m <sup>3</sup> 1 mg/m <sup>3</sup> = 1.554 ppm	ATSDR 2003

## 2.2. Nonlethal Toxicity

No human studies documenting specific fluorine exposure levels and time of exposure were found for acute, irreversible effects. Limited data are available on reversible, non-disabling effects of fluorine gas to humans. In many of the studies, details of the exposures, particularly the exposure times, were not given. Fluorine has a characteristic, pungent odor (O'Neil et al. 2001). The odor threshold for fluorine is 0.10-0.20 ppm (Rickey 1959; Amoore and Hautala 1983). Available human data are summarized in Table 5-3 and discussed below.

Rickey (1959) reported on an outdoor spill test conducted by the U.S. Air Force. Two volunteers walked into the dispersed cloud downwind of a test spill. The measured concentration was 25 ppm which the men were able to tolerate; a specific exposure time was not stated. Following the exposure, both men developed sore throats and chest pains that lasted 6 h. The author stated that 20-50 ppm cannot be tolerated by humans but did not give additional data to support the statement.

**TABLE 5-3 Summary of Irritant Effects in Humans**

Concentration (ppm)	Exposure Time	Effects	Reference
10	Not stated	“Tolerated”	Belles 1965
10	15 min	No irritation of eyes, nose, or respiratory tract	Keplinger and Suissa 1968
10	3-5 min every 15 min for 2-3 h	slight irritation to the eyes and skin; no respiratory difficulty	Keplinger and Suissa 1968
15-25	Three breaths	Eye and nasal irritation	Belles 1965
25	Not stated	Tolerated; sore throats and chest pains of 6 h duration	Rickey 1959
25	5 min	Slight irritation to eyes, inhaled intermittently without difficulty	Keplinger and Suissa 1968
50	3 min	Irritating to eyes and slightly irritating to nose	Keplinger and Suissa 1968
67	1 min	Irritating to eyes and nose but not unbearable	Keplinger and Suissa 1968
78	1 min	Irritating to eyes and nose; caused coughing when inhaled	Keplinger and Suissa 1968
100	0.5 min	Very irritating to eyes and nose; no “after effects”	Keplinger and Suissa 1968
100	1 min	Very irritating to eyes and nose (subjects did not inhale); slightly irritating to the skin	Keplinger and Suissa 1968
100-200	Not stated	Reaction with skin and body hair	Belles 1965

Belles (1965) reported a series of tests involving nine male volunteers. All tolerated repeated short-term exposure to 10 ppm without “intolerable” discomfort. Concentrations of 15 to 25 ppm caused some eye and nasal irritation to the majority of subjects after just three breaths. Skin exposure tests indicated that reaction with body hair and dermal irritation may be expected between 100 and 200 ppm.

Keplinger and Suissa (1968) exposed five adult volunteers (19-50 years of age) to concentrations up to 100 ppm via a face mask. These tests were designed to test for irritation only. A concentration of 10 ppm for up to 15 min was reported to be nonirritating to the eyes and nose. A concentration of 25 ppm for 5 min caused slight irritation to the eyes but could be inhaled without respiratory difficulty. A concentration of 50 ppm for 3 min was irritating to the eyes and slightly irritating to the nose. Concentrations of 67 to 100 ppm for 1 min were irritating to the eyes and nose and became uncomfortable after a few seconds. The subjects reported the 67 ppm concentration as being less irritating than cigarette smoke in the eye. The subjects did not inhale at the 100 ppm concentration; inhalation exposure to 78 ppm caused coughing. The 100 ppm concentration caused slight irritation of the skin and a “sticky” feeling. According to the authors, the eyes were the most sensitive indicator of irritation in humans. Keplinger and Suissa (1968) also reported that a few repeated exposures at a concentration of 10 ppm for 3 to 5 min every 15 min over a 2- to 3-h time period caused only slight irritation to the eyes and skin. No respiratory difficulty was reported.

Lyon (1962) reported a lack of significant medical findings in 61 workers exposed to fluorine concentrations in excess of 0.1 ppm. Over a nine-year period, yearly average air concentrations ranged from 0.3 to 1.4 ppm (range <0.1 to 24.7 ppm). Workers were exposed either for 50-60% of their work time for periods of 7-9 months or 10% of their work time at the highest concentrations. Average daily urine fluorine excretion was 1.1 mg/L. Medical records of workers exposed to average yearly concentrations up to 1.2 ppm (range, 0.0-17 ppm) were evaluated for the last four years of exposure. These workers reported fewer incidences of respiratory complaints or diseases than a similar group of 2000-3000 nonexposed workers. Usefulness of the study is limited by the lack of fluorine determination in urine of unexposed workers and the inability of the measurement technique to differentiate between fluorine and hydrogen fluoride. However, the author noted that samples were taken only when the characteristic odor of fluorine was present and the characteristic odor of hydrogen fluoride was absent. In contrast, Machle and Evans (1940) reviewed several monitoring studies in which undefined exposures to fluorine in industry resulted in increased asthmatic attack frequency over that in the non-exposed population.

There is potential for individuals to become sensitized to halogens following acute exposure. A review of studies on drinking water fluoridation and a study with rabbits treated with sodium fluoride did not indicate that immune reactions occurred (ATSDR 2003).

### **2.3. Developmental/Reproductive Toxicity**

No studies were located regarding reproductive or developmental effects in humans after inhalation exposure to fluorine. Fluoride is rapidly absorbed following oral ingestion, crosses the placenta in limited amounts, and is found in placental and fetal tissue (ATSDR 2003). Studies on the incidence of reproductive or developmental effects in areas using fluoridated water have found no correlation between fluoridation levels and birth defects (ATSDR 2003).

### **2.4. Genotoxicity**

No data concerning the genotoxicity of fluorine in humans were identified in the available literature.

### **2.5. Carcinogenicity**

Although several studies indicated an increase in respiratory cancers among workers engaged in several industries where they could be exposed to hydrogen fluoride or fluoride dusts, the concomitant exposure to other chemicals and smoking status of the workers, along with the lack of clear exposure concentration make the studies of questionable relevance (ATSDR 2003). There is no carcinogenicity data for fluoride gas.

### **2.6. Summary**

No human data involving acute lethal exposures were located. Limited data are available on reversible, non-disabling effects of fluorine gas to humans. In many of the studies, details of the exposures, particularly the duration of exposure, were not given. In a fairly well reported study with human volunteers, 10 ppm for 15 min caused no irritation of the eyes, nose, or respiratory tract and 10 ppm for 3 to 5 min every 15 min for 2 to 3 h caused slight irritation to the eyes and skin but no respiratory difficulty.

## **3. ANIMAL TOXICITY DATA**

### **3.1. Acute Lethality**

Data on acute lethal concentrations of fluorine for exposure durations of 5 min to 7 h are available for the rat, mouse, guinea pig, and rabbit. A study with the dog involved repeated exposure. Data on single acute exposures are summarized in Table 5-4.

**TABLE 5-4** Summary of Acute Lethal Inhalation Data in Laboratory Animals

Species	Concentration (ppm)	Exposure Time	Effect <sup>a</sup>	Reference
Rat	10,000	5 min	100% mortality	Eriksen 1945; Stokinger 1949
	1000	30 min	100% mortality	
	500	1 h	100% mortality	
	200	3 h	100% mortality	
	100	7 h	54% mortality	
Rat	700	5 min	LC <sub>50</sub>	Keplinger and Suissa 1968
	390	15 min	LC <sub>50</sub>	
	270	30 min	LC <sub>50</sub>	
	185	1 h	LC <sub>50</sub>	
Mouse	10,000	5 min	100% mortality	Eriksen 1945; Stokinger 1949
	1000	30 min	100% mortality	
	500	1 h	100% mortality	
	200	3 h	100% mortality	
	100	7 h	96% mortality	
Mouse	600	5 min	LC <sub>50</sub>	Keplinger and Suissa 1968
	375	15 min	LC <sub>50</sub>	
	225	30 min	LC <sub>50</sub>	
	150	1 h	LC <sub>50</sub>	
Guinea pig	10,000	5 min	100% mortality	Eriksen 1945; Stokinger 1949
	1000	30 min	100% mortality	
	500	1 h	100% mortality	
	200	3 h	90% mortality	
	100	7 h	no mortality	
Guinea pig	395	15 min	LC <sub>50</sub>	Keplinger and Suissa 1968
	170	1 h	LC <sub>50</sub>	
Rabbit	10,000	5 min	100% mortality	Eriksen 1945; Stokinger 1949
	1000	30 min	100% mortality	
	500	1 h	100% mortality	
	200	3 h	100% mortality	
	100	7 h	88% mortality	
Rabbit	820	5 min	LC <sub>50</sub>	Keplinger and Suissa 1968
	270	30 min	LC <sub>50</sub>	

<sup>a</sup>LC<sub>50</sub> and 100% mortality values were obtained at 14 days post exposure.

### 3.1.1. Dogs

No studies on single exposures were located. In short-term, repeated exposures, groups of five dogs (sex and strain unspecified) were administered fluorine at concentrations of 0.5, 2, 5, and 16 ppm for up to 35 days (Stokinger 1949). The exposure regime (not stated) was apparently 5-6 h/day, 5 days/week for a total exposure of 170 h. Concentrations were estimated by metering; no analyses were made. At the two higher concentrations, dogs exhibited seizures followed by death. At the 16 ppm exposure, mortality was 100% by the 60<sup>th</sup> h of exposure. No toxic symptoms and no deaths were observed at the two lower

concentrations. Histological changes included moderate to moderately severe hemorrhage and liver congestion in 4 of 4 animals at 16 ppm, red discoloration of the lungs, mild bronchitis, and bronchiectasis in 4 of 5 dogs at 5 ppm, pulmonary hemorrhage and edema in 2 of 5 dogs at 2 ppm, and no consistent significant damage at 0.5 ppm.

### **3.1.2. Rats**

Eriksen (1945) and Stokinger (1949) reported the same study in which a fluorine concentration of 10,000 ppm for an exposure time of 5 min was fatal to rats (sex and strain unspecified) within 24 h, with the majority of deaths occurring by the end of the exposure period. Thirty minutes of exposure to 1000 ppm caused 87% mortality and mortality reached 100% by 14 days post exposure. A concentration of 500 ppm for 1 h caused 90% mortality by the end of the exposure period. Percent mortality increased at 24 h post exposure, and at 14 days, all animals were dead. By 4 days post exposure, mortality was 100% for rats exposed to 200 ppm for 3 h. At 14 days after exposure to 100 ppm for 7 h, 54% of the animals were dead.

Autopsy results indicated that fluorine gas was severely corrosive to the respiratory tract as shown by bronchial and alveolar necrosis. Death was attributed to respiratory failure resulting from acute pulmonary damage involving edema, emphysema, and hemorrhage. Gross observations of animals surviving the 100 and 200 ppm concentrations and sacrificed 14 days post exposure revealed that lung damage was either slight or had undergone substantial repair. Kidney abnormalities including general engorgement, slight edema, slight swelling of the cortex and inflammation of the medulla were observed (frequency not stated) at 14 days post exposure but not at the end of the exposure period. Technical problems in monitoring fluorine gas levels make the quantitative exposure level data unreliable in this study; however, qualitative results from these experiments are useful.

