AGENDA ITEM 6

RULE SUMMARY

Subject: **Amendment to Acceptable Ambient Level for Arsenic** (514)

Rule Citation	What is Changed	Purpose of Change (Why)	Who is Affected and How	Impacts
15A NCAC 02D .1104 *Toxic Air Pollutant Guidelines*	The Acceptable Ambient Level (AAL) value for arsenic and arsenic-containing inorganic compounds (arsenic compounds) of 2.3×10^{-7} milligrams per cubic meter (mg/m^3) has changed to 2.1×10^{-6} mg/m^3 on an annual average basis.	In response to a request made by the North Carolina Division of Air Quality (DAQ), the Secretary's Science Advisory Board for Toxic Air Pollutants (NCSAB) reassessed the AAL for arsenic compounds. Based on up-to-date information and risk assessment methods widely accepted and used by regulatory bodies, the NCSAB recommends an update to the AAL for these compounds.	There are three groups of affected parties: 1. Currently 450 facilities with emissions of arsenic compounds required to have an air quality permit. Reduced regulatory burden due to amendments as 137 fewer facilities are affected.	The analysis assumed $196,000 in annualized avoided costs begin the first year due to less restrictive permit conditions or not installing add-on controls. These cumulative avoided costs reach $980,000 within the five year period of analysis, assuming two percent more of the potentially affected facilities each year experience these cost savings.
15A NCAC 02Q .0711 *Emission Rates Requiring a Permit* 15A NC	The corresponding value for toxic air pollutant permitting emissions rates (TPER) for arsenic compounds has changed from 0.016 pounds per year to 0.053 pounds per year.	The TPER must likewise be changed because its value is derived directly from the AAL value.	2. Less DAQ compliance modeling demonstration review effort due to a higher TPER affecting fewer facilities. 3. The North Carolina general public.	Annual avoided cost for DAQ modeling effort of $14,700. May reduce regulatory burden without compromising the health based guidelines of the NCSAB.

15A NCAC 02D .1104 is proposed for amendment as follows:

15A NCAC 02D .1104 TOXIC AIR POLLUTANT GUIDELINES

A facility shall not emit any of the following toxic air pollutants in such quantities that may cause or contribute beyond the premises (adjacent property boundary) to any significant ambient air concentration that may adversely affect human health. In determining these significant ambient air concentrations, the Division shall be guided by the following list of acceptable ambient levels in milligrams per cubic meter at 77° F (25° C) and 29.92 inches (760 mm) of mercury pressure (except for asbestos):

Pollutant (CAS Number)	Annual (Carcinogens)	24-hour (Chronic Toxicants)	1-hour (Acute Systemic Toxicants)	1-hour (Acute Irritants)
acetaldehyde (75-07-0)				27
acetic acid (64-19-7)				3.7
acrolein (107-02-8)				0.08
acrylonitrile (107-13-1)		0.03	1	
ammonia (7664-41-7)				2.7
aniline (62-53-3)			1	
arsenic and inorganic arsenic compounds	~~2.3×10^{-7}~~ 2.1×10^{-6}			
asbestos (1332-21-4)	2.8×10^{-11} fibers/ml			
aziridine (151-56-4)		0.006		
benzene (71-43-2)	1.2×10^{-4}			
benzidine and salts (92-87-5)	1.5×10^{-8}			
benzo(a)pyrene (50-32-8)	3.3×10^{-5}			
benzyl chloride (100-44-7)			0.5	
beryllium (7440-41-7)	4.1×10^{-6}			
beryllium chloride (7787-47-5)	4.1×10^{-6}			
beryllium fluoride (7787-49-7)	4.1×10^{-6}			
beryllium nitrate (13597-99-4)	4.1×10^{-6}			
bioavailable chromate pigments, as chromium (VI) equivalent	8.3×10^{-8}			
bis-chloromethyl ether (542-88-1)	3.7×10^{-7}			
bromine (7726-95-6)				0.2

Pollutant (CAS Number)	Annual (Carcinogens)	24-hour (Chronic Toxicants)	1-hour (Acute Systemic Toxicants)	1-hour (Acute Irritants)
1,3-butadiene (106-99-0)	4.4×10^{-4}			
cadmium (7440-43-9)	5.5×10^{-6}			
cadmium acetate (543-90-8)	5.5×10^{-6}			
cadmium bromide (7789-42-6)	5.5×10^{-6}			
carbon disulfide (75-15-0)		0.186		
carbon tetrachloride (56-23-5)	6.7×10^{-3}			
chlorine (7782-50-5)		0.0375		0.9
chlorobenzene (108-90-7)		2.2		
chloroform (67-66-3)	4.3×10^{-3}			
chloroprene (126-99-8)		0.44	3.5	
cresol (1319-77-3)			2.2	
p-dichlorobenzene (106-46-7)				66
dichlorodifluoromethane (75-71-8)		248		
dichlorofluoromethane (75-43-4)		0.5		
di(2-ethylhexyl)phthalate (117-81-7)		0.03		
dimethyl sulfate (77-78-1)		0.003		
1,4-dioxane (123-91-1)		0.56		
epichlorohydrin (106-89-8)	8.3×10^{-2}			
ethyl acetate (141-78-6)			140	
ethylenediamine (107-15-3)		0.3	2.5	
ethylene dibromide (106-93-4)	4.0×10^{-4}			
ethylene dichloride (107-06-2)	3.8×10^{-3}			
ethylene glycol monoethyl ether (110-80-5)		0.12	1.9	
ethylene oxide (75-21-8)	2.7×10^{-5}			
ethyl mercaptan (75-08-1)			0.1	
fluorides		0.016	0.25	
formaldehyde (50-00-0)				0.15
hexachlorocyclopentadiene (77-47-4)		0.0006	0.01	
hexachlorodibenzo-p-dioxin (57653-85-	7.6×10^{-8}			

Pollutant (CAS Number)	Annual (Carcinogens)	24-hour (Chronic Toxicants)	1-hour (Acute Systemic Toxicants)	1-hour (Acute Irritants)
7)				
n-hexane (110-54-3)		1.1		
hexane isomers except n-hexane				360
hydrazine (302-01-2)		0.0006		
hydrogen chloride (7647-01-0)				0.7
hydrogen cyanide (74-90-8)		0.14	1.1	
hydrogen fluoride (7664-39-3)		0.03		0.25
hydrogen sulfide (7783-06-4)		0.12		
maleic anhydride (108-31-6)		0.012	0.1	
manganese and compounds		0.031		
manganese cyclopentadienyl tricarbonyl (12079-65-1)		0.0006		
manganese tetroxide (1317-35-7)		0.0062		
mercury, alkyl		0.00006		
mercury, aryl and inorganic compounds		0.0006		
mercury, vapor (7439-97-6)		0.0006		
methyl chloroform (71-55-6)		12		245
methylene chloride (75-09-2)	2.4×10^{-2}		1.7	
methyl ethyl ketone (78-93-3)		3.7		88.5
methyl isobutyl ketone (108-10-1)		2.56		30
methyl mercaptan (74-93-1)			0.05	
nickel carbonyl (13463-39-3)		0.0006		
nickel metal (7440-02-0)		0.006		
nickel, soluble compounds, as nickel		0.0006		
nickel subsulfide (12035-72-2)	2.1×10^{-6}			
nitric acid (7697-37-2)				1
nitrobenzene (98-95-3)		0.06	0.5	
n-nitrosodimethylamine (62-75-9)	5.0×10^{-5}			
non-specific chromium (VI)	8.3×10^{-8}			

