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Subject: A History on the development of CGA P-20 and ISO 10298

It was stated by CGA in ISO TC58 SC2 N1131 Result of systematic review of ISO 10298:2010 "Determination of toxicity of a gas or gas mixture" that

There are inconsistencies between LC_{50} values in ISO 10298 and CGA P-20 that should be resolved/harmonized (for example, diethyl zinc, chloromethane, hydrogen chloride, triethylaluminum, etc.)

I would like to help resolve this by offering some history as well as the basis for how we derived the latest LC_{50} values.

History:
I participated on the original CGA Task Force to develop pamphlet P-20 "**Standard for the Classification of Toxic Gas Mixtures".** (Specialty Gas Docket 86-08) This effort was led by Jay Harding of Air Liquide and took over 4 years of continuous effort to develop a table of LC_{50} values. Besides myself, the only remaining member so this original Task Force is Mike Injaian and Dave Sonneman. We retained the services of Dr. Carol Maslansky, a noted Toxicologist to help us obtain relevant studies and to determine their validity. She also made recommendations for gases that did not have appropriate data and/or adjusted for rat data that was not 1 hour exposures. Jay was also able to locate Vernot who conducted many of the studies for the Air Force in the 1960's and 1970's. He was working for API in 1989 and Jay arranged to meet with him.

In a Dec 1989 meeting Jay presented to ISO Toxicity meeting (US, Canada, UK, France and Germany) the results of the Task Force review. There was agreement that ISO10298 and CGA P-20 define LC_{50} values as being white albino rats with a 1 hour exposure observed for 14 days in the absence of relevant values would be provisionally assigned by Committee. There was also agreement on the use of a modified Haber calculation to estimate 1 hour LC_{50} values based on studies with varying exposure times. The attached table 3 Toxic Categories was what was presented to ISO. The table following were the references that were used to develop the LC_{50} values. These were the basis for the initial P-20T standard in 1990 (Tentative Standard for the Classification of Toxic Gas Mixtures). The table Gas Comparison CGA/ISO summarized the differences in compounds listed between CGA and ISO. Note that diethylzinc and triethylaluminum appears on the ISO list and not on the CGA list.

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After the adoption of P-20T there continued to be information sharing. On March 12, 1992 the CGA Task Force met with Jim Osteen and George Cushmac of DOT to compare data between CGA, DOT and ISO. Dr. Michael Kunde from Germany assisted the ISO Working Group on the review of data. Jay Harding was also an active member of the ISO Working Group in an attempt to harmonize the values. In 1994 P-20 was revised to update some values and to add compounds listed in the proposed ISO standard. ISO 10298 was approved in 1995.

In a Aug 2005 letter I submitted to Specialty Gas and TC58 SC2 WG7 the following information based on more recent testing. I suggested a review and updating of the LC_{50} values.

1. **Arsine LC_{50} of 178 ppm –** The original 20 ppm value was derived from mouse data. Later rat data shows a value of 178 ppm. This is so different than what has been used that this will be left to the reader (US EPA OPPT, Arsine - Proposed Acute Exposure Guideline Levels (AEGLs) "Public Draft" Fax-On-Demand item #4922 (IRDC reports))
2. **Boron Trifluoride LC_{50} of 873 ppm –** better value from later testing (Rusch, B.M., Hoffman, G.M., McConnell, R.F., and Rinehart, W.E. "Inhalation Toxicity Studies with Boron Trifluoride" Toxicol. Appl. Pharmacol. (1986) Vol. 83, pp 69-78)
3. **Hydrogen Selenide LC_{50} of 51 ppm –** original value of 2 ppm was from a guinea pig. (Zwart, A., Arts, J.H.E., Ten Berge, W.F., and Appleman, L.M. "Alternative Acute Inhalation Toxicity Testing by Determination of the Concentration-Time-Mortality Relationship: Experimental Comparison with Standard LC50 Testing," Reg. Tox. and Pharm., Vol. 15, 1992, pp. 278-290)
4. **Nitric Oxide LC_{50} of 158 ppm –** assumes that the NO will oxidize to NO_2 , (Gray, E., Patton, F.M., Goldberg, S.B. and Kaplan, E., "Toxicity of the Oxides of Nitrogen II. Acute Inhalation Toxicity of Nitrogen Dioxide, Red Fuming Nitric Acid, and White Fuming Nitric Acid," Archives of Industrial Hygiene and Occupational Medicine, (1954) Vol. 10, pp 418-422)
5. **Silicon Tetrafluoride LC_{50} of 922 ppm –** original was derived from mouse data (Scheel, L.D., Lane, W.C., Coleman, W.E., "The Toxicity of Polytetrafluoroethylene Pyrolysis Products—Including Carbonyl Fluoride and a Reaction Product, Silicon Tetrafluoride," Am. Ind. Hyg. Assoc. Journal, (1968) Jan-Feb., pp 41-48)