Keplinger and Suissa (1968) exposed groups of 10 Osborne-Mendel rats (sex unspecified) to measured concentrations of fluorine for periods of 5, 15, 30, or 60 min. The LC<sub>50</sub> values were 700, 390, 270, and 185 ppm, respectively. Few signs of intoxication were observed immediately after exposure except for irritation of the eyes and nose. Death occurred approximately 12 to 18 h after exposure. A few deaths were recorded after 24 h. Animals that lived for 48 h post exposure generally survived the 14-day observation period. Animals exposed to high concentrations died of respiratory failure with the lungs showing diffuse congestion and hemorrhage; no damage occurred in other organs. No deaths were reported in rats tested at 50% of the LC<sub>50</sub> for each of the time periods.

Repeated daily exposures of rats (sex and strain unspecified) to concentrations of 0.5, 2, 5, and 16 ppm were conducted over a period of 21-35 days (Stokinger 1949). The exposure regime (not stated) was apparently 5-6 h/day, 5 days/week. Rats exposed at the two highest concentrations had symptoms of

coarsening and stiffening of the fur and irritation of the eyes and nose; these symptoms were mild at the two lower concentrations. Mortalities at the end of the exposure period were 0, 8, 27, and 50% at 0.5, 2, 5, and 16 ppm, respectively. A 10% weight loss occurred at the 16 ppm exposure concentration, but weight gains occurred at the lower exposure concentrations. Blood and hematology parameters were unchanged at all concentrations. Severe pulmonary irritation, oral lesions, and testicular degeneration occurred at 16 ppm; no grossly observable lung changes occurred at the two lower concentrations.

### 3.1.3. Mice

Eriksen (1945) and Stokinger (1949) exposed mice (sex and strain unspecified) to fluorine concentrations ranging from 100 to 10,000 ppm for 7 h to 5 min, respectively. Concentrations of 10,000 ppm for 5 min, 1000 ppm for 30 min, 500 ppm for 1 h, and 200 ppm for 3 h were 100% fatal by the end of a 14-day post-exposure period. A concentration of 100 ppm for 7 h resulted in 96% mortality. The majority of animals that died did so by the end of the exposure period. Autopsies indicated that fluorine gas was severely corrosive to the respiratory tract as shown by edema, emphysema, and hemorrhage. Death was attributed to respiratory failure resulting from acute pulmonary damage. As noted in Section 3.1.2., technical problems in monitoring fluorine gas levels make the quantitative exposure level data unreliable; however, qualitative results from these experiments are useful.

Keplinger and Suissa (1968) exposed groups of 10 Swiss-Webster mice (sex unspecified) to measured concentrations of fluorine for periods of 5, 15, 30, or 60 min. The  $LC_{50}$  values for the mice for the four respective time intervals were 600, 375, 225, and 150 ppm. Few signs of intoxication were observed immediately after exposure except for irritation of the eyes and nose. Death occurred approximately 12 to 18 h after exposure. A few deaths were recorded after 24 h. Animals that lived for 48 h post exposure generally survived the 14-day observation period. No deaths were reported in mice tested at 50% of the  $LC_{50}$  for each of the time periods. Animals exposed to high concentrations died of respiratory failure with the lungs showing diffuse congestion and hemorrhage; no damage occurred in other organs.

### 3.1.4. Guinea Pigs

Eriksen (1945) and Stokinger (1949) exposed guinea pigs (sex and strain unspecified) to fluorine concentrations ranging from 100 to 10,000 ppm for exposure times of 7 h to 5 min, respectively. Concentrations of 10,000 ppm for 5 min, 1000 ppm for 30 min, and 500 ppm for 1 h were 100% fatal by the end of a 14-day post exposure period. A concentration of 200 ppm for 3 h resulted in 90% mortality, and a concentration of 100 ppm for 7 h resulted in no mortality. The majority of animals that died did so by the end of the exposure period. Au-

topsies indicated that fluorine gas was severely corrosive to the respiratory tract as shown by edema, emphysema, and hemorrhage. Death was attributed to respiratory failure resulting from acute pulmonary damage. Sublethal concentrations produced gross changes in the liver and kidneys (not further described). As noted in Section 3.1.2., technical problems in monitoring fluorine gas levels make the quantitative exposure level data unreliable; however, qualitative results from these experiments are useful.

Keplinger and Suissa (1968) exposed groups of five New England guinea pigs (sex unspecified) to measured concentrations of fluorine for periods of 15 or 60 min. LC<sub>50</sub> values were 395 ppm at 15 min and 170 ppm at 60 min. Few signs of intoxication were observed immediately after exposure except for irritation of the eyes and nose. Cause of death and organ pathology were the same as discussed for the rat and mouse above.

### **3.1.5. Rabbits**

Eriksen (1945) and Stokinger (1949) exposed rabbits (sex and strain unspecified) to fluorine concentrations ranging from 100 to 10,000 ppm for 7 h to 5 min, respectively. Concentrations of 10,000 ppm for 5 min, 1000 ppm for 30 min, 500 ppm for 1 h, and 200 ppm for 3 h were 100% fatal by the end of a 14-day post exposure period. A concentration of 100 ppm for 7 h resulted in 88% mortality. The majority of animals that died did so by the end of the exposure period. Autopsies indicated that fluorine gas was severely corrosive to the respiratory tract as shown by edema, emphysema, and hemorrhage. In rabbits, pulmonary hemorrhage was a more important component of lung damage than in other species. Death was attributed to respiratory failure resulting from acute pulmonary damage. "Infectious processes" were present in the lungs of some survivors. As noted in Section 3.1.2., technical problems in monitoring fluorine gas levels make the quantitative exposure level data unreliable; however, qualitative results from these experiments are useful.

Keplinger and Suissa (1968) exposed groups of 5 New England rabbits (sex unspecified) to measured concentrations of fluorine for two time periods. LC<sub>50</sub> values for exposures of 5 and 30 min were 820 and 270 ppm, respectively. Clinical signs and organ pathology were the same as for the rat and mouse discussed above.

In short-term, repeated exposures, rabbits (sex and strain unspecified) were administered fluorine at concentrations of 0.5, 2, 5, and 16 ppm for up to 35 days (Stokinger 1949). The exposure regime was not stated, but was presumably 5 h/day for a total exposure of 170 h. At the two higher concentrations, mortality was 100%; at 2 ppm, 2 of 10 rabbits died; and at 0.5 ppm, 1 of 18 rabbits died. Histological changes included liver congestion and moderate to moderately severe lung hemorrhage in 4 of 4 animals at 16 ppm and moderate pulmonary irritation and slight liver damage in 4 of 5 animals at 5 ppm. At 2 ppm

there was mild bronchial inflammation in 3 of 4 animals, and at 0.5 ppm there was little or no pulmonary damage.

### **3.2. Nonlethal Toxicity**

Studies conducted at concentrations that were less than lethal are summarized in Table 5-5. Data are presented for the dog, rat, mouse, guinea pig, and rabbit. The latter four species were exposed to concentrations approximating 50, 25, and 12.5% of their respective LC<sub>50</sub> values for exposure durations of 5, 15, 30, and 60 min.

#### **3.2.1. Dogs**

Dogs (sex and strain unspecified) exposed to 93 ppm for 60 min had symptoms of irritation, cough, slight labored breathing, and vomiting (Keplinger and Suissa 1968). Examinations at 7 to 14 days post exposure revealed small areas of hemorrhage in the lungs. Dogs exhibited only eye irritation at an exposure of 68 ppm for 1 h. No irritation or gross pathologic changes in the lung were evident following exposure to 38 ppm for 1 h. In short-term, repeated exposures, dogs treated with fluorine at a concentration of 0.5 ppm for up to 35 days (presumably 5 h/day) showed no significant lung damage (Stokinger 1949).

#### **3.2.2. Rats**

Sublethal effects of inhalation exposure to fluorine were assessed in Osborne-Mendel rats (sex unspecified) exposed to concentrations of 500 ppm and 350 ppm (71% and 50% of the 5-min LC<sub>50</sub> values) for 5 min, 195 ppm (50% of the 15-min LC<sub>50</sub>) for 15 min, and 140 ppm (50% of the 30-min LC<sub>50</sub>) for 30 min (Keplinger and Suissa 1968). Very few signs of intoxication were observed immediately after exposure. Rats exposed to these concentrations experienced marked irritation of the eyes and respiratory tract immediately after exposure, and labored breathing and lethargy were observed several hours later. At sacrifice (up to 45 days post exposure), there was moderate to severe diffuse congestion of the lungs.

Sublethal exposures produced kidney and liver damage (Keplinger and Suissa 1968). Kidney damage was characterized by focal areas of coagulation necrosis in the cortex and focal areas of lymphocytic infiltration throughout the cortex and medulla. Liver damage included coagulation necrosis, periportal hemorrhages, and diffuse cloudy swelling. Kidney damage occurred at the same concentrations as lung involvement. Liver involvement occurred only at the highest sublethal concentrations. No-effect concentrations for organ pathology were 79 ppm for 5 min, 65 ppm for 15 min, 51 ppm for 30 min, and 30 ppm for 60 min.