Pollutant (CAS Number)	Annual (Carcinogens)	24-hour (Chronic Toxicants)	1-hour (Acute Systemic Toxicants)	1-hour (Acute Irritants)
compounds, as chromium (VI) equivalent				
pentachlorophenol (87-86-5)		0.003	0.025	
perchloroethylene (127-18-4)	1.9×10^{-1}			
phenol (108-95-2)			0.95	
phosgene (75-44-5)		0.0025		
phosphine (7803-51-2)				0.13
polychlorinated biphenyls (1336-36-3)	8.3×10^{-5}			
soluble chromate compounds, as chromium (VI) equivalent		6.2×10^{-4}		
styrene (100-42-5)			10.6	
sulfuric acid (7664-93-9)		0.012	0.1	
tetrachlorodibenzo-p-dioxin (1746-01-6)	3.0×10^{-9}			
1,1,1,2-tetrachloro-2,2,- difluoroethane (76-11-9)		52		
1,1,2,2-tetrachloro-1,2- difluoroethane (76-12-0)		52		
1,1,2,2-tetrachloroethane (79-34-5)	6.3×10^{-3}			
toluene (108-88-3)		4.7		56
toluene diisocyanate, 2,4- (584-84-9) and 2,6- (91-08-7) isomers		0.0002		
trichloroethylene (79-01-6)	5.9×10^{-2}			
trichlorofluoromethane (75-69-4)			560	
1,1,2-trichloro-1,2,2- trifluoroethane (76-13-1)				950
vinyl chloride (75-01-4)	3.8×10^{-4}			
vinylidene chloride (75-35-4)		0.12		
xylene (1330-20-7)		2.7		65

History Note: *Authority G.S. 143-215.3(a)(1); 143-215.107(a)(3),(4),(5); 143B-282; S.L. 1989, c. 168, s. 45;*

Eff. May 1, 1990;

Amended Eff. September 1, 1992; March 1, 1992;

Temporary Amendment Eff. July 20, 1997;

Amended Eff. _____; March 1, 2010; June 1, 2008; April 1, 2005; April 1, 2001; July 1, 1998.

15A NCAC 02Q .0711 is proposed for amendment as follows:

15A NCAC 02Q .0711 EMISSION RATES REQUIRING A PERMIT

(a) A permit to emit toxic air pollutants is required for any facility whose actual (or permitted if higher) rate of emissions from all sources are greater than any one of the following toxic air pollutant permitting emissions rates:

Pollutant (CAS Number)	Carcinogens lb/yr	Chronic Toxicants lb/day	Acute Systemic Toxicants lb/hr	Acute Irritants lb/hr
acetaldehyde (75-07-0)				6.8
acetic acid (64-19-7)				0.96
acrolein (107-02-8)				0.02
acrylonitrile (107-13-1)		0.4	0.22	
ammonia (7664-41-7)				0.68
aniline (62-53-3)			0.25	
arsenic and inorganic arsenic compounds	~~0.016~~ 0.053			
asbestos (1332-21-4)	1.9 X 10^{-6}			
aziridine (151-56-4)		0.13		
benzene (71-43-2)	8.1			
benzidine and salts (92-87-5)	0.0010			
benzo(a)pyrene (50-32-8)	2.2			
benzyl chloride (100-44-7)			0.13	
beryllium (7440-41-7)	0.28			
beryllium chloride (7787-47-5)	0.28			
beryllium fluoride (7787-49-7)	0.28			
beryllium nitrate (13597-99-4)	0.28			
bioavailable chromate pigments, as chromium (VI) equivalent	0.0056			
bis-chloromethyl ether (542-88-1)	0.025			
bromine (7726-95-6)				0.052
1,3-butadiene (106-99-0)	11			
cadmium (7440-43-9)	0.37			
cadmium acetate (543-90-8)	0.37			
cadmium bromide (7789-42-6)	0.37			
carbon disulfide (75-15-0)		3.9		

carbon tetrachloride (56-23-5)	460			
chlorine (7782-50-5)		0.79		0.23
chlorobenzene (108-90-7)		46		
chloroform (67-66-3)	290			
chloroprene (126-99-8)		9.2	0.89	
cresol (1319-77-3)			0.56	
p-dichlorobenzene (106-46-7)				16.8
dichlorodifluoromethane (75-71-8)		5200		
dichlorofluoromethane (75-43-4)		10		
di(2-ethylhexyl)phthalate (117-81-7)		0.63		
dimethyl sulfate (77-78-1)		0.063		
1,4-dioxane (123-91-1)		12		
epichlorohydrin (106-89-8)	5600			
ethyl acetate (141-78-6)			36	
ethylenediamine (107-15-3)		6.3	0.64	
ethylene dibromide (106-93-4)	27			
ethylene dichloride (107-06-2)	260			
ethylene glycol monoethyl ether (110-80-5)		2.5	0.48	
ethylene oxide (75-21-8)	1.8			
ethyl mercaptan (75-08-1)			0.025	
fluorides		0.34	0.064	
formaldehyde (50-00-0)				0.04
hexachlorocyclopentadiene (77-47-4)		0.013	0.0025	
hexachlorodibenzo-p-dioxin (57653- 85-7)	0.0051			
n-hexane (110-54-3)		23		
hexane isomers except n-hexane				92
hydrazine (302-01-2)		0.013		
hydrogen chloride (7647-01-0)				0.18
hydrogen cyanide (74-90-8)		2.9	0.28	
hydrogen fluoride (7664-39-3)		0.63		0.064
hydrogen sulfide (7783-06-4)		1.7		
maleic anhydride (108-31-6)		0.25	0.025	
manganese and compounds		0.63		
manganese cyclopentadienyl tricarbonyl (12079-65-1)		0.013		

manganese tetroxide (1317-35-7)		0.13		
mercury, alkyl		0.0013		
mercury, aryl and inorganic compounds		0.013		
mercury, vapor (7439-97-6)		0.013		
methyl chloroform (71-55-6)		250		64
methylene chloride (75-09-2)	1600		0.39	
methyl ethyl ketone (78-93-3)		78		22.4
methyl isobutyl ketone (108-10-1)		52		7.6
methyl mercaptan (74-93-1)			0.013	
nickel carbonyl (13463-39-3)		0.013		
nickel metal (7440-02-0)		0.13		
nickel, soluble compounds, as nickel		0.013		
nickel subsulfide (12035-72-2)	0.14			
nitric acid (7697-37-2)				0.256
nitrobenzene (98-95-3)		1.3	0.13	
n-nitrosodimethylamine (62-75-9)	3.4			
non-specific chromium (VI) compounds, as chromium (VI) equivalent	0.0056			
pentachlorophenol (87-86-5)		0.063	0.0064	
perchloroethylene (127-18-4)	13000			
phenol (108-95-2)			0.24	
phosgene (75-44-5)		0.052		
phosphine (7803-51-2)				0.032
polychlorinated biphenyls (1336-36- 3)	5.6			
soluble chromate compounds, as chromium (VI) equivalent		0.013		
styrene (100-42-5)			2.7	
sulfuric acid (7664-93-9)		0.25	0.025	
tetrachlorodibenzo-p-dioxin (1746- 01-6)	0.00020			
1,1,1,2-tetrachloro-2,2,- difluoroethane (76-11-9)		1100		
1,1,2,2-tetrachloro-1,2- difluoroethane (76-12-0)		1100		
1,1,2,2-tetrachloroethane (79-34-5)	430			
toluene (108-88-3)		98		14.4

toluene diisocyanate,2,4-(584-84-9) and 2,6- (91-08-7) isomers		0.003		
trichloroethylene (79-01-6)	4000			
trichlorofluoromethane (75-69-4)			140	
1,1,2-trichloro-1,2,2-trifluoroethane (76-13-1)				240
vinyl chloride (75-01-4)	26			
vinylidene chloride (75-35-4)		2.5		
xylene (1330-20-7)		57		16.4

(b) For the following pollutants, the highest emissions occurring for any 15-minute period shall be multiplied by four and the product shall be compared to the value in Paragraph (a). These pollutants are:

(1) acetaldehyde (75-07-0);
(2) acetic acid (64-19-7);
(3) acrolein (107-02-8);
(4) ammonia (7664-41-7);
(5) bromine (7726-95-6);
(6) chlorine (7782-50-5);
(7) formaldehyde (50-00-0);
(8) hydrogen chloride (7647-01-0);
(9) hydrogen fluoride (7664-39-3); and
(10) nitric acid (7697-37-2).