The Specialty Gas Committee elected not to act on this information. TC58 SC2 WG7 however took an active role over the next 3 years to gather more data and to provide a Toxicologist, Dr. Sylvie Tissot, a OECD French National Coordinator to review the data for all of the gases in ISO 10298. Air Products also provided a Toxicologist, Carrie Hamilton to do the same for the CGA. As part of this effort we made every effort to insure that the appropriate studies were referenced and the values defendable.

A key compromise from this effort was the agreement on the LC_{50} value for HF. This value affected many other fluoride gas LC_{50} values that were derived based on hydrolysis to HF. (See attached letter)

The Working Group also agreed that 10298 would only focus on compressed gases. Liquids that are used for gas mixtures would be summarized in a separate Appendix (A.2) as informative. There was little effort to try to seek additional data for these. It was also agreed to remove the tables for FTSC since that is now addressed in ISO 14456 Gas properties and associated classification (FTSC) codes. The revised standard was approved on June 12, 2008.

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LC_{50} Differences

I would like to address some of the questions

1. Chloromethane LC_{50} was changed from 8,300 ppm to 5,133 was a change by Dr. Tissot based on a more relevant study. (IZMEROV, N.F., et al. Toxicometric Parameters of Industrial Toxic Chemicals Under Single Exposure, Moscow, Centre of International Projects, GKNT, 1982 in IUCLID). There was no reference listed in the 1996 ISO 10298, just a notation that it was time adjusted mouse data. P-20 adopted the value from ISO.
2. My comments Oct 14, 2008 to CGA regarding triethylaluminum (TEAl) and diethyl zinc (DEZ) was incorporated in the CGA comments to TC58 SC2 WG7.

   "The organometallic compounds are not acutely toxic. Since they are violently water reactive and pyrophoric, they will react immediately in air to inert compounds like Zinc Oxide and Aluminum Oxide. Assignment of a conservative value of 10 ppm would suggest that they are more toxic than Arsine or Hydrogen Selenide"

   This was discussed and ISO 10298 was changed to reflect this opinion. SDS from many DEZ and TEAl manufacturing companies have been reviewed, Akzo Nobel, Dow Electronics, SAFC, none listed toxicity as a hazard. As noted earlier, CGA in the 1994 revision insert these compounds based on the listing in ISO 10298.

3. Hydrogen chloride has been listed as having an LC_{50} of 3120 ppm since P-20 was developed and was based on a Vernot study in 1977. Based on P-20 ISO adopted the same value in 1995.This was far better than the DOT value of 1175 ppm. Both toxicologist agreed in the 2008 review that the HARTZELL, G.E., PACKHAM, S.C., GRAND, A.F. and SWITZER, W.G. Modeling of toxicological effects of fire gases: III. Quantification of post-exposure lethality of rats from exposure to HCl. J Fire Sci, 3, 1985, pp. 195-207 was a more accurate study. This concluded a value of 2810 ppm. I cannot remember the reasons for this determination. As noted by Jay Harding in the comparison of DOT and CGA values, a variance of 25% in values between studies is not significant to a toxicologist. Especially when using earlier studies that were not as well controlled. This difference is 10%.