**TABLE 5-5** Summary of Sublethal Effects in Laboratory Animals

Species	Concentration (ppm)	Exposure Time	Effect <sup>a</sup>	Reference
Dog	93	1 h	irritation, cough, slight labored breathing, vomiting, small areas of hemorrhage in lungs	Keplinger and Suissa 1968
	93	15 min	slight lung congestion	
	68	1 h	eye irritation	
	38	1 h	no effect	
Rat	500	5 min	marked signs of intoxication, severe changes in lungs	Keplinger and Suissa 1968; Keplinger 1969
	350	5 min	moderate lung congestion	
	325	5 min	moderate lung congestion	
	175	5 min	labored breathing; mild lung congestion	
	150	5 min	very mild lung congestion	
	88	5 min	no effect	
Rat	195	15 min	irritation, labored breathing, moderate diffuse congestion	Keplinger and Suissa 1968
	98	15 min	very mild lung congestion	
	49	15 min	no effect	
Rat	140	30 min	irritation of eyes and nose, slight labored breathing, moderate diffuse lung congestion	Keplinger and Suissa 1968; Keplinger 1969
	68, 70	30 min	very mild lung congestion	
	35	30 min	no effect	
Rat	140	1 h	severe diffuse lung congestion, kidney and liver changes	Keplinger and Suissa 1968; Keplinger 1969
Rat	93	1 h	eye irritation and labored breathing; mild diffuse lung congestion	Keplinger and Suissa 1968; Keplinger 1969
	75	1 h	mild diffuse lung congestion	
	47	1 h	very mild diffuse lung congestion	
	28	1 h	no effect	

Mouse	467	5 min	marked irritation of eyes and respiratory tract, labored breathing, severe diffuse lung congestion	Keplinger and Suissa 1968; Keplinger 1969
	321	5 min	moderate diffuse lung congestion	
	300	5 min	eye irritation and labored breathing; moderate diffuse lung congestion	
	174	5 min	slightly labored breathing; very mild diffuse lung congestion	
	130	5 min	very mild lung congestion	
	79	5 min	no effect	
Mouse	350, 359	15 min	severe diffuse lung congestion to congestion with hemorrhages	Keplinger and Suissa 1968; Keplinger 1969
	265, 285	15 min	moderate diffuse lung congestion	
	188	15 min	eye irritation and labored breathing; moderate diffuse lung congestion	
	87	15 min	very mild diffuse lung congestion	
	65	15 min	no effect	
Mouse	113	30 min	eye irritation and labored breathing; mild diffuse lung congestion	Keplinger and Suissa 1968; Keplinger 1969
	64, 67	30 min	very mild lung congestion	
	32	30 min	no effect	
Mouse	75	1 h	eye irritation and labored breathing, severe diffuse lung congestion	Keplinger and Suissa 1968; Keplinger 1969
	55	1 h	very mild lung congestion	
	50	1 h	labored breathing; mild diffuse lung congestion	
	30	1 h	very mild diffuse lung congestion	
	15	1 h	no effect	
Guinea pig	198	15 min	eye irritation and labored breathing; mild diffuse lung congestion	Keplinger and Suissa 1968
	70	15 min	no effect	

**TABLE 5-5 Continued**

Species	Concentration (ppm)	Exposure Time	Effect <sup>a</sup>	Reference
Guinea pig	135	1 h	eye irritation and labored breathing; mild diffuse lung congestion	Keplinger and Suissa 1968
	73	1 h	no effect	
Guinea pig	100	7 h	severe damage to the respiratory system	Eriksen 1945; Stokinger 1949
Rabbit	410	5 min	eye irritation and labored breathing; moderate diffuse lung congestion	Keplinger and Suissa 1968
	134	5 min	slightly labored breathing	
	51	5 min	no effect	
Rabbit	135	30 min	eye irritation, very mild diffuse congestion	Keplinger and Suissa 1968
	71	30 min	no irritation, very mild diffuse congestion	
	32	30 min	no effect	

<sup>a</sup>Measured up to 45 days post exposure; serial sacrifice revealed that effects did not become worse with time and, in some cases, lung changes showed some regression starting 7 days post-exposure.

Mild effects of inhalation exposure to fluorine were assessed in rats exposed to concentrations equal to 25% of the LC<sub>50</sub> values for exposure times of 5, 15, 30, and 60 min (175, 98, 70, and 47 ppm, respectively) (Keplinger and Suissa 1968). Rats exposed to these concentrations experienced eye irritation, slightly labored breathing and very mild to mild diffuse congestion of the lungs. No-effect levels and exposure times were 88 ppm for 5 min, 49 ppm for 15 min, 35 ppm for 30-min, and 28 ppm for 60 min.

Groups of 10 Osborne-Mendel rats were treated with single and repeated exposures of fluorine (Keplinger 1969). Single exposures occurred for 5 min at concentrations of 85-150 ppm and 256-450 ppm, for 30 min at 46-68 ppm, and for 60 min at 45-75 ppm and 88-170 ppm. The animals were sacrificed immediately after exposure or at 7, 14, 21, or 45 days after the last exposure; however, the day of sacrifice for each test was not reported. Gross pathology results were not well described, and results of each individual test were not reported; those results that were reported are summarized in Table 5-5. Single exposures for 5 min at 85-150 ppm induced very mild lung congestion and some kidney changes, but no liver lesions. At the higher concentrations, 256-450 ppm, moderate diffuse congestion of the lungs and gross damage (primarily discoloration) of the liver and kidneys occurred. Following exposure to 46-68 ppm for 30 min, the livers were grossly normal while the lungs and kidneys showed slight gross pathologic changes. Exposure for 60 min at the lower concentration range resulted in lung and kidney changes but no effect on the liver. At the higher concentration range, severe diffuse congestion and hemorrhages of the lungs were observed. Both the kidneys and livers showed gross changes.

Keplinger (1969) also reported on repeated exposure. Lung, kidney and liver effects in rats exposed four times at daily to weekly intervals to various concentrations were compared with effects following a single treatment at the same concentration. Effects on the lungs (congestion, hemorrhage), kidneys, and liver were greater following the single exposure than following the repeated weekly exposures. For example, four repeated exposures to 30 ppm for 60 min every other day produced lesser effects than a single exposure to 30 ppm for 60 min; sacrifice occurred immediately after the last or single exposure (Keplinger 1969).

### 3.2.3. Mice

Sublethal effects of inhalation exposure to fluorine were assessed in Swiss-Webster mice exposed to concentrations equal to 78% of the 5-min LC<sub>50</sub> (467 ppm) and 50% of the 5-min, 15-min, 30-min, and 1-h LC<sub>50</sub> values (300, 188, 113, and 75 ppm, respectively) (Keplinger and Suissa 1968). A few additional tests were carried out at concentrations between the LC<sub>50</sub> and 50% of the LC<sub>50</sub> (Keplinger 1969). Very few signs of intoxication were observed immediately after exposure. Mice exposed to 467 ppm for 5 min experienced marked irritation of the eyes and respiratory tract immediately after exposure and la-

bored breathing and lethargy were observed several hours later. At sacrifice there was severe diffuse congestion of the lungs. At concentrations equal to 50% of the 5-min, 15-min, and 60-min LC<sub>50</sub> values, mice showed moderate to severe diffuse congestion of the lungs.

In mice exposed to sublethal concentrations (specific concentrations not stated) there was some evidence of gross damage to the lungs, liver, and kidneys (Keplinger and Suissa 1968). Histological examination of the lungs revealed massive hemorrhages into the alveolar spaces and coagulation necrosis of alveoli with peribronchial lymphocytic proliferation. After 7 days there was proliferation of septal cells, macrophages and lymphocytes. Beginning at 7 days post exposure, livers showed coagulation necrosis, periportal hemorrhages and diffuse cloudy swelling. Focal areas of coagulation necrosis appeared in the cortex of the kidney and focal areas of lymphocytic infiltration appeared throughout the cortex and medulla. Concentrations that caused no effects in the lungs did not cause effects in the liver or kidneys. Damage occurred in both the lung and kidney at the same concentration; liver changes occurred at higher concentrations. Although not specifically stated for each species, some or all of these same effects occurred in other species to the same or a lesser degree.

Mild effects were observed in mice at 174 ppm (5 min), 87 ppm (15 min), 67 ppm (30 min), and 50 ppm (60 min) (Keplinger and Suissa 1968). No-effect concentrations for organ pathology were 79 ppm for 5 min, 65 ppm for 15 min, 51 ppm for 30 min, and 30 ppm for 60 min. Four repeated exposures such as 30 ppm for 60 min every other day produced lesser effects than a single exposure of the same magnitude; sacrifice occurred immediately after the last or single exposure (Keplinger 1969).

#### **3.2.4. Guinea pigs**

Disabling, irreversible effects were not observed in New England guinea pigs exposed to concentrations lower than the LC<sub>50</sub> values (Keplinger and Suissa 1968). In guinea pigs exposed to 50% of the 15-min LC<sub>50</sub> (198 ppm), signs of eye and respiratory irritation and labored breathing and gross lung changes of mild diffuse congestion were present. At exposures to concentrations of 100 and 70 ppm for 5 min, mild effects were occasionally observed. For the 60-min exposures, eye and respiratory irritation and mild diffuse congestion of the lung were observed at 135 ppm (79% of the 60-min LC<sub>50</sub>) and no effects were observed at 73 ppm (43% of the 60-min LC<sub>50</sub>).

#### **3.2.5. Rabbits**

Eye and respiratory irritation and moderate diffuse congestion of the lungs were observed in New Zealand rabbits exposed to 410 ppm for 5 min (50% of the 5-min LC<sub>50</sub>) (Keplinger and Suissa 1968). Effects in rabbits at 16% of the

5-min LC<sub>50</sub> (134 ppm) and 50% of the 30-min LC<sub>50</sub> (135 ppm) were slight to mild (Keplinger and Suissa 1968). In short-term, repeated exposures, rabbits administered fluorine at a concentration of 0.5 ppm for up to 35 days (presumably 5 h/day) showed little or no lung damage (Stokinger 1949).

### 3.3. Developmental and Reproductive Toxicity

No studies addressing developmental or reproductive effects following acute inhalation exposure to fluorine were located.

### 3.4. Genotoxicity

No data on inhalation exposures were located in the available literature. Genotoxicity studies were conducted with sodium fluoride or potassium fluoride. Negative results were found for *Salmonella typhimurium* TA100, TA1535, TA1537, and TA98 with or without metabolic activation, and positive results were found in the mouse lymphoma (with and without activation), sister chromatid exchange (with and without activation), and chromosome aberration tests (without activation) (NTP 1990), but generally at doses that produced cellular toxicity (ATSDR 2003).

### 3.5. Chronic Toxicity and Carcinogenicity

No carcinogenicity studies using acute or longer-term inhalation exposure were located. Because inhaled fluorine would exert its systemic effects as fluoride ion, oral studies of fluoride administration may be relevant. A chronic oral carcinogenicity study in which sodium fluoride was administered to male and female rats and mice in the drinking water resulted in equivocal evidence of bone cancer in male rats, but not in female rats or mice of either gender (NTP 1990). The cancer was a rare bone osteosarcoma. Another chronic oral study, with sodium fluoride administered in the feed found no evidence of cancer in male or female rats (Maurer et al. 1990).

### 3.6. Summary

LC<sub>50</sub> concentrations for the mouse, rat, guinea pig, and rabbit from the study of Keplinger and Suissa (1968) are summarized in Table 5-6 and graphed in Figure 5-1. With the exception of the 5-min LC<sub>50</sub> for the rabbit, the LC<sub>50</sub> values for all four species at the different exposure times were not statistically significantly different. Additionally, a 7-h LC<sub>54</sub> value of 100 ppm for the rat was available (Eriksen 1945; Stokinger 1949).

**TABLE 5-6** Summary of LC<sub>50</sub> Data in Animals (ppm)

Exposure Time	Rat	Mouse	Guinea Pig	Rabbit
5 min	700	600	—	820
15 min	390	375	395	—
30 min	270	225	—	270
60 min	185	150	170	—

Abbreviation: A dash (—) indicates no data.

Source: Keplinger and Suissa 1968. Reprinted with permission; copyright 1968, *Journal of Industrial Hygiene and Toxicology*.

No data on acute inhalation and developmental toxicity were located. Genotoxicity was observed only at concentrations that were toxic to cells (ATSDR 2003). Chronic and carcinogenicity studies with oral administration of sodium fluoride resulted in equivocal evidence of cancer in one study (NTP 1990) and no evidence of cancer in a second study (Maurer et al. 1990).