History Note: *Authority G.S. 143-215.3(a)(1); 143-215.108; 143B-282; S L. 1989, c. 168, s. 45;*
Rule originally codified as part of 15A NCAC 02H .0610;
Eff. July 1, 1998;
Amended Eff. _____; January 1, 2010; June 1, 2008; April 1, 2005; February 1, 2005; April 1, 2001.

North Carolina Department of Environment and Natural Resources
Division of Air Quality

Beverly Eaves Purdue
Governor

Sheila C. Holman
Director

Dee Freeman
Secretary

MEMORANDUM

To: Sheila Holman, Director
Division of Air Quality

From: Reginald C. Jordan, Ph.D., CIH, Liaison,
Secretary's Science Advisory Board on Toxic Air Pollutants

Re: Completed NCSAB Recommendation for the Revision of the AAL for Arsenic and Inorganic Arsenic Compounds

Date: January 26, 2012

I have attached the completed risk assessment of arsenic and inorganic arsenic compounds by the Secretary's Science Advisory Board on Toxic Air Pollutants (NCSAB). The NCSAB has determined that the Acceptable Ambient Level for this toxic air pollutant be revised from its existing concentration of 2.3 x 10^{-7} mg/m^3 to a concentration within an interval of concentrations, and has recommended an appropriate revised AAL concentration within that range. A lung cancer health endpoint was chosen based on human epidemiological studies. These recommendations are summarized as follows:

Compound	NCSAB Recommended Range	NCSAB Recommended Revised AAL	DAQ Averaging Time
Arsenic and Inorganic Arsenic Compounds	1.6 x 10^{-6} - 3.0 x 10^{-6} mg/m^3	2.1 x 10^{-6} mg/m^3	Annual average

cc: Joelle Burleson, Supervisor
Rules Development Branch
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Lori Cherry, Supervisor
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Risk Assessment for Arsenic and Inorganic Arsenic Compounds

Executive Summary

In response to a request made by the North Carolina Division of Air Quality (DAQ), the Secretary's Science Advisory Board for Toxic Air Pollutants (NCSAB) has reassessed arsenic and arsenic-containing inorganic compounds and recommends an update to the Acceptable Ambient Level (AAL) for these compounds. An AAL is an airborne concentration above which a toxic air pollutant may be considered to have an adverse effect on human health. The current AAL for arsenic and inorganic arsenic-containing compounds, established in 1990, is 2.3×10^{-7} mg/m^3, averaged annually. Upon review of the updated toxicological and epidemiological literature, the NCSAB recommends revising the AAL to 2.1×10^{-6} mg/m^3, the central estimate within an exposure range from a lower bound of 1.6×10^{-6} mg/m^3 to an upper bound of 3.0×10^{-6} mg/m^3. This updated AAL is based on an estimated lifetime excess risk of 1 additional lung cancer death per 1,000,000 population over a 78-year lifespan.

I. Background Information

Arsenic (CAS 7440-38-2), abbreviated As, is a grey-colored allotropic metalloid that occurs naturally in the Earth's crust. It has an atomic number of 33 and a molecular weight of 74.92 g/mole. Arsenic commonly exists in the -3, 0, +3, and +5 oxidation states.

Arsenic is found at low concentrations (about 3 - 4 ppm) in soils and water throughout the world (California OEHHA 2001). Refining of arsenic-containing ores, including copper and lead smelting, is the major source of emissions of arsenic dust and inorganic arsenic compounds. Since 1985, the United States has had no domestic production of arsenic. Both arsenic and arsenic trioxide are imported, primarily from China and Japan (arsenic), and Chile and Morocco (arsenic trioxide), and have been important secondary sources (Brooks 2002). The most commonly produced form of inorganic arsenic is arsenic trioxide, As_2O_3. It is used as a raw material for the production of other inorganic arsenic compounds, organic arsenic compounds, and alloys. It is produced at an estimated 3000 tons per year: an estimated 1000 tons per year from mining and smelting by-products and 2000 tons per year reclaimed from metal and

electrical waste (European Chemicals Agency 2010). Galvanizing, soldering, and etching processes requiring the treatment of metal with strong acids are possible sources of arsine gas, AsH_3. Arsine is used to provide arsenic as a doping agent in the semiconductor industry. Combustion of fossil fuels can also result in the emission of particulate arsenic compounds as well as arsine.

According to latest USEPA National Air Toxics Assessment (NATA) report (U.S. Environmental Protection Agency 2011) (of year 2005 data), the mean ambient air concentration of arsenic statewide in North Carolina is 3.8×10^{-7} mg/m^3. Table 1 summarizes emissions by source type and percent contribution for North Carolina:

Table 1 – Contributions to Ambient Air from Source Types in North Carolina

Source Type	Approximate Contribution to Ambient Air Concentration, %
Point	3
Nonpoint	6
Mobile	3
Background	88

The most complete and current emissions inventory available containing source category data is the 2008 National Emissions Inventory (NEI). Using the 2008 NEI data, arsenic emissions were totaled by source category. The results indicate that Point Sources are the predominant source of arsenic emissions in NC (Table 2):

Table 2 – Arsenic Emissions by Source Category

Source Category	As Emissions, tons per year	As Emissions, % of total
Point	6.1	92
Mobile	0.5	7
Nonpoint	0.05	1

Using NAICS (North American Industrial Classification System) categories, the predominant industrial category for arsenic emissions is electrical power generation, transmission and distribution. Significant category contributors in North Carolina are shown in Table 3:

Table 3 – Arsenic Emissions, Contribution by NAICS Source Category

% Contribution to Arsenic Emissions	NAICS Category Description
74	Electrical Power Generation, Transmission and Distribution
13	Pulp, Paper and Paper Mills
6	Wood Products, Glass Mfg, Clay Mfg, Textiles, Pesticide Mfg, Polymers
4	National Security and International Affairs
3	Other