In closing, considerable effort was put into the revision of ISO 10298 by CGA and EIGA member companies. If more recent test reports are found or if these is still a conflict, every effort should be made to have it reviewed by a Toxicologist to validate the values as was done originally for P-20 and for the revised ISO 10298 standard. I am available to discuss this further.

Regards

Eugene Ngai

Enclosures

Rev. 1/2/90

T A B L E 3 T O X I C C A T E G O R I E S

PRODUCT	TOXICITY LEVEL PPM	ISO ADJUSTED VALUE	DESCRIPTION	[200 ppm] CATEGORY A > or = %	[5000 ppm] CATEGORY D > or = %	200 ppm using ISO (0 = no adj. made)	5000 ppm using ISO
AMMONIA - - - - - - - - - -	14070		LC50 RAT	N/A	N/A	0.0	0.0
ARSINE	26	20	LC50 MUS time adj.	13.000	0.520	10.0	0.4
BORON TRICHLORIDE	2541		LC50 RAT	N/A	50.820	0.0	0.0
BORON TRIFLUORIDE	806	800	LC50 RAT time adj.	N/A	16.120	N/A	16.0
BROMINE CHLORIDE - - - - -	2860		Est. from HBr	N/A	57.200	0.0	0.0
CARBON MONOXIDE	3760		LC50 RAT time adj.	N/A	75.200	0.0	0.0
CARBONYL FLUORIDE	360		LC50 RAT	N/A	7.200	0.0	0.0
CARBONYL SULFIDE	712	900	Est. from H2S	N/A	14.240	N/A	18.0
CHLORINE - - - - - - - - - -	293		LC50 RAT	N/A	5.860	0.0	0.0
CHLORINE PENTAFLUORIDE	122		LC50 RAT	61.000	2.440	0.0	0.0
CHLORINE TRIFLUORIDE	299		LC50 RAT	N/A	5.980	0.0	0.0
CYANOGEN	350		LC50 RAT	N/A	7.000	0.0	0.0
CYANOGEN CHLORIDE	118	80	LC50 RAT time adj.	59.000	2.360	40.0	1.6
DIBORANE - - - - - - - - - -	160	80	LC50 RAT time adj.	80.000	3.200	40.0	1.6
DICHLOROSILANE	314		LC50 RAT	N/A	6.280	0.0	0.0
DIETHYLAMINE	8000		LC50 RAT time adj.	N/A	N/A	0.0	0.0
DIMETHYLAMINE	13620	11000	LC50 RAT time adj.	N/A	N/A	N/A	N/A
ETHYLAMINE	16000		LC50 RAT time adj.	N/A	N/A	0.0	0.0
ETHYLENE OXIDE - - - - - - -	2920	2900	LC50 RAT time adj.	N/A	58.400	N/A	58.0
ETHYL FLUORIDE	>26%			---DELETE---	---DELETE---	---DELETE---	
FLUORINE	185		LC50 RAT	92.500	3.700	0.0	0.0
GERMANE	26	20	Est. from AsH3	13.000	0.520	10.0	0.4
HEXAFLUOROACETONE	481	470	LC50 RAT time adj.	N/A	9.620	N/A	9.4
HYDROGEN BROMIDE - - - - -	2860		LC50 RAT	N/A	57.200	0.0	0.0
HYDROGEN CHLORIDE	3120		LC50 RAT	N/A	62.400	0.0	0.0
HYDROGEN FLUORIDE	1276		LC50 RAT	N/A	25.520	0.0	0.0
HYDROGEN IODIDE	2860		Est. from HBr	N/A	57.200	0.0	0.0