The only experimental data available for longer-term exposures was the 7-h exposure of rats, mice, guinea pigs and rabbits to 100 ppm which resulted in an over-all mortality of 60% (Eriksen 1945; Stokinger 1949). At this exposure concentration and duration, the mouse and rabbit were the most sensitive species as indicated by high mortality, the rat was intermediate in sensitivity, and the guinea pig was the least sensitive species with no mortality.

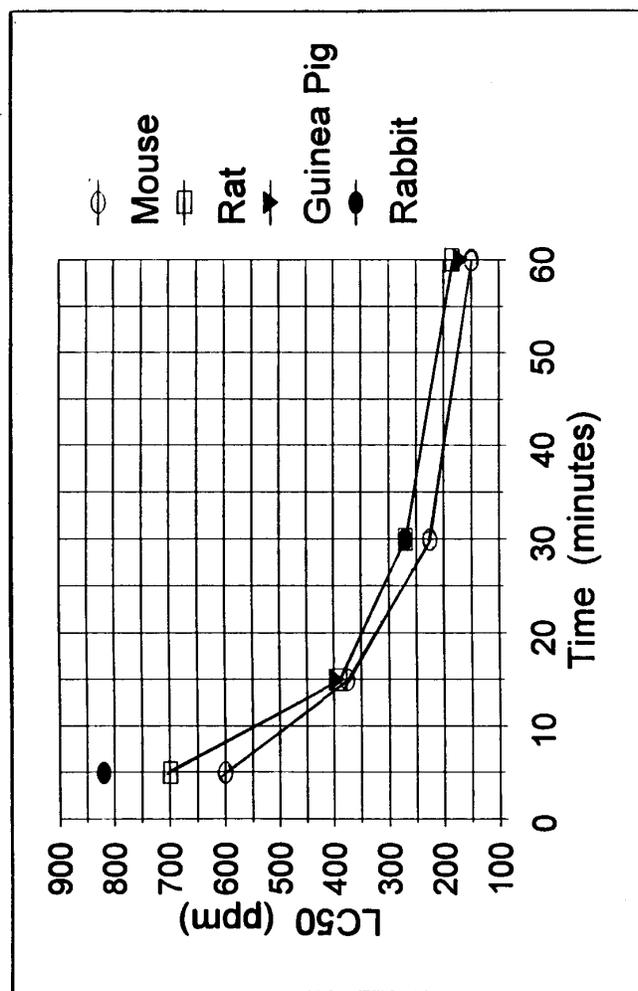
Lowest values for disabling, irreversible effects; nondisabling, reversible effects; and no-effect concentrations for various exposure periods for each species are summarized in Table 5-7. In many cases, the listed concentration is the only tested concentration.

## 4. SPECIAL CONSIDERATIONS

### 4.1. Metabolism and Disposition

Pharmacokinetic data from acute exposures were not available. Metabolic/kinetic considerations are not relevant regarding the determination of AEGL values as animals die of acute respiratory failure. Fluorine is hygroscopic and will react with the moist mucus membranes of the respiratory passages.

Following inhalation, fluorine may be absorbed by the lungs, particularly following the formation of hydrofluoric acid by reaction with moisture in the lungs. Fluoride from the circulating blood is deposited in the bone where it substitutes for the hydroxyl group of hydroxyapatite, the principal mineral component of bone. Renal excretion of fluoride is rapid; accumulation in the kidney occurs as fluoride is concentrated in the urine for elimination (Teitelbaum 2001).



**FIGURE 5-1** LC<sub>50</sub> values for four species of animals. The continuous lines represent values for the mouse and rat. Source: Keplinger and Suissa 1968. Reprinted with permission; copyright 1968, *Journal of Industrial Hygiene and Toxicology*.

**TABLE 5-7** Summary of Nonlethal Effects in Animals<sup>a</sup>

Species	Exposure Time	Disabling Effects (ppm)	Nondisabling Effects (ppm)	No Effect (ppm)
Dog	5 min	—	—	—
	15 min	—	93	—
	30 min	—	—	—
	60 min	93	68	38
Rat	5 min	325	150	88
	15 min	195	98	49
	30 min	140	70	35
	60 min	140	47	28
Mouse	5 min	300	130	79
	15 min	188	87	65
	30 min	—	64, 67	32
	60 min	75	30	15
Guinea pig	5 min	—	—	—
	15 min	—	198	70
	30 min	—	—	—
	60 min	—	135	73
Rabbit	5 min	410	134	51
	15 min	—	—	—
	30 min	—	135	32
	60 min	—	—	—

<sup>a</sup>Effects include both irritation and organ lesions.

A dash (—) indicates no data.

Source: Keplinger and Suissa 1968. Reprinted with permission; copyright 1968, *Journal of Industrial Hygiene and Toxicology*.

#### 4.2. Mechanism of Toxicity

Although fluorine reacts with water vapor in the moist respiratory passages, some fluorine persists in saturated water vapor for periods up to 1 h (Slabbey and Fletcher 1958). Therefore, it is likely that some of the inhaled fluorine will persist in the elemental form in the saturated air of the respiratory tract and will be carried into the lungs. The available studies show that damage to the respiratory tract, particularly the lung (edema, emphysema, and hemorrhage), is the major pathology associated with acute exposure to fluorine (Eriksen 1945; Stokinger 1949; Keplinger and Suissa 1968; Keplinger 1969). Fluorine is characterized as a severe irritant to the eyes, mucous membranes, skin, and lungs (NRC 1984; ACGIH 2004). Serious systemic effects are unlikely to occur from an acute exposure. In the studies summarized in Table 5-5, the eye and tissues of the respiratory tract sustain the impact of an acute exposure. Therefore, the concentration of fluorine in the inhaled air and not the absorbed dose is the primary determinant of effects.

### 4.3. Structure-Activity Relationships

The combined human and animal data on fluorine are sufficient for derivation of inhalation exposure guidelines and the use of structure-activity comparisons is not necessary. Like hydrogen chloride (HCl) and chlorine (Cl<sub>2</sub>), fluorine is an irritant to the eyes, skin, and respiratory tract. When compared with mortality data for HCl and chlorine (Cl<sub>2</sub>), fluorine is more toxic than HCl and slightly more toxic than Cl<sub>2</sub> to laboratory rodents. Mortality data indicate that HF is more toxic than HCl but less toxic than F<sub>2</sub> to laboratory rodents (Wohlslagel et al. 1976; Teitelbaum 2001; ATSDR 2003; NRC 2004). Kusewitt et al. (1989) exposed Fischer 344 rats to hydrogen halides at concentrations of 100 to 1000 ppm for 30 min. Tissue injury was confined to the nasal region with relative toxicities of HF>HCl>HBr.

Penetration of any chemical to the lungs depends on water solubility. The more water soluble halides are scrubbed in the upper respiratory passages, and there is less penetration to the bronchioles and lungs. Fluorine decomposes water, forming HF, OF<sub>2</sub>, hydrogen peroxide, oxygen, and ozone (O'Neil et al. 2001). The same reaction is predicted to occur in the moist respiratory passages. However, some unreacted fluorine will penetrate to the lungs. The water solubility of chlorine is 0.092 mol/L (25°C), and the water solubility of bromine is 0.214 mol/L (20°C). For the end point of lethality, the order of water solubility is also the order of toxicity, i.e., fluorine is poorly scrubbed and therefore more easily penetrates to the lungs, resulting in lower LC<sub>50</sub> values than for the other halogens. For example, the 1-h LC<sub>50</sub> values for chlorine in the rat range from 293-455 ppm (NRC 2004), whereas, the value for fluorine in the Keplinger and Suissa 1968 study is 185 ppm. Both chlorine and bromine are more readily scrubbed in the upper respiratory tract than is fluorine.

### 4.4. Concentration-Exposure Duration Relationship

When data are lacking for desired exposure times, scaling across time may be based on the relationship between acute toxicity (concentration) and exposure duration (ten Berge et al. 1986). The only available data for scaling across time are LC<sub>50</sub> data for the rat, mouse, and guinea pig for 5, 15, 30, and 60-min exposure durations. These data show that the association between concentration and exposure duration is a logarithmic one and the equations derived from the empirical data by regression analysis are expressed as  $C^n \times t = k$  (where C = concentration, t = time in minutes, and k is a constant). For the three species the equations derived from the LC<sub>50</sub> data are

$$\begin{aligned}C^{1.87} \times t &= 1.05 \times 10^6 \text{ ppm-min (rat)} \\C^{1.77} \times t &= 4.45 \times 10^5 \text{ ppm-min (mouse)} \\C^{1.64} \times t &= 2.79 \times 10^5 \text{ ppm-min (guinea pig)}\end{aligned}$$

Therefore, the relationship between concentration and time in approximately  $C^2 \times t = k$ . Appendix A contains a graph of this relationship for the mouse data.

## **4.5. Other Relevant Information**

### **4.5.1. Susceptible Populations**

No data on susceptible populations were located. Fluorine is highly irritating and corrosive to the tissues of the respiratory tract. The direct action of fluorine on the respiratory tract is not expected to vary greatly among most individuals. Although no data on fluorine exposures and asthmatics were located, studies with chlorine indicate that, compared with the general population, the respiratory tract of some asthmatics may be very reactive to the presence of irritant gases (NRC 2004). Machle and Evans (1940) reviewed several monitoring studies in which undefined exposures to fluorine in industry resulted in increased asthmatic attack frequency compared to that in the non-exposed population.

### **4.5.2. Species Variability**

A comparison of the animal and human data indicates that humans may be more sensitive to the irritant effects of fluorine than animals in that experimental animals suffered no gross effects at concentrations that humans found intolerable. For example, a concentration of 73 ppm for 1 h was a no-effect concentration for the guinea pig, but humans could not inhale 78 ppm for a short time without coughing.

Rats and rabbits exposed to 10,000 ppm of fluorine exhibited similar pulmonary damage; however, pulmonary hemorrhage was extensive in the rabbit whereas it was absent or extremely slight in the rat (Eriksen 1945; Stokinger 1949). At concentrations of 200 ppm and above, mortality rates were similar for rats, mice, rabbits, and guinea pigs for the different time periods. Guinea pigs succumbed more rapidly than the other three species at the three highest exposure levels (10,000, 1000, and 500 ppm), but showed less mortality at the 200 ppm level and no mortality at the 100 ppm level. These data, although slightly conflicting at times, do not indicate great species variability in response to fluorine exposures.

In another study, the 5-, 15-, 30-, and 60-min LC<sub>50</sub> values for the rat, mouse, rabbit, and guinea pig were remarkably similar with only slightly lower values for the mouse compared to the other species (Keplinger and Suissa 1968). In all cases, death resulted from acute pulmonary edema and consequent respiratory failure. The similarity in LC<sub>50</sub> values for each time period suggests similar species sensitivity.