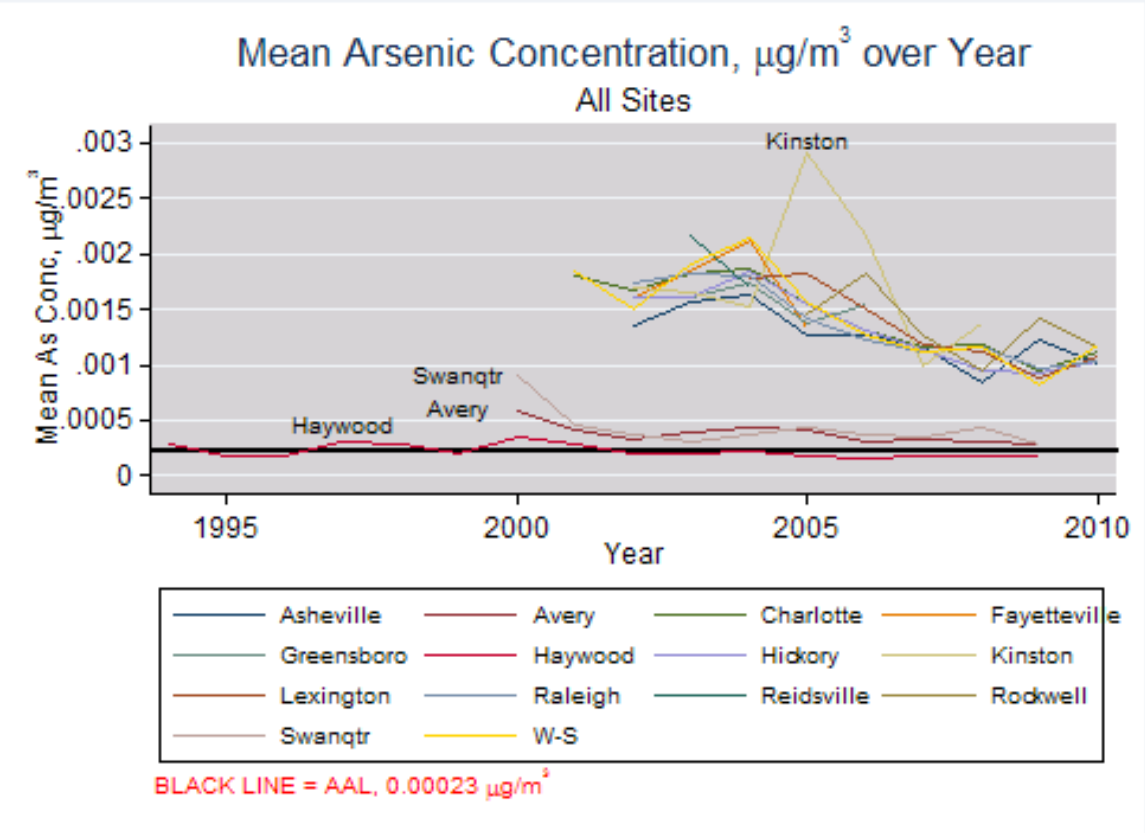
For electrical power generators, transmitters, and/or distributors, fuels used for power generation are reported in Table 4:

Table 4 – Arsenic Emissions by Fuel Type

Fuel	As Emissions, tons per year	As Emissions, % of total
Coal	5.9	96
Other	0.2	4

The NC Division of Air Quality has been analyzing particulate matter in the ambient air in North Carolina for arsenic since 1994. In Figure 1, mean arsenic concentration by monitoring location is plotted against year and compared with the current (historical) AAL:

Figure 1 – Arsenic Concentration in Ambient Air by Site and Year



Except for the monitoring location in Haywood County, the mean annual arsenic concentrations at all other monitoring locations exceed the AAL for every year in which sampling was performed. These data are available in the EPA Air Quality System (AQS) database.

Acceptable Ambient Level (AAL) History

The current AAL for arsenic and inorganic arsenic compounds of 2.3×10^{-7} mg/m^3 became effective in 1990. This AAL was based on an EPA (U.S. Environmental Protection Agency 1984) Unit Risk Factor of 4.29×10^{-3} $(\mu g/m^3)^{-1}$, and was associated with an upper bound estimate of excess cancer risk of 10^{-6}:

$$AAL = \frac{excess\ risk}{IUR} = \frac{10^{-6}}{4.29\times10^{-3}\left(\frac{\mu g}{m^3}\right)^{-1}} = 2.3\times10^{-4}\,\frac{\mu g}{m^3} = 2.3\times10^{-7}\,\frac{mg}{m^3}$$

II. Animal Studies

Acute and Chronic Non-Cancer Endpoints

Developmental Studies

Mouse and rat studies have been conducted to determine the potential developmental toxicity of arsenic.

Nagymajtenyi et. al. (Nagymajtenyi, Selypes et al. 1985) investigated chromosomal damage and fetotoxic effects in pregnant CFLP mice exposed to various concentrations of As_2O_3 aerosol spray. Study details were poorly documented and provided no information on the generation and/or analysis of the chamber atmosphere. Four groups (8-11 per group) of pregnant mice were exposed to As_2O_3 aerosol spray for 4 hours per day on the 9th, 10th, and 12th gestational days. Control mice were exposed to distilled water aerosol. Mice were sacrificed on the 18th gestational day. No information was provided on maternal toxicity. Fetuses were removed and examined. Livers of ten fetuses from each exposure group were examined for chromosomal damage. Twenty mitoses in each fetus were scored for chromosomal damage and 10% of these were karyotyped. The experimental data are shown in Table 5.

Table 5 - Nagymajtenyi Data

Group	As_2O_3 Exposure Concentration (mg/m^3)	Number of Litters	Avg. Number of Living Fetuses per Mother	Number of Fetuses Examined	Dead Fetuses (%)	Avg. Fetal Weight (g)	Number of Fetuses with Retarded Growth
Control	0	8	12.5	100	8	1.272 ±0.02	1
1	0.26 ±0.01	8	12.5	100	12	1.225 ±0.03*	2
2	2.9 ±0.04	8	12.8	100	13	1.146 ±0.03*	3
3	28.5 ±0.3	11	9.6	100	29	0.981 ±0.04*	51*

* Significantly different from Control ($p < 0.05$). NOTE: Nagymajtenyi et al analyzed body weights from several fetuses per litter but do not appear to have taken litter effects into account. When litter effects are ignored, statistical tests indicate greater statistical significance than is warranted by the data.

From the Nagymajtenyi data, the exposure concentration of 0.26 mg/m^3 was determined by OEHHA (California OEHHA 2000) to be a LOAEL based on decreased fetal weight. ATDSR does not consider a % weight reduction from control of less than 10% to be significant (from these data, the weight reduction experienced at 0.26 mg/m^3 was 3.7%), while OEHHA considers any statistically significant decrease in fetal weight a concern. The NCSAB agrees with the ATSDR approach, in that while a 3.7% decrease in fetal weight may be reported as statistically significant, it does not appear to be biologically significant. OEHHA based their Chronic Inhalation Reference Exposure Level of 0.03 µg As/m^3 on these data (average exposure to LOAEL group = 33 µg As/m^3, Total Uncertainty Factor = 1000).

Holson (Holson, Stump et al. 1999) investigated developmental toxicity of inhaled As_2O_3 aerosol in female Crl:CD®(SD)BR rats under GLP conditions. A preliminary range-finding study (8-10 mated dams/group) was conducted in addition to a definitive exposure study. Exposure was to the whole body for 6 hours/day beginning 14 days before mating. Exposure was continued through mating to gestational day 19. Aerosol concentration was measured periodically to estimate exposure concentrations. Control animals in the range-finding study were kept in a separate room from the exposed animals. Controls for the definitive study were handled in the same manner as exposed animals, except they breathed filtered air. In the range-finding study, maternal mortality was seen at 25 mg/m^3 and maternal rales were

observed in the 10 and 25 mg/m^3 groups and; 10 mg/m^3 was selected to be the highest exposure level in the definitive study. In the definitive study, groups of 24 female rats were exposed for 6 h/day to 0.3, 3, and 10 mg/m^3 As_2O_3 aerosol (MMAD for lowest to highest exposure groups: 2.1, 1.9, and 2.2 µm). No significant maternal effects were reported for the control and two lower exposure groups. At 10 mg/m^3, rats exhibited rales and dried red material around the nose, and it was observed that there were statistically significant differences in food consumption and net body weight gain in the high exposure group compared to controls. A NOAEL of 3 mg/m^3 and a LOAEL of 10 mg/m^3 were reported based on these maternal effects. Intrauterine parameters (mean numbers of corpora lutea, implantation sites, resorptions and viable fetuses, and mean fetal weights) were unaffected by treatment. No exposure-related malformations or variations were noted at any exposure level. Definitive study data are shown in the table below:

Table 6 - Holson Data

Group	As_2O_3 Exposure Concentration (mg/m^3)	Number of Litters	Mean Net Maternal Body Wt Change (g+/- SD)	Number of Fetuses Examined	Total No. with Malformations (fetus/litter)	No. Live Fetuses per Litter (mean ± SD)	Avg. Fetal Weight (g ± SD)
Control	0	22	72.6±15.7	336	0/0	15.3 ± 2.16	3.7 ±0.17
1	0.3	23	72.6±16.9	354	1/1	15.4 ± 1.97	3.7 ±0.22
2	3.0	24	81.4±16.9	375	2/2	15.6 ± 3.15	3.7 ±0.20
3	10	23	60.1±14.1*	367	0/0	16.0 ± 1.64	3.5 ±0.32

* Significantly different from Control ($p < 0.05$)

In summary, exposure of female rats to arsenic trioxide dusts at levels up to 10 mg/m^3 did not result in any evidence of developmental toxicity, but did cause maternal toxicity in this study. Findings seen in the Nagymajtenyi et al., 1985 study were not reproduced in the rat study that used a more robust study design. These findings may have been due to maternal toxicity at the high dose of 28.5 mg/m^3 since the dose of 25 mg/m^3 in the rat caused mortality.

Immunological Studies

Aranyi (Aranyi, Bradof et al. 1985) and co-workers investigated the effects of exposure to arsenic trioxide on bactericidal activity in the lung. CD-1 mice were exposed for 3 hours to As_2O_3 aerosol (MMAD = 0.4 µm). Exposure concentrations ranged from 125 – 1000 µg/m^3. Changes in infectivity were evaluated by observation of changes in susceptibility to a radiolabeled streptococcal aerosol, ^{35}S-labeled Klebsiella pneumoniae. Mortality increased significantly after infection challenge and decreases in bactericidal activity were noted after single 3-hour exposures to 270, 500, and 940 µg As/m^3. It was also observed that multiple (5 and 20) 3-hour exposures to 500 µg As/m^3 significantly increased mortality and decreased bactericidal activity. Decreases in bactericidal activity were noted only after 20 3-hour exposures at 125 or 250 µg As/m^3. A NOAEL was reported at 0.123 mg/m^3.

Chronic Studies

ATSDR(ATSDR 2008) reports "…animal data on the health effects of inorganic arsenic following inhalation exposure are limited to studies that did not evaluate a suitable range of health effects. Lacking suitable studies upon which to base the MRLs, no inhalation MRLs were derived for inorganic arsenic." Additionally, the NCSAB finds that animal studies are not particularly robust, and should not be used as the basis for an AAL based on chronic exposure to arsenic.

Cancer Endpoints

Since human epidemiological studies were available for this risk assessment, animal studies were not reviewed in depth.

III. Human Studies

Acute and Chronic Non-Cancer Endpoints

ATSDR(ATSDR 2008) reports "…Adequate human studies evaluating dose-response relationships for noncancer end points were not located for inorganic arsenic…"

Perry(Perry, Bowler et al. 1948) reported on clinical manifestations of disease in workers in a factory that produced sodium arsenite powder. Airborne arsenic levels were determined by sampling. Hair and urine analyses were also performed. ATSDR(ATSDR 2008) reported a NOAEL for a respiratory endpoint of 0.613 mg As/m^3 for the Perry study based on observed

differences in chest x-rays and respiratory performance (vital capacity and exercise tolerance tests) in workers studied. ATDSR also reported a LOAEL of 0.078 mg As/m^3 for a dermal endpoint (mild pigmentation keratosis of skin). Lagerkvist (Lagerkvist, Linderholm et al. 1986) investigated vasospastic (blood vessel spasm leading to vasoconstriction) tendency in 47 workers at a copper smelter. Lagerkvist reports that "…increased vasospastic reactivity in the fingers and Raynaud's phenomenon in smelter workers seems to be due to functional alterations in the vessels caused by inhalation of arsenic." ATSDR (ATSDR 2008) reports a LOAEL for this study to be 0.36 mg/m^3. Lagerkvist (Lagerkvist and Zetterlund 1994) investigated nerve conduction velocity (NCV) in 43 copper smelter workers and 46 controls in a 5 year follow-up to a previous study (Blom, Lagerkvist et al. 1985). The results were extrapolated to a long term exposure of mean duration of 28 years. Lagerkvist reported the greatest difference in NCV was in the tibial and sural nerves. The time-weighted average exposure reported as a LOAEL for decreased NCV in ATSDR(ATSDR 2008) was 0.36 mg/m^3. This time-weighted average (TWA) was derived from estimations of Lagerkvist et al. that the mean exposure duration to Rönnskär smelter arsenic workers was 23 years: 16 years at 500 µg/m^3 and 7 years at 50 µg/m^3.

Cancer Endpoints

Several epidemiological studies address the carcinogenicity of inhaled arsenic and arsenic compounds. These studies were conducted in smelter operations, where the predominant form of arsenic was particulate arsenic trioxide(ATSDR 2008).

A. Asarco Copper Smelter - Tacoma, Washington

Enterline and co-workers (Enterline and Marsh 1982; Enterline, Henderson et al. 1987a; Enterline, Marsh et al. 1987b; Enterline, Day et al. 1995) have been investigating risk of respiratory cancer in workers occupationally exposed to arsenic compounds at the Asarco copper smelter in Tacoma, Washington from 1940-1964. The 1995 update follows the cohort of Asarco workers (2,802 workers, 84,916 person-years) through 1986. Airborne arsenic levels were measured in the air of plant departments where arsenic levels were deemed to be elevated. While air sampling was begun in 1938 and conducted in only selected departments, urine samples were collected beginning in

1948 from all workers and analyzed for arsenic concentration. Information on worker smoking was not collected. Urinary arsenic levels were converted to air concentrations by comparison of actual air measurement data with urinary arsenic concentration of workers in sample plant departments. Also in the 1995 update, Enterline reported a cumulative mortality of 1,583 (1,061 deaths were reported in the 1987 update); 188 deaths due to respiratory cancer (104 reported in 1987). The SMR for respiratory cancer was reported to be 209.7 for the entire study cohort ($p < 0.01$). The cumulative arsenic exposure was reported to range from <0.75-45+ mg/m^3-yr. Additional significant increases in Standard Mortality Ratios (SMR) related to arsenic exposure were found for cancers of the large intestine, bone, buccal cavity and larynx, rectum and kidney for this cohort.