## 5. DATA ANALYSIS FOR AEGL-1

### 5.1. Summary of Human Data Relevant to AEGL-1

A number of authors report 10 ppm as a concentration that caused either no discomfort or sensory irritation (Belles 1965; Keplinger and Suissa 1968). A higher level of 25 ppm caused eye irritation during a 5-min exposure (Keplinger and Suissa 1968), sore throat and chest pains that lasted for 6 h (duration of exposure not specified but presumed short) (Rickey 1959), and eye and nasal irritation after three breaths (Belles 1965). Humans were also exposed to 10 ppm for 3 to 5 min every 15 min over a 2- to 3-h period with only slight irritation to the eyes and skin (Keplinger and Suissa 1968).

### 5.2. Summary of Animal Data Relevant to AEGL-1

The animal data indicated that at 25% of the  $LC_{50}$ , there were mild signs of intoxication characterized by slight labored breathing and closed eyes (Keplinger and Suissa 1968). Below 25% of the  $LC_{50}$  there were no gross signs of lung pathology. Using the data of Keplinger and Suissa (1968) and Keplinger (1969), Ricca (1970) estimated the no-effect concentration with respect to lung, liver, and kidney pathology (based on  $C \times t$  values) at 15% of the rat  $LC_{50}$  concentration. For the 1-h exposure, this concentration would be 28 ppm.

However, absence of apparent effects and gross signs of intoxication does not ensure that slight irritation or discomfort did not take place. No-effect concentrations are listed in Table 5-7. No-effect concentrations for the rat are 35 ppm for 30 min and 28 ppm for 60 min. For the mouse, the 30- and 60-min no-effect concentrations are 32 ppm and 15 ppm, respectively; the 60-min no-effect concentrations for the dog and guinea pig are 39 and 73 ppm, respectively. For all species, the 30-min no-effect concentrations range from 32 to 35 ppm and the 60-min no-effect concentrations range from 15 to 73 ppm. These values do not necessarily indicate the relative sensitivity of the species but, rather, reflect the experimental concentrations selected by the researchers.

### 5.3. Derivation of AEGL-1

Because human data for irritant effects are available, they should be used to derive the AEGL-1. The data of Keplinger and Suissa (1968) are the most comprehensive for humans exposed to 10 ppm. The 10 ppm concentration for 15 min was reported as a no-effect level for eye and nasal irritation but can be considered the threshold for notable discomfort as the next highest concentration tested, 25 ppm, produced slight to moderate discomfort. The 15-min time was the longest exposure duration for which no irritation was reported. An intraspecies uncertainty factor of 3 was applied to this NOAEL value because the con-

tact irritation from the highly corrosive fluorine is not expected to vary greatly among individuals, including susceptible individuals (NRC 2001). Although no data on asthmatics were found, the uncertainty factor of 3 is considered adequate to protect this sensitive subpopulation because the value is a NOAEL and because shorter-term, repeated exposures produced only slight irritation in healthy individuals. The value is supported by a second study in which volunteers “tolerated” exposure to 10 ppm for an undefined period of time (Belles 1965).

The clinical and experimental data base for human and animal exposures is limited to a single study (Keplinger and Suissa 1968). Other than the review of fluorine industrial exposures by Machle and Evans (1940) in which asthma attacks occurred more frequently in the industry than in non-exposed populations, no data on sensitive populations were found. A modifying factor of 2 was applied based on this limited database. The resulting value of 1.7 ppm (10 ppm/6) was used across all AEGL-1 exposure durations (Table 5-8 and Appendix B) because at mildly irritating concentrations there is accommodation to irritating gases. This value is supported by limited workplace monitoring data: workers exposed to fluorine at average yearly concentrations up to 1.2 ppm (range, 0.0-17 ppm) over a four-year period reported fewer incidences of respiratory complaints or diseases than a similar group of nonexposed workers (Lyon 1962). The workers are assumed to encompass a small range of sensitivity; the additional intraspecies uncertainty factor of 3 was considered sufficient to protect sensitive individuals.

A category plot of the animal and human data in relation to the AEGL values can be found in Appendix C.

## **6. DATA ANALYSIS FOR AEGL-2**

### **6.1. Summary of Human Data Relevant to AEGL-2**

Irritant effects were noted in human volunteers at concentrations of 25 ppm for 5 min and 50 ppm for 3 min. Irritant effects at these concentrations were described as slight and are below the discomfort described by the AEGL-2 definition. The concentration of 67 ppm for 1 min was described as irritating to the eyes and nose but not unbearable. This description is similar to that of the AEGL-2, but the exposure period is extremely short.

### **6.2. Summary of Animal Data Relevant to AEGL-2**

In the animal studies, Keplinger and Suissa (1968) characterized the symptoms of exposure equivalent to approximately 25% of the LC<sub>50</sub> as mild with slightly labored breathing, closed eyes, and mild to very mild lung congestion. For the respective species, 30-min concentrations corresponding to 20-25%

of the LC<sub>50</sub> were 70 ppm (rat), 67 ppm (mouse), and 71 ppm (rabbit). One-hour concentrations corresponding to 20-43% of the LC<sub>50</sub> were 47 ppm (rat), 30 ppm (mouse), and 73 ppm (no-effect concentration for guinea pig); these data are summarized in Table 5-7.

### 6.3. Derivation of AEGL-2

Mild lung congestion was chosen as the threshold for irreversible or other serious, long-lasting effects as defined by the AEGL-2. The mouse was chosen as the most sensitive species although the experimental results for respective exposure periods for the tested species are very similar. The single data set (Keplinger and Suissa 1968) was extensive, being based on five species and four exposure durations. The mildest effects noted in the Keplinger and Suissa (1968) study were very mild or mild diffuse congestion which were observed at approximately 25% (20-43%) of the LC<sub>50</sub> values. The rapid change in effects as the LC<sub>50</sub> is successively halved indicates the steepness of the dose-response curve for fluorine.

The mouse 30-min and 1-h values which caused very mild lung congestion were chosen for calculation of the AEGL-2 values. These concentrations are 67 ppm (30% of the 30-min LC<sub>50</sub>) and 30 ppm (20% of the 60-min LC<sub>50</sub>), respectively. An interspecies uncertainty factor of 1, an intraspecies uncertainty factor of 3, and a modifying factor of 2 were then applied to these numbers to derive the AEGL-2 (see discussion of uncertainty factors for AEGL-3). Extrapolation across time was based on the equation for the mouse,  $C^{1.77} \times t = k$ . The 4- and 8- h values were scaled from the 1-h value (see Appendix B for calculations). The values are listed in Table 5-9. The 8-h-AEGL-2 value was set equal to the 4-h value because at low concentrations the hygroscopic fluorine would react with and/or be scrubbed by the nasal passages, and because at mildly irritating concentrations, adaptation to sensory irritation occurs.

Although human exposure for durations longer than 1 min were to concentrations below the definition of the AEGL-2, a comparison of the human data with the derived values can be made. Extrapolating the 3-min exposure to 50 ppm from the data of Keplinger and Suissa (1968) to a 30-min time period results in a value of 13.6 ppm. The effects during this exposure, eye irritation (not otherwise specified) and slight nose irritation, are below the definition of the AEGL-2.

**TABLE 5-8** AEGL-1 Values for Fluorine

10-min	30-min	1-h	4-h	8-h
1.7 ppm (2.6 mg/m <sup>3</sup> )				

**TABLE 5-9** AEGL-2 Values for Fluorine

10-min	30-min	1-h	4-h	8-h
20 ppm (31 mg/m <sup>3</sup> )	11 ppm (17 mg/m <sup>3</sup> )	5.0 ppm (7.8 mg/m <sup>3</sup> )	2.3 ppm (3.6 mg/m <sup>3</sup> )	2.3 ppm (3.6 mg/m <sup>3</sup> )

## 7. DATA ANALYSIS FOR AEGL-3

### 7.1. Summary of Human Data Relevant to AEGL-3

No information on irreversible or life-threatening effects caused by fluorine in humans was located. A concentration of 50 ppm was characterized as irritating and concentrations of 67-100 ppm were “very irritating and became uncomfortable after a few seconds.”

### 7.2. Summary of Animal Data Relevant to AEGL-3

In the animal studies, Keplinger and Suissa (1968) characterized the symptoms of exposure equivalent to 50% of the LC<sub>50</sub> values as “dyspnea, lethargy, red nose, and swollen eyes.” No deaths occurred in any species (dog, rat, mouse, guinea pig, rabbit) at approximately 50% of the respective LC<sub>50</sub> values. All species tested at 50% of the LC<sub>50</sub> survived for up to 45 days post exposure. Effects ranged from disabling, characterized by respiratory irritation and labored breathing with severe diffuse lung congestion (mouse, 50% of the 1-h LC<sub>50</sub>), to practically non-disabling, characterized by no eye or nose irritation and very mild diffuse lung congestion (guinea pig, 43% of the 1-h LC<sub>50</sub>). At 50% of the 15-min LC<sub>50</sub>, guinea pigs showed signs of respiratory irritation and labored breathing and gross changes in the lungs of mild diffuse congestion. Mice were tested at 50, 34, 20, and 10% of the LC<sub>50</sub> for a 60-min exposure period. At a concentration equal to 50% of the 60-min LC<sub>50</sub>, the mouse showed signs of irritation and labored breathing and severe diffuse congestion of the lungs. At concentrations equal to 34 and 20% of the 60-min LC<sub>50</sub>, effects in the mouse were mild and very mild diffuse congestion, respectively, whereas the guinea pig, tested at 43% of its 60-min LC<sub>50</sub> suffered no effects. The dog was tested at a concentration closer to one-third (93 ppm) rather than one-half of the 1-h LC<sub>50</sub> concentration for the other species; at this concentration effects on the lungs were slight and would be more likely defined as an AEGL-2 level of effect. From the data involving effects at concentrations lower than the LC<sub>50</sub> values for the various time periods, the guinea pig appears to be the least sensitive species and the mouse is the most sensitive species. The only experimental data available for longer term exposures was the 7-h exposure of rats, mice, guinea pigs and rabbits to 100 ppm which resulted in an over-all mortality of 60% (Eriksen 1945; Stokinger 1949). The extrapolated data of Keplinger and Suissa (1968), 7-h LC<sub>50</sub> values of 65 and 50 ppm for the rat and mouse, respectively, yield more conservative concentrations.

### 7.3. Derivation of AEGL-3

The LC<sub>50</sub> values for the rat and mouse are very close for the 15, 30, and 60 min time periods (Keplinger and Suissa 1968). At 15 and 60 min, the mouse, rat, and guinea pig LC<sub>50</sub> values are almost identical (Table 5-6). At 30 min the mouse, rat, and rabbit LC<sub>50</sub> values are very close. The strong concordance of the LC<sub>50</sub> values between four animal species at three time points presents a strong case for the conclusion that lethality is a function of the concentration of fluorine in the air. Therefore, the exposure concentration equals the dose for fluorine and there is no need for scaling factors among species. Keplinger and Suissa (1968) demonstrated that at 50% of the LC<sub>50</sub> there were no deaths in five tested species in a total of 13 tests conducted over a 5- to 60-min exposure duration. Therefore, 50% of the LC<sub>50</sub> concentration was chosen as the NOEL for “life threatening effects.” The mouse was chosen as the most sensitive species although all of the LC<sub>50</sub> values were very similar. The 60-min value of 75 ppm was used as the basis for the AEGL-3.