B. Anaconda Copper Smelter - Montana

Brown and Chu(Brown and Chu 1983b; Brown and Chu 1983c), Lee-Feldstein(Lee-Feldstein 1986) and Lubin and co-workers(Lubin, Pottern et al. 2000; Lubin, Moore et al. 2008) have investigated the risk of respiratory cancer in a cohort of 8,014 workers occupationally exposed to arsenic during the years 1938-1958 at an Anaconda copper smelter in Montana. The cohort was divided into three categories based on level of arsenic exposure (low = 0.29 mg/m^3, medium = 0.58 mg/m^3, high = 11.3 mg/m^3 x exposure reduction factor due to use of personal protective equipment). Of the 8,014 workers in the original cohort, about 3,200 (approximately evenly split between those under 30 years old and those between 30-39 years old) quit their jobs. To minimize the impact of unmeasured exposures on workers who quit, Lubin not only analyzed data from the full cohort, but also on a “restricted cohort” consisting of current workers as well as those 50 years old or older who quit working at the smelter. Follow-up in this cohort of workers is through 1989 (256,850 person-years for full cohort; 144,851 for a restricted cohort). Lubin reported 446 lung cancer deaths in the follow-up study compared with 302 as reported by Lee-Feldstein. The range of cumulative arsenic exposure was reported to be 1 – 26.2+ mg/m^3-yr with a mean cumulative arsenic exposure of 5.4 mg/m^3-yr. An SMR of 156 ($p < 0.001$) for respiratory cancer was

reported for the full cohort; an SMR of 187 ($p < 0.001$) was reported for a restricted cohort.

C. Rönnskär Copper Smelter - Sweden

Lung cancer mortality and arsenic exposure was investigated by Järup, et. al.(Jarup, Pershagen et al. 1989) and by Viren, et.al. (Viren and Silvers 1994) using a cohort of 3,916 Swedish male smelter workers employed for at least three months from 1928-1967 (127,189 person-yrs of exposure). 106 lung cancer deaths were reported with an SMR of 372. Viren also reported that the SMR for those employees hired prior to 1940 was 428 compared with an SMR of 302 for those hired after 1940. This cohort was followed through 1981. Cumulative arsenic exposure was determined to range from < 0.25 – 100+ mg/(m^3-yr). Järup reported an SMR of 372 ($p < 0.001$) for lung cancer and further stated that lung cancer mortality was related to average intensity of arsenic exposure, but not to duration – given a fixed level of cumulative arsenic exposure, inhalation of higher concentrations of arsenic over shorter durations of time were more hazardous that exposure to lower concentrations of arsenic over longer durations. With a 10 year minimum latency, an exposure intensity of <0.1 mg/m^3 was associated with a significant SMR of 317. Significant SMRs of 376 and 637 were noted with a cumulative arsenic exposure levels of <0.25 and (0.25 to <1) mg-years/m^3.

D. United Kingdom Tin Smelter

Binks (Binks, Doll et al. 2005) investigated lung cancer mortality and exposure to carcinogens (arsenic, lead, cadmium, polonium, antimony, sulfur dioxide) in a cohort of 1,462 workers (35,942 person-yrs of exposure) at the Capper Pass and Sons Limited tin smelter located in North Humberside, UK. This smelter was purchased in 1967 by Rio Tinto. The cohort consisted of workers employed for at least 12 months between November 1, 1967 and July 28, 1995. The latest year of follow-up was 2001. Binks reported an SMR of 161 for lung cancer (95% CI: 124 – 204) ($p < 0.001$). Jones (Jones, Atkin et al. 2007) combined the Binks mortality data with area and personal measurement data to investigate the relationship between lung cancer mortality and measures of exposure. Using available personnel records of employee work histories

and exposure measurements, matrices of exposure for several airborne particulates were compiled: arsenic, cadmium, lead, antimony, and polonium-210. To assess worker exposure prior to 1972 (where no exposure measurement data were collected), three extrapolation methods were devised to assess exposure: (A) Constant extrapolation in each process area, as the mean of the levels in the three earliest years for which data were available; (B) Extrapolation in each process area with a linear increasing trend from baseline to values 2-fold higher in the early 1940s, based on a weak trend seen in average exposure levels over the period 1972–91; (C) Extrapolation in each process area from baseline to values 2-fold higher in 1960, subsequently, declining linearly to values one-half of the baseline in 1937. Lung cancer mortality was investigated using Poisson regression on cumulative exposure. No significant association was determined between lung cancer mortality and cumulative exposure to arsenic. However, when cumulative exposure was weighted by time since exposure and age, a significant association was determined to exist. Increased prevalence of smoking with the cohort of workers studied enhances this association.

IV. Carcinogenic Mode of Action (MOA)

Arsenic is a known human carcinogen, but a definitive MOA for the various –cancer has not been generally accepted at this time. It is well accepted that the mechanisms of arsenic-induced carcinogenesis are complex and multifactorial and also may be target-site specific. As recently reviewed by Tokar (Tokar, Benbrahim-Tallaa et al. 2010) historically, conventional rodent cancer bioassays had provided -inconsistent evidence of the carcinogenicity of inorganic arsenic compounds. However, in a 2-year NTP inhalation bioassay, gallium arsenide did induce a dose-dependent increase in the incidence of lung adenomas and combined lung adenoma/carcinomas in female, but not male rats (NTP, 2000). Studies of inorganic arsenic using whole-life rodent exposures (i.e., including pre-natal and/or peri-natal exposures) have clearly demonstrated that arsenic does induce cancer in multiple organs ((Tokar, Benbrahim-Tallaa et al. 2010; Tokar, Diwan et al. 2011).

In addition, other in vivo rodent studies have established that inorganic arsenic can act together with other agents to enhance tumorigenesis (Tokar, Benbrahim-Tallaa et al. 2010). Regarding genotoxicity, there is little evidence that inorganic arsenic acts as a point mutagen, and a multitude of effects of arsenic on cell signaling have been reported. However, there are numerous other MOAs proposed for arsenic, including: cell proliferation, altered DNA repair, DNA methylation, oxidative stress, co-carcinogenesis, and tumor promotion.

(1) Genotoxicity

In Vitro Studies

Rossman (ATSDR 2008) reported that arsenite did not induce mutation in tests that selected for E. coli tryptophan^{+} revertants or in Chinese hamster ovary cells selecting for ouabain-(ATPase) or thioguanine-resistant (HPRT) mutants, while Hei (Hei, Liu et al. 1998) reported that arsenite does induce large deletion mutations in hamster-human hybrid cells.

There are multiple reports of dose-dependent chromosomal aberrations (chromatid gaps, breaks and fragmentation, endoreduplication, and chromosomal breaks), DNA-protein crosslinking, and sister chromatid exchanges in hamster embryo cells, human lymphocytes, and fibroblasts following exposure to inorganic arsenic (Rossman, Stone et al. 1980; Larramendy, Popescu et al. 1981; Lee, Huang et al. 1985b; Wiencke and Yager 1991; Jha, Noditi et al. 1992; Kochhar, Howard et al. 1996; Rasmussen and Menzel 1997). Arsenite is reported to be more potent than arsenate.

In Vivo Studies

Deknudt and Tinwell (DeKnudt, Leonard et al. 1986; Tinwell, Stephens et al. 1991) have reported a linear dose-dependent increase in micronucleated polychromatic erythrocytes in somatic cells of mice administered arsenite. Chromatid gaps and breaks, and chromosomal rearrangements have been observed in bone marrow cells of mice administered arsenite (Das, RoyChoudbury et al. 1993; RoyChoudbury, Das et al. 1996). Studies have reported that clastogenic effects have been reduced in mice pre-treated with garlic extract before exposure to arsenite (Das, RoyChoudbury et al. 1993;

RoyChoudbury, Das et al. 1996). Tice (Tice, Yager et al. 1997) reported that hepatic methyl donor status may affect arsenic-induced genotoxicity.