Fluorine is a contact-site, direct-acting toxicant; there is no metabolic or pharmacokinetic component to fluorine-induced effects and there is likely to be little difference between species or among individuals in the response of biological tissues to fluorine exposure. The fact that the LC<sub>50</sub> values for four species were essentially identical, and the mechanism of action is direct chemical (corrosive) destruction of lung tissue would argue for the use of an uncertainty factor of 1 when extrapolating from animals to man. However, the data used to develop the AEGL-3 were obtained primarily from one laboratory and not confirmed elsewhere. Therefore, a modifying factor of 2 is used for this uncertainty. A factor of 3 is added to account for variability in human susceptibility (fluorine is a highly reactive, corrosive gas whose effect on the respiratory tissues is not expected to differ greatly among individuals). The combined uncertainty/modifying factor is 6. Concentrations were scaled across time using the  $C^{1.77} \times t = k$  relationship. Scaling from the 1-h experimental value to the 8-h exposure duration was considered realistic based on the similarity of extrapolated LC<sub>50</sub> values from the Keplinger and Suissa (1968) study and the 7-h experimental values from the Eriksen (1945) and Stokinger (1949) study. The 8-h value was set equal to the 4-h value as was done for the AEGL-2. Values are summarized in Table 5-10 and calculations are in Appendix B.

## 8. SUMMARY OF AEGLS

### 8.1. AEGL Values and Toxicity End Points

In summary, the AEGL values for various levels of effects and various time periods were derived using the following methods. The AEGL-1 was based on a study with human volunteers in which a concentration of 10 ppm administered for 15 min produced no irritation of the eyes, nose, or respiratory tract.

**TABLE 5-10** AEGL-3 Values for Fluorine

10-min	30-min	1-h	4-h	8-h
36 ppm (56 mg/m <sup>3</sup> )	19 ppm (29 mg/m <sup>3</sup> )	13 ppm (20 mg/m <sup>3</sup> )	5.7 ppm (8.8 mg/m <sup>3</sup> )	5.7 ppm (8.8 mg/m <sup>3</sup> )

This value was divided by 3 to account for differences in human sensitivity. Although no data on asthmatics, potentially susceptible populations were found, the fact that healthy humans have “tolerated” short-term exposures to 17 ppm indicates that the uncertainty factor of 3 is sufficient. A modifying factor of 2 was applied based on a limited data base. Because accommodation to the irritant effects of irritant gases occurs at mildly irritating concentrations, the derived value of 1.7 ppm was applied across all AEGL-1 time intervals.

In the absence of relevant human data, animal data were used to derive the AEGL-2 and AEGL-3 values. AEGL-2 values were derived based on concentrations equal to 25% of the LC<sub>50</sub> values from a study with the most sensitive species, the mouse. These concentrations, 67 and 30 ppm for 30- and 60 min exposures, respectively, produced only very mild lung congestion. An uncertainty factor of 3 for differences in human sensitivity and a modifying factor of 2 for the use of a single data set were then applied to these numbers. Extrapolation across time was based on the regression equation for LC<sub>50</sub> values and exposure times in the mouse,  $C^{1.77} \times t = k$ .

The AEGL-3 values were based on data using the laboratory mouse in which severe effects but no deaths were noted at 50% of the 30- and 60-min LC<sub>50</sub> values (113 and 75 ppm, respectively). A concentration equal to 50% of the 60-min LC<sub>50</sub> was selected from the mouse studies and scaled to other exposure times using the equation  $C^{1.77} \times t = k$ . An uncertainty factor of 3 for differences in human sensitivity and a modifying factor of 2 for the fact that the data set came from one laboratory and was not confirmed elsewhere were applied.

The AEGLs are summarized in Table 5-11. A summary of the derivations is contained in Appendix D.

## 8.2. Comparison with Other Standards and Guidelines

Standards and guidance levels for workplace and community exposures are listed in Table 5-12. The AEGL values are very close to other guidelines for emergency exposures. The NIOSH IDLH 30-min value refers to respirator use, but is slightly higher (25 ppm) than the 30-min AEGL-3 of 19 ppm. The NIOSH IDLH is based on the observation of Rickey (1959) that two men were able to tolerate 25 ppm very briefly but both developed sore throats and chest pains that lasted 6 h; 50 ppm could not be tolerated. The definitions of the preliminary ERPGs correspond to the three AEGLs. The ERPG 1-h values were recently changed from 2, 7.5, and 10 ppm to 0.5, 5, and 20 ppm, reasonably close to the AEGL values. Documentation for the values was not given in this source. The

NRC Emergency Exposure Guidance Levels (EEGLs) are for occupational exposures and not the general public. The 30- and 60-min EEGLs are 10 and 7.5 ppm whereas the 30- and 60-min AEGL-2 values are 11 and 5 ppm. The EEGL guidelines are based on the human and animal data of Keplinger and Suissa (1968).

Although the populations are not comparable, the ACGIH TLV-TWA and STEL of 1 and 2 ppm, respectively, are similar to the AEGL-1 value of 1.7 ppm. The ACGIH TLV-TWA guideline is based on the lack of significant medical findings in workers exposed to fluorine for 7 years (Lyon 1962) coupled with evidence of tolerance development in animals (Keplinger 1969). The ACGIH TLV-STEL is based on the human study in which exposures to 10 ppm, repeated for 3 to 5 min every 15 min for 2-3 h, produced only slight irritation to the eyes and skin (Keplinger and Suissa 1968). The OSHA PEL-TWA is also based on the Lyon (1962) study; however, OSHA and NIOSH believed that the Lyon study did not involve 61 workers continually exposed but instead was a compilation of data on workers who may have had some short-term exposure to fluorine. Thus, their TWA is 10 times lower than that of ACGIH. Neither NIOSH nor OSHA have promulgated short-term exposure limits (STELs). The German MAK and Dutch MAC peak limits are both 0.2 ppm.

### 8.3. Data Adequacy and Research Needs

Data from human studies are sparse and used healthy human subjects; exposures were usually short-term, with some exposure durations not stated. The study by Keplinger and Suissa (1968) used several short exposure durations and concentrations were measured. Data from animal studies used five species and encompassed a wide range of exposure concentrations and exposure durations, but none of the durations was for longer than 1 h for less than lethal effects. The animal studies were undertaken 27-47 years ago and analytical techniques have improved since then. The data base for human studies is inadequate (except for the AEGL-1) and the data base for animal studies is adequate, at least for 30- and 60-min exposures.

**TABLE 5-11** Summary of AEGL Values

Classification	Exposure Duration				
	10-min	30-min	1-h	4-h	8-h
AEGL-1 <sup>a</sup> (Nondisabling)	1.7 ppm (2.6 mg/m <sup>3</sup> )				
AEGL-2 <sup>b</sup> (Disabling)	20 ppm (31 mg/m <sup>3</sup> )	11 ppm (17 mg/m <sup>3</sup> )	5.0 ppm (7.8 mg/m <sup>3</sup> )	2.3 ppm (3.6 mg/m <sup>3</sup> )	2.3 ppm (3.6 mg/m <sup>3</sup> )
AEGL-3 (Lethal)	36 ppm (56 mg/m <sup>3</sup> )	19 ppm (29 mg/m <sup>3</sup> )	13 ppm (20 mg/m <sup>3</sup> )	5.7 ppm (8.8 mg/m <sup>3</sup> )	5.7 ppm (8.8 mg/m <sup>3</sup> )

<sup>a</sup>AEGL-1 values held constant across time because of accommodation to mildly irritating concentrations of irritant gases.

<sup>b</sup>30-min and 1-h AEGL-2 values are based on separate data points.

**TABLE 5-12** Extant Standards and Guidelines for Fluorine

Guideline	Exposure Duration				
	10 min	30 min	1 h	4 h	8 h
AEGL-1	1.7 ppm	1.7 ppm	1.7 ppm	1.7 ppm	1.7 ppm
AEGL-2	20 ppm	11 ppm	5.0 ppm	2.3 ppm	2.3 ppm
AEGL-3	36 ppm	19 ppm	13 ppm	5.7 ppm	5.7 ppm
ERPG-1 (AIHA) <sup>a</sup>			0.5 ppm		
ERPG-2 (AIHA)			5 ppm		
ERPG-3 (AIHA)			20 ppm		
EEGL (NRC) <sup>b</sup>	15 ppm	10 ppm	7.5 ppm		
IDLH (NIOSH) <sup>c</sup>		25 ppm			
REL-TWA (NIOSH) <sup>d</sup>					0.1 ppm
PEL-TWA (OSHA) <sup>e</sup>					0.1 ppm
TLV-TWA (ACGIH) <sup>f</sup>					1 ppm
TLV-STEL (ACGIH) <sup>g</sup>					2 ppm
MAK (Germany) <sup>h</sup>					0.1 ppm
MAK Peak Limit (Germany) <sup>i</sup>					0.2 ppm
MAC Peak Limit (The Netherlands) <sup>j</sup>					0.2 ppm? (0.5mg/m3)
OELV-LLV (Sweden)					0.1 ppm
OELV-STV (Sweden)	0.3 ppm (15 min.)				

<sup>a</sup>ERPG (Emergency Response Planning Guidelines, American Industrial Hygiene Association (AIHA 2004).

The ERPG-1 is the maximum airborne concentration below which it is believed nearly all individuals could be exposed for up to 1 h without experiencing other than mild, transient adverse health effects or without perceiving a clearly defined objectionable odor.

The ERPG-2 is the maximum airborne concentration below which it is believed nearly all individuals could be exposed for up to 1 h without experiencing or developing irreversible or other serious health effects or symptoms that could impair an individual's ability to take protective action.

The ERPG-3 is the maximum airborne concentration below which it is believed nearly all individuals could be exposed for up to 1 h without experiencing or developing life-threatening health effects.

<sup>b</sup>EEGL (Emergency Exposure Guidance Levels, National Research Council (NRC 1984).

The EEGL is the concentration of contaminants that can cause discomfort or other evidence of irritation or intoxication in or around the workplace, but avoids death, other severe acute effects and long-term or chronic injury.

<sup>c</sup>IDLH (Immediately Dangerous to Life and Health, National Institute of Occupational Safety and Health) (NIOSH 1996) represents the maximum concentration from which one could escape within 30 min without any escape-impairing symptoms, or any irreversible health effects.

<sup>d</sup>REL-TWA (Recommended Exposure Limits - Time Weighted Average, National Institute of Occupational Safety and Health) (NIOSH 2005) is defined analogous to the ACGIH-TLV-TWA.

<sup>e</sup>PEL-TWA (Permissible Exposure Limits - Time Weighted Average, Occupational Health and Safety Administration) (NIOSH 2005) is defined analogous to the ACGIH-TLV-TWA, but is for exposures of no more than 10 h/day, 40 h/week.