(2) Co-Mutagenesis

Studies by Lee, Okui, and Li (Lee, Oshimura et al. 1985a; Okui and Fujiwara 1986; Li and Rossman 1991) indicate that inorganic arsenic (including arsenite, As_2O_3, and arsenate) is co-mutagenic with other chemicals and UV light in mammalian cells: a synergistic increase in UV-induced chromatid and chromosomal aberrations and mutation at the HPRT locus in Chinese hamster ovary cells is produced after UV-treated cells are exposed to inorganic arsenic. Lee(Lee, Oshimura et al. 1985a) reported no co-mutagenic effect of arsenic with UV-induced sister chromatid exchanges or ouabain resistance. Wiencke (Wiencke and Yager 1991) reported that chromosomal aberrations in lymphocytes induced by diepoxybutane, a DNA crosslinking agent, are potentiated after exposure to arsenite. Jha (Jha, Noditi et al. 1992) reported that chromosomal aberrations induced by x-rays or UV light in fibroblasts are potentiated after exposure to arsenite.

(3) Gene Amplification

Lee (Lee, Tanaka et al. 1988) suggests that arsenic enhances amplification of the gene that codes for the enzyme dihydrofolate reductase, and that this gene amplification may play a role in its carcinogenic effect. Cells had a 2- to 11-fold increased copy number of the dihydrofolate reductase gene. Arsenite (active in the 0.2 – 0.8 µM range) was more potent than arsenate (active in the 1 – 4 µM range). This hypothesized MOA is based on observations that arsenic is carcinogenic, but not a point mutagen, and oncogenes are amplified in several animal and human tumors. Woloson (Woloson 1990) found arsenic-induced gene amplification in Syrian Hamster Embryo (SHE) cells, and Katakura (Katakura and Chang 1989) reported arsenite-resistant trypanosomes.

(4) Altered DNA Repair

Okui (Okui and Fujiwara 1986) reports that inorganic arsenic (arsenite more potent than arsenate) inhibits the DNA excision repair of thymine dimers in human fibroblasts. Li (Li and Rossman 1989) note that DNA ligase activity in nuclear extracts is decreased by

arsenite (55% at 10 µM), but the enzyme is not directly inhibited (Li and Rossman 1989; Hu, Su et al. 1998). Hu noted that arsenite might indirectly inhibit DNA ligase activity by altering cellular redox levels or affecting signal transduction pathways or altering phosphorylation of proteins linked to DNA ligase activity. In addition, with purified human DNA repair enzymes, Hu observed that arsenite increased DNA polymerase beta, O^6-methyl-guanine-DNA methyltransferase and DNA ligases I, II, and III. Yager (Yager and Wiencke 1997) observed a dose-dependent decrease of the enzyme poly(ADP-ribose) polymerase in human T-call lymphoma cells (at 10 µM arsenite, there is an approximately 50% decrease in enzyme activity and 80% cell viability). Kitchin (Kitchin 2001) states "…The theory that altered DNA repair is the cause of arsenic carcinogenesis is particularly attractive because trivalent arsenic species, such as arsenite, can bind strongly to dithiols as well as free sulfhydryl groups. Such protein binding could induce inhibited DNA repair, mutation in key genetic sites, or increased cell proliferation which can lead to subsequent mutation via inhibited DNA repair."

(5) Altered DNA Methylation

Counts (Counts and Goodman 1995) suggests that DNA methylation may have a prominent role in cancer development. Mass (Mass and Wang 1997) reported that arsenite increased resistance of the p53 promoter region to cleavage by the restriction enzyme *Hpa*II. This resistance to cleavage indicates that more methylated cytosine was present within the p53 gene. Methylated cytosine can alter the ability of transcription factors to bind to DNA, which would modify gene expression. Arsenate was determined to be less potent than arsenite. Zhao (Zhao, Young et al. 1997) found that the DNA of arsenite- transformed rat liver TRL 1215 cells was globally hypomethylated and that the effect was dependent on dose and length of exposure. Zhong (Zhong and Mass 2001) observed both hypo- and hyper-methylation of DNA in human lung cells after several weeks of arsenite exposure, suggesting that altered methylation within a specific DNA sequence may be more important than the magnitude of DNA methylation.

(6) Oxidative Stress

Arsenic appears to induce oxidative stress both in in vivo and in vitro studies (Brown and Rush 1984; Keyse and Tyrell 1989). Liu (Liu, Athar et al. 2001) reports that within 5 minutes after exposure of human-hamster hybrid cells to arsenite, reactive oxygen species are detected. Wang (Wang and Huang 1994) found that catalase and superoxide dismutase reduce arsenite-induced micronuclei in CHO cells, and Nordenson (Nordenson and Beckman 1991) has reported that SCE were reduced as well. Lee (Lee and Ho 1994) found that the antioxidants vitamin E, methylamine, and benzyl alcohol reduced the killing of human fibroblasts by arsenite.

The main sources of reactive oxygen species generated after exposure to arsenite are NADPH oxidase (Brown and Chu 1983; U.S. Environmental Protection Agency 1984) (from (Sumi, Shinkai et al. 2010)); inhibition of mitochondrial respiration (Lee-Feldstein 1983); and inhibition of glutathione peroxidase (Higgins, Welch et al. 1982) and thioredoxin reductase (Enterline and Marsh 1982). In addition, in the presence of iron, arsenite undergoes a Fenton reaction and may generate reactive oxygen species directly (Brown and Chu 1983a) (from (Druwe and Vaillancourt 2010)). In vivo chronic exposure to arsenite (300 ug/L) in rats leads to depletion of glutathione and increased lipid peroxidation (Lee and Fraumeni 1969; Chaudury, Basu et al. 1999).

Oxidative DNA damage has been detected in many cell types exposed to arsenite (Brown and Chu 1983a; Chen, Lin-Shiau et al. 1998). Chronic oral dimethylarsenic acid (DMA^V) exposure was shown to lead to an increased incidence in lung tumors in *Ogg−/−* mice (the mouse knockout for 8-oxoguanine DNA-glycosylase 1 which is key in repair of oxidative DNA damage) but not in the DNA-repair competent *Ogg+/+* mice (Kinoshita et al., 2007), implicating some form of oxidative DNA damage as a possible means for tumor formation due to arsenic.

(7) Cell Proliferation

Brown (Brown and Kitchin 1996) reported increased ornithine decarboxylase (ODC) activity (an indicator of cell proliferation) in rat liver with arsenite exposure at 1.6 mg/kg. Germolec (Germolec, Yoshida et al. 1996) observed the proliferation of human keratinocytes after exposure to arsenite in culture, and also reported (Germolec,

Spalding et al. 1997) epidermal thickening and hyperkeratinosis in the skin of transgenic mice administered arsenite in drinking water. After an 8-week exposure to arsenite, Trouba (Trouba, Wauson et al. 2000a) observed that multiple genes and proteins involved in proliferative signaling and mitogenesis in murine fibroblasts were affected. A greater proportion of arsenite-exposed fibroblasts entered the S-phase of the cell cycle than controls. The exposed cells also expressed positive regulators of proliferation (*c-myc* and E2F-1) and decreased expression of negative regulators (MAP kinase phosphatase-1 and $p27^{kip1}$). Trouba (Trouba, Wauson et al. 2000b) also reported the inhibition of insulin/dexamethasone-induced differentiation of murine preadipocytes at nontoxic doses of arsenite. Vogt (Vogt and Rossman 2001) investigated expression of Cyclin D in arsenite-exposed normal human fibroblasts. After 14 days of exposure to a low dose (0.1 µM) of arsenite, Cyclin D expression was increased. Since arsenite affects the cell cycle, arsenite may alter cell proliferation.