<sup>f</sup>TLV-TWA (Threshold Limit Value - Time Weighted Average, American Conference of Governmental Industrial Hygienists) (ACGIH 2004) is the time-weighted average concentration for a normal 8-h workday and a 40-h workweek, to which nearly all workers may be repeatedly exposed, day after day, without adverse effect.

<sup>g</sup>TLV-STEL (Threshold Limit Value - Short Term Exposure Limit, American Conference of Governmental Industrial Hygienists) (ACGIH 2004) is defined as a 15-min TWA exposure which should not be exceeded at any time during the workday even if the 8-h TWA is within the TLV-TWA. Exposures above the TLV-TWA up to the STEL should not be longer than 15 min and should not occur more than 4 times per day. There should be at least 60 min between successive exposures in this range.

<sup>h</sup>MAK (Maximale Arbeitsplatzkonzentration [Maximum Workplace Concentration-German Research Association] (DFG 2002) is defined analogous to the ACGIH-TLV-TWA.

<sup>i</sup>MAK Spitzenbegrenzung (Peak Limit [give category]) (German Research Association 2002) (DFG 2002) constitutes the maximum average concentration to which workers can be exposed for a period up to 30 min with no more than 2 exposure periods per work shift; total exposure may not exceed 8-h MAK.

<sup>j</sup>MAC (Maximaal Aanvaarde Concentratie [Maximal Accepted Concentration] Dutch Expert Committee for Occupational Standards, The Netherlands) (MSZW 2004) is defined analogous to the ACGIH-TLV-TWA.

<sup>k</sup>OELV -LLV(Occupational Exposure Limit Value-Level Limit Value).

<sup>l</sup>OELV -CLV(Occupational Exposure Limit Value-Ceiling Limit Value) (Swedish Work Environment Authority 2005) is the maximum acceptable average concentration (time-weighted average) of an air contaminant in respiratory air. An occupational exposure limit value is either a level limit value (one working day) or a ceiling limit value (15 min or some other reference time period), and short time value (A recommended value consisting of a time-weighted average for exposure during a reference period of 15 min).

Although data from one study could be used to estimate the concentration-exposure duration relationships for several animal species ( $C^n \times t = k$ ), the longest exposure duration was only 1 h. The study of Eriksen (1945) and Stokinger (1949), although flawed due to difficulty in monitoring the test concentrations, tend to support the extrapolation to longer exposure times. Their single data

point for the rat, 54% mortality at a concentration of 100 ppm for 7 h, when extrapolated to a 1-h exposure gives an approximate LC<sub>50</sub> of 300 ppm (the actual concentration is probably lower due to chamber losses [Ricca 1970]). This value is within a factor of 2 of the 1-h LC<sub>50</sub> for the rat of 187 ppm in the Keplinger and Suissa study.

The total body of data on the sublethal and lethal effects of fluorine is reasonably consistent. The mechanism of action is understood. Although most of the experimental exposures were of short duration, at least one additional experimental value is consistent with the derived time-scaling relationship. Application of an intraspecies uncertainty factor of 3 to the human data, an interspecies uncertainty factor of 1 to the animal data, and a modifying factor of 2 to reasonably consistent but limited human and animal data is appropriate to insure the safety of the values.

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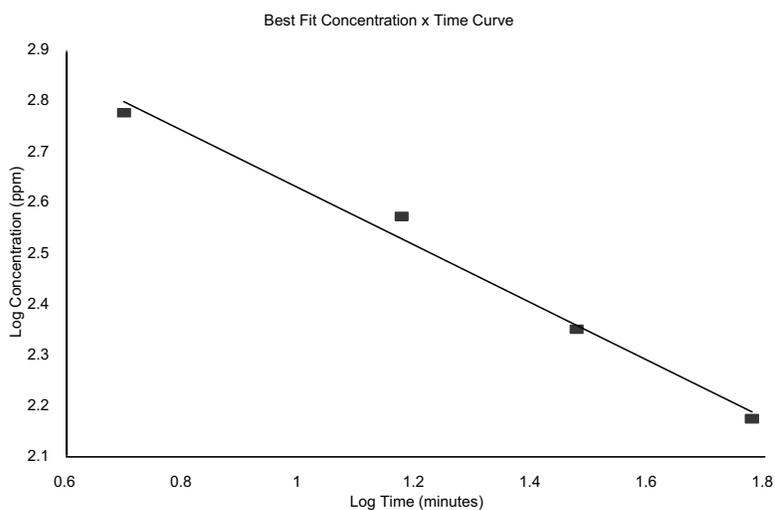
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APPENDIX A

Time-Scaling Graph for Fluorine



**FIGURE A-1** LC<sub>50</sub> values for the mouse. Source: Keplinger and Suissa 1968. Reprinted with permission; copyright 1968, *Journal of Industrial Hygiene and Toxicology*.

Time (minutes)	Concentration (ppm)	Log time	Log concentration
5	600	0.6990	2.7782
15	375	1.1761	2.5740
30	225	1.4771	2.3522
60	150	1.7782	2.1761

Regression Output:

Intercept	3.1958
Slope	-0.5658
R Squared	0.9872
Correlation	-0.9936
Degrees of Freedom	2
Observations	4

n = 1.77  
k = 444989

## APPENDIX B

### Derivation of AEGL Values for Fluorine

#### Derivation of AEGL-1

Key Study:	Keplinger and Suissa 1968
Toxicity end point:	No irritant effects in humans exposed to 10 ppm for 15 min
Scaling:	Not used; because accommodation to low concentrations of fluorine, the values were not time-scaled
Uncertainty factor:	3 for differences in human sensitivity (an uncertainty factor of 3 rather than 10 was used because 10 ppm for 15 min is a no-effect level; in addition, fluorine reacts chemically with the tissues of the respiratory tract and effects are unlikely to differ among individuals).
Modifying factor:	2 to account for a single data set.
Calculation:	$10 \text{ ppm}/6 = 1.7 \text{ ppm}$

#### Derivation of AEGL-2

Key Study:	Keplinger and Suissa 1968
Toxicity end point:	Very mild diffuse lung congestion in mice exposed to 67 ppm for 30 min and 30 ppm for 1 h.
Scaling:	$C^{1.77} \times t = k$ (ten Berge et al. 1986)
Uncertainty factors:	1 for interspecies differences (four species had similar $LC_{50}$ values) 3 to account for differences in human sensitivity (the toxicity end point is a mild effect level and the toxic effect is due to a chemical reaction with biological tissue of the respiratory tract which is unlikely to be different among individuals).
Modifying factor:	2 to account for a single data set.
Calculations:	$(67 \text{ ppm}/6)^{1.77} \times 30 \text{ min} = 2091 \text{ ppm}^{1.77} \cdot \text{min}$ $(30 \text{ ppm}/6)^{1.77} \times 60 \text{ min} = 1035.92 \text{ ppm}^{1.77} \cdot \text{min}$
10-min AEGL-2	$C^{1.77} \times 10 \text{ min} = 2091 \text{ ppm}^{1.77} \cdot \text{min}$ $C = 20 \text{ ppm}$
30-min AEGL-2	$67 \text{ ppm}/6 = 11 \text{ ppm}$
1-h AEGL-2	$30 \text{ ppm}/6 = 5 \text{ ppm}$
4-h AEGL-2	$C^{1.77} \times 240 \text{ min} = 1035.92 \text{ ppm}^{1.77} \cdot \text{min}$ $C = 2.3 \text{ ppm}$
8-h AEGL-2	Because of accommodation to low concentrations of irritant gases, the 8-h value was set equal to the 4-h value. $C = 2.3 \text{ ppm}$

### Derivation of AEGL-3

Key Study:	Keplinger and Suissa 1968
Toxicity end point:	Severe diffuse lung congestion in mice exposed to 75 ppm for 1 h.
Scaling:	$C^{1.77} \times t = k$ (ten Berge et al. 1986)
Uncertainty factors:	1 for interspecies differences (four species had similar LC <sub>50</sub> values) 3 to account for differences in human sensitivity (the toxic effect is due to a chemical reaction with biological tissue of the respiratory tract which is unlikely to be different among individuals).
Modifying factor:	2 to account for a single data set.
Calculations:	$(75 \text{ ppm}/6)^{1.77} \times 60 \text{ min} = 5244.23 \text{ ppm}^{1.77} \cdot \text{min}$
10-min AEGL-3	$C^{1.77} \times 10 \text{ min} = 5244.23 \text{ ppm}^{1.77} \cdot \text{min}$ C = 36 ppm
30-min AEGL-3	$C^{1.77} \times 30 \text{ min} = 5244.23 \text{ ppm}^{1.77} \cdot \text{min}$ C = 19 ppm
60-min AEGL-3	75 ppm/6 = 13 ppm
4-h AEGL-3	$C^{1.77} \times 240 \text{ min} = 5244.23 \text{ ppm}^{1.77} \cdot \text{min}$ C = 5.7 ppm
8-h AEGL-3	Because of accommodation to low concentrations of irritant gases, the 8-h value was set equal to the 4-h value. C = 5.7 ppm

APPENDIX C  
Category Graph of Toxicity Data and AEGL Values for Fluorine

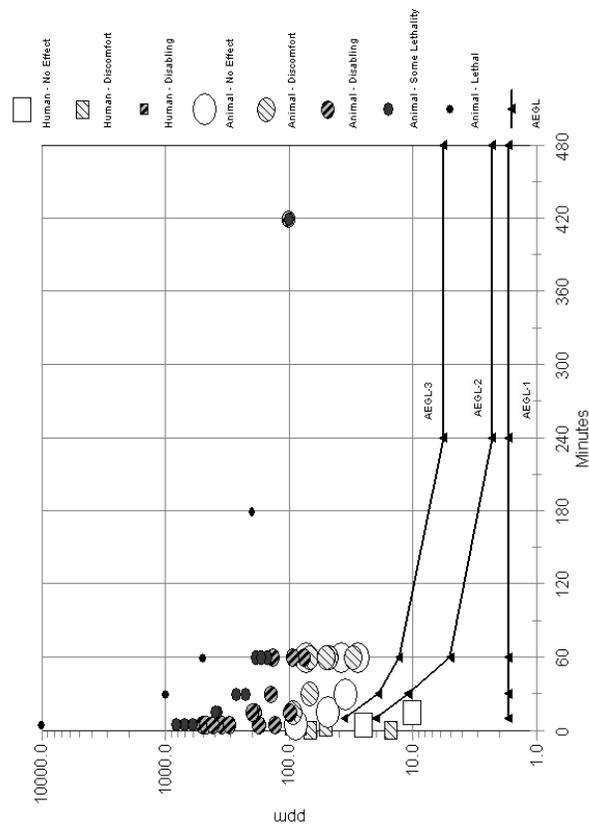


FIGURE C-1 Category graph of toxicity data and AEGL values for fluorine.