(8) Intracellular signaling pathways involved in cell proliferation and apoptosis

Arsenite-induced alterations in intracellular oxidation/reduction reactions, DNA methylation and/or DNA damage result in the activation of a number of signaling pathways. Activation of the early response genes is thought to be a response to arsenite-induced cellular stress via changes in intracellular redox status (Druwe and Vaillancourt 2010). Stress response transcription factors, such as activator protein-1 (AP-1) and nuclear factor-kappa B (NF-*k*B) are an important part of these early responses, and regulate the expression of a variety of downstream target genes, such as pro-inflammatory genes that are involved in cellular antioxidant defense mechanisms (Kapahi, Takahashi et al. 2000). Activation of these stress response transcription factors is dependent upon arsenic concentration and cell type. In addition, arsenite activates Nrf2, a transcription factor which is a regulator of a number of antioxidant enzymes (Wang, Li et al. 2008).

A link between arsenite, reactive oxygen species and cell proliferation has been suggested through mitogen-activated protein kinases (MAPK). MAPK signaling is induced by inorganic and organic forms of arsenic in a variety of cell types (reviewed in

(Druwe and Vaillancourt 2010)). Some of the main kinases that have been studied include p38, Jnk, Erk, Pi3k/Akt (reviewed in (Sumi, Shinkai et al. 2010)).

With regard to other transcription factors that are responsible for DNA damage-induced signaling, p53 is thought to be a major target for arsenicals. Sumi, Shinkai et al. 2010 report, "It has been reported that iAsIII and As2O3, but not iAsV, caused p53 induction in a dose- and time-dependent manner in HeLa cells, human osteosarcoma U2OS cells and human gastric cancer MGC-803 cells (Salazar, Ostrosky-Wegman et al. 1997; Filippova and Duerksen-Hughes 2003; Zhang, Cao et al. 2005), and dimethylated arsenicals have also been shown to induce an increase in the cellular p53 level in U2OS cells, whereas monomethylated arsenicals had no effect (Filippova and Duerksen-Hughes 2003). This suggests that the ability of arsenic to activate p53 is dependent on its chemical composition and oxidation state."

V. Quantitative Assessment

Chronic Exposure, Non-Cancer Endpoints

The NCSAB, like ATSDR(ATSDR 2008) found limited evidence for the evaluation of chronic exposure to inorganic arsenic with non-cancer endpoints. Most of these studies have generated either negative or equivocal results (Tokar, Benbrahim-Tallaa et al. 2010). Further, the NCSAB has determined that an AAL based on a cancer endpoint is sufficient to protect the public from adverse health effects resulting from chronic exposure to arsenic-bearing particulate matter.

Chronic Exposure, Cancer Endpoints

Animal Studies

The NCSAB did not use animal studies as a basis for the revision of the arsenic AAL because these studies do not appear to be sufficiently robust to be used for this purpose.

Human Studies

Three epidemiological studies have been determined to be key studies:

- Enterline 1995 (Asarco copper smelter study)
- Lubin 2000 and Lubin 2008 (Montana copper smelter study)

- Järup 1989 (Rönnskär copper smelter).

The development of a revised AAL is based on the work of Valdez-Flores and Sielkin (Valdez-Flores and Sielkin 2011) as it was presented to the NCSAB at their January, 2011 meeting. In the Valdez-Flores – Sielkin (V-S) analysis of the data from these selected studies, a Poisson dose-response model used was:

$$E\left(O_j\right) = \alpha \times E_{oj} \times \left(1 + \beta \times d_j\right)$$

where:

$E(O_j)$ = expected number of cancer cases for exposure group j

E_{oj} = expected number of background cancer cases for exposure group j

α = accounts for possible differences in cancer background rates between study population and reference population

β = slope factor by which background risk increases with cumulative exposure

d_j = cumulative exposure for the jth exposure group j

Using this dose-response model, V-S derived maximum likelihood estimates of the model parameters, as shown in Table 6:

Table 7 – Maximum Likelihood Estimates of Model Parameters

Study	Intercept MLE (α)	Slope MLE (β) $(\mu g/m^3\text{-}yr)^{-1}$	Standard Error Slope (β)	95% UCL Slope (β) $(\mu g/m^3\text{-}yr)^{-1}$
Asarco	1.46[a] 2.02[b]	3.15e-05	1.48e-05	5.59e-05
Montana	0.94	5.75e-05	1.61e-05	8.4e-05
Ronnskar	2.37[a] 2.81[b]	2.92e-05	1.63e-05	5.61e-05

a: intercept for workers hired before 1940
b: intercept for workers hired after 1940

Modeling the combined (three studies) dose-response data with a common intercept model yields:

- β(MLE, combined data) = 5.46e-05 $(\mu g/m^3 \cdot yr)^{-1}$ and
- SE (combined data) = 9.84e-06 $(\mu g/m^3 \cdot yr)^{-1}$

A life table analysis was then conducted using this Poisson model, β(MLE, upper (95%) and lower (5%) confidence bounds, combined data), North Carolina age-specific lung cancer mortality rates (males, all races, 2009, http://www.cdc.gov/nchs/nvss/bridged_race/data_documentation.htm#vintage2009), baseline survival to beginning of age category data (U.S., all races, all sexes, 2000 census), with the intercept parameter α set equal to 1. Airborne concentrations of arsenic were iteratively input to the Poisson model until the resulting estimated lifetime excess risk of death from lung cancer was 1×10^{-6}. Based on the output from this life table analysis, Table 7 lists the following candidate AALs derived for constant and continuous 78-year exposures:

Table 8 – Candidate AALs

Exposure Range Category	AAL Candidate, mg/m^3
Central Estimate	2.1×10^{-6}
Lower Bound	1.6×10^{-6}
Upper Bound	3.0×10^{-6}

The central estimate AAL candidate represents a 9-fold increase of the AAL from its current value of 2.3×10^{-7} mg/m^3. As mentioned previously, the current arsenic AAL is based on an EPA unit risk factor derived in the 1984 EPA Health Assessment document (HAD) (U.S. Environmental Protection Agency 1984). This URF was derived as the geometric mean of the overall unit risk estimates for the occupational exposure studies at the Montana smelter and an occupational study at the Asarco smelter Table 7-35, page 7-114 of that report:

Table 9 – Unit Risk Estimates (from Table 7-35, 1984 EPA Health Assessment Document)

Exposure Source	Study	Unit Risk*	Geometric Mean Unit Risk	Final Estimated Unit Risk
Anaconda smelter (Montana)	Brown & Chu Lee-Feldstein Higgins	1.25×10^{-3} 2.8×10^{-3} 4.9×10^{-3}	2.56×10^{-3}	
				4.29×10^{-3}
ASARCO smelter (Tacoma)	Enterline & Marsh	6.81×10^{-3} 7.60×10^{-3}	7.19×10^{-3}	

* unit risk estimates were based on absolute-risk linear models

As described previously, these epidemiological data have been updated since the issuance of the 1984 EPA HAD to include a total of 341,766 person-years of follow up for the Montana and Tacoma smelters having 634 additional lung cancer deaths. Ronnskar smelter data with 127, 189 person-years of follow up and 106 lung cancer deaths was combined with the data from the Tacoma and Montana studies in the V-S analysis relied upon by the NCSAB.

VI. Recommendations

A. Chronic Endpoint

No recommendation.

B. Carcinogenic Endpoint

The NCSAB recommends that the current AAL for arsenic be revised to 2.1×10^{-6} mg/m^3, the central estimate within an exposure range having a lower bound of 1.6×10^{-6} mg/m^3 and an upper bound of 3.0×10^{-6} mg/m^3. Because arsenic is a known human carcinogen, the Division of Air Quality has assigned an annual averaging time for this AAL.

VII. References

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