**APPENDIX D**

**Derivation Summary for Fluorine AEGLs**

**AEGL-1 VALUES**

10-min	30-min	1-h	4-h	8-h
1.7 ppm	1.7 ppm	1.7 ppm	1.7 ppm	1.7 ppm
Key Reference: Keplinger, M.L., and L.W. Suissa. 1968. Toxicity of fluorine short-term inhalation. <i>Am. Ind. Hyg. Assoc. J.</i> 29(1):10-18.				
Test Species/Strain/Number: 5 human subjects				
Exposure Route/Concentrations/Durations: Inhalation: 10-100 ppm for various exposure durations.				
Effects: 10 ppm for 15 min: no eye, nose or respiratory irritation (basis for AEGL-1) 25 ppm for 5 min: eye irritation 50 ppm for 3 min: irritating to eyes, slightly irritating to nose 67 ppm for 1 min: irritating to eyes and nose 100 ppm for 1 min: very irritating to eyes and nose; subjects did not inhale				
End Point/Concentration/Rationale: 10 ppm for 15 min resulted in no sensory irritation in healthy human subjects. Although this value is below the definition of an AEGL-1, it provides the longest exposure duration for which no irritation is reported. All studies indicated that fluorine is highly irritating and corrosive.				
Uncertainty Factors/Rationale: Total uncertainty factor: 3 Interspecies: Not applicable, human subjects were tested Intraspecies: 3- The effect was a NOAEL for sensory irritation. Limited workplace monitoring data showed that workers exposed to fluorine at average yearly concentrations up to 1.2 ppm (range, 0.0-17 ppm) over a four-year period reported fewer incidences of respiratory complaints or diseases than a similar group of nonexposed workers (Lyon 1962). The workers are assumed to encompass a small range of sensitivity; the additional intraspecies uncertainty factor of 3 was considered sufficient to protect sensitive individuals.				
Modifying Factor: 2 - to account for a limited data base.				
Animal to Human Dosimetric Adjustment: Not applicable; human data used.				
Time Scaling: Not applied; at mildly irritating concentrations, adaptation to sensory irritation occurs.				
Data Adequacy: The key study was well conducted and documented; data in supporting studies were limited.				

**AEGL-2 VALUES**

10-min	30-min	1-h	4-h	8-h
20 ppm	11 ppm	5.0 ppm	2.3 ppm	2.3 ppm

Key Reference: Keplinger, M.L., and L.W. Suissa. 1968. Toxicity of fluorine short-term inhalation. *Am. Ind. Hyg. Assoc. J.* 29(1):10-18.

Test Species/Strain/Number: Swiss-Webster mice (sex not stated), 10/exposure group

Exposure Route/Concentrations/Durations:

Inhalation: 38, 79, 174, 300, 467, 600 ppm for 5 min

32, 65, 87, 188, 375 ppm for 15 min

16, 32, 67, 113, 225 ppm for 30 min

15, 30, 50, 75, 150 ppm for 1 h

Effects (the 30-min and 1-h exposures were considered):

30-min exposures:

16 ppm: no toxic signs, no gross lung pathology

32 ppm: no toxic signs, no gross lung pathology

67 ppm: no toxic signs, very mild diffuse lung congestion (basis for AEGL-2)

13 ppm: irritation and labored breathing, mild diffuse lung congestion

225 ppm: LC<sub>50</sub>

1-h exposures:

15 ppm: no toxic signs, no gross lung pathology

30 ppm: no toxic signs, very mild diffuse lung congestion (basis for AEGL-2)

50 ppm: labored breathing, mild diffuse lung congestion

75 ppm: irritation and labored breathing, severe diffuse lung congestion

150 ppm: LC<sub>50</sub>

End Point/Concentration/Rationale: 67 ppm for 30 min and 30 ppm for 1 h resulted in very mild diffuse lung congestion. Very mild lung congestion was considered the threshold for serious long-lasting effects such as severe lung congestion, seen at the next highest level tested.

Uncertainty Factors/Rationale:

Total uncertainty factor: 3

Interspecies: 1 - The effect (lung congestion) as well as LC<sub>50</sub> values reported in the study were very similar for the rat, rabbit, and guinea pig (indicating similar species sensitivity). With the exception of the 5-min LC<sub>50</sub> value for the rabbit, the LC<sub>50</sub> values for all four species at 15, 30, and 60 min were very similar.

Intraspecies: 3 - At the AEGL-2 concentrations, the effect of irritant gases is expected to be directly damaging to the tissues. The corrosive effect is not expected to differ greatly among individuals.

Modifying Factor: 2 - to account for a limited data base.

Animal to Human Dosimetric Adjustment: Not applied.

Time Scaling:  $C^n \times t = k$  where  $n = 1.77$ ; based on regression analysis of the mouse (the most sensitive species) LC<sub>50</sub> data from the study conducted at 5, 15, 30, and 60 min (Keplinger and Suissa 1968). The 10-min value was time scaled from the 30-min value and the 4-h value was time scaled from the 1-h value. The 8-h value was set equal to the 4-h value because at low concentrations the hygroscopic fluorine would react with or be scrubbed by the nasal passages.

Data Adequacy: The key study was well conducted and documented; there were limited confirming data from other laboratories.

**AEGL-3 VALUES**

10-min	30-min	1-h	4-h	8-h
36 ppm	19 ppm	13 ppm	5.7 ppm	5.7 ppm

Key Reference: Keplinger, M.L., and L.W. Suissa. 1968. Toxicity of fluorine short-term inhalation. *Am. Ind. Hyg. Assoc. J.* 29(1):10-18.

Test Species/Strain/Number: Swiss-Webster mice (sex not stated), 10/exposure group

Exposure Route/Concentrations/Durations:

Inhalation: 38, 79, 174, 300, 467, 600 ppm for 5 min

32, 65, 87, 188, 375 ppm for 15 min

16, 32, 67, 113, 225 ppm for 30 min

5, 30, 50, 75, 150 ppm for 1 h

Effects: The 1-h substudy using the mouse was considered

15 ppm: no toxic signs, no gross lung pathology

30 ppm: no toxic signs, very mild diffuse lung congestion (basis for AEGL-2)

50 ppm: labored breathing, mild diffuse lung congestion

75 ppm: irritation and labored breathing, severe diffuse lung congestion

150 ppm: LC<sub>50</sub>

End Point/Concentration/Rationale: 75 ppm for 1 h resulted in irritation and labored breathing and severe diffuse lung congestion in the mouse. No deaths occurred. Severe diffuse lung congestion was considered the threshold for lethality.

Uncertainty Factors/Rationale:

Total uncertainty factor: 3

Interspecies: 1 - The effects (lung congestion) as well as LC<sub>50</sub> values reported in the study were very similar for the rat, rabbit, and guinea pig (indicating similar species sensitivity). With the exception of the 5-min LC<sub>50</sub> for the rabbit, the LC<sub>50</sub> values for all four species at 15, 30, and 60 min were very similar. Thus, the concentration:end point did not differ greatly among species.

Intraspecies: 3 - Lung congestion at a specific concentration is not expected to differ greatly among individuals.

Modifying Factor: 2 - to account for a limited data base

Animal to Human Dosimetric Adjustment: Not applied.

Time Scaling:  $C^n \times t = k$  where  $n = 1.77$ ; based on regression analysis of the mouse (the most sensitive species) LC<sub>50</sub> data from the study conducted at 5, 15, 30, and 60 min (Keplinger and Suissa 1968). The values were time scaled from the 1-h data. The 8-h value was set equal to the 4-h value as was done for the AEGL-2. The safety of setting the 8-h value equal to the 4-h value is supported by another study in which a 7-h exposure to 100 ppm resulted in an overall 60% mortality in four species (Eriksen 1945; Stockinger 1949). The time-scaled 7-h LC<sub>50</sub> values from the key study for the mouse (50 ppm) and rat (65 ppm) are lower.

Data Adequacy: The key study was well conducted and documented, but there were limited confirming data from other laboratories.

**Center for Disease Control**

**(CDC)**

**&**

**National Institute for Occupational Safety and Health**

**(NIOSH)**



May 1994

## Documentation for Immediately Dangerous To Life or Health Concentrations (IDLHs)

### Fluorine

**CAS number:** 7782-41-4

**NIOSH REL:** 0.1 ppm (0.2 mg/m<sup>3</sup>) TWA

**Current OSHA PEL:** 0.1 ppm (0.2 mg/m<sup>3</sup>) TWA

**1989 OSHA PEL:** Same as current PEL

**1993-1994 ACGIH TLV:** 1 ppm (1.6 mg/m<sup>3</sup>) TWA, 2 ppm (3.1 mg/m<sup>3</sup>) STEL

**Description of Substance:** Pale-yellow to greenish gas with a pungent, irritating odor.

**LEL:** . . Nonflammable Gas

**Original (SCP) IDLH:** 25 ppm

**Basis for original (SCP) IDLH:** The chosen IDLH is based on the statement by AIHA [1965] that "2 men were able to tolerate 25 ppm very briefly but both developed sore throats and chest pains lasting 6 hours; 50 ppm could not be tolerated [Rickey 1959]."

**Existing short-term exposure guidelines:** National Research Council [NRC 1984] Emergency Exposure Guidance Levels (EEGLs):

10-minute EEGL: 15 ppm

30-minute EEGL: 10 ppm

60-minute EEGL: 7.5 ppm

#### ACUTE TOXICITY DATA

##### Lethal concentration data:

Species	Reference	LC <sub>50</sub> (ppm)	LC <sub>Lo</sub> (ppm)	Time	Adjusted 0.5-hr LC (CF)	Derived value
Rat	Keplinger and Suissa 1968	185	-----	1 hr	231 ppm (1.25)	23 ppm
Mouse	Keplinger and Suissa 1968	150	-----	1 hr	188 ppm (1.25)	19 ppm

Rabbit	Keplinger and Suissa 1968	270	-----	30 min	270 ppm (1.0)	27 ppm
G. pig	Keplinger and Suissa 1968	170	-----	1 hr	213 ppm (1.25)	21 ppm

**Human data:** It has been reported that 2 men were able to tolerate 25 ppm very briefly but both developed sore throats and chest pains that lasted 6 hours; 50 ppm could not be tolerated [Rickey 1959]. Volunteers tolerated 10 ppm for 15 minutes with a minimum of irritation [Ricca 1970]. Intermittent exposures to 10 ppm were repeated every 3 to 5 minutes for 15 minutes over 2 to 3 hours with only slight irritation of the eyes and skin noted [Ricca 1970]. Much irritation of the eyes have been noted at 100 ppm, but with no aftereffects after only 30 seconds [Grant 1974]. It has been observed that exposures up to 30 ppm for 5 to 30 minutes had no ill effects [Lyon 1962].

**Revised IDLH:** 25 ppm [Unchanged]  
**Basis for revised IDLH:** Based on acute inhalation toxicity data in humans [Grant 1974; Lyon 1962; Ricca 1970; Rickey 1959], the original IDLH for fluorine (25 ppm) is not being revised at this time.

**REFERENCES:**

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