HYDROGEN SELENIDE	2.8	2	LC50 GPG	1.400	0.056	1.0	0.0
HYDROGEN SULFIDE - - - - -	712		LC50 RAT	N/A	14.240	0.0	0.0
METHYLAMINE	7000		LC50 MUS	N/A	N/A	0.0	0.0
METHYL BROMIDE	1164	850	LC50 MUS	N/A	23.280	N/A	17.0
METHYL CHLORIDE	>7%	8300	LC50 UNK time adj.	---DELETE---	---DELETE---	---DELETE---	
METHYL CHLOROSILANE	1200		Est. twice Dichlor			0.0	0.0
METHYL DICHLOROSILANE - -	600		LC50 RAT time adj.	N/A	12.000	0.0	0.0
METHYL MERCAPTAN	1350		LC50 RAT time adj.	N/A	27.000	0.0	0.0
NITRIC OXIDE (+some N2O4)	115		LC50 RAT for NO2	57.500	2.300	0.0	0.0
NITROGEN DIOXIDE	115		LC50 RAT	57.500	2.300	0.0	0.0
NITROGEN TRIFLUORIDE	6700		LC50 RAT	N/A	N/A	0.0	0.0
NITROGEN TRIOXIDE - - - -	57		calc. N2O3=NO+NO2	28.500	1.140	0.0	0.0
NITROSYL CHLORIDE	115		Est. from NO2	57.500	2.300	0.0	0.0
OXYGEN DIFLUORIDE	2.6		LC50 RAT	1.300	0.052	0.0	0.0
PERCHLORYL FLUORIDE	770		LC50 RAT time adj.	N/A	15.400	0.0	0.0
PHOSGENE	5		LC50 RAT time adj.	2.500	0.100	0.0	0.0
PHOSPHINE - - - - - - - - -	22	20	LC50 RAT time adj.	11.000	0.440	10.0	0.4
PHOSPHOROUS PENTAFLUORIDE	255	250	Est. 1/5 of HF	N/A	5.104	N/A	5.0
SELENIUM HEXAFLUORIDE	50		LC50 RAT adj.	25.000	1.000	0.0	0.0
SILICON TETRAFLUORIDE	319		LC50 RAT for HF/4	N/A	6.380	0.0	0.0
STIBINE	40	90	IDLH	20.000	0.800	45.0	1.8
SULFUR DIOXIDE - - - - - - -	2520		LC50 RAT	N/A	50.400	0.0	0.0
SULFUR TETRAFLUORIDE	319		LC50 RAT for HF/4	N/A	6.380	0.0	0.0
SULFURYL FLUORIDE	3020		LC50 RAT	N/A	60.400	0.0	0.0
TELLURIUM HEXAFLUORIDE	25		LC50 RAT adj.	12.500	0.500	0.0	0.0
TRIFLUOROACETYLCHLORIDE	12		Est. as Trichloro.	6.000	0.240	0.0	0.0
TUNGSTEN HEXAFLUORIDE - -	1276		Est. from HF	N/A	25.520	0.0	0.0

NOTE: COS data is LCLO MUS time adj.; CH3Br is LC50 RAT time adj.; CH3Cl is LC50MUS time adj.; SbH3 is LCLO GPG.

Attachment 2, Ngai to CGA, History of CGA P-20 and ISO 10298

TOXIDOC5.WK1 1/2/90 this includes latest ISO data

No.	SYMBOL	TOXICITY LEVEL PPM		DESCRIPTION	DOCUMENTATION	
01	NH3 -----	14070		LC50 RAT	Appleman, L. M., et al, 1982. Male rat only, more conservative.	
02	AsH3	20	*	LC50 MUS time adj.	Levvy, 1947, from National Research Council, 1984. Should be ~26 ppm.	****
03	BCl3	2541		LC50 RAT	Vernot, E.H., et al, 1977. Males only, more susceptible.	
04	BF3	800	*	LC50 RAT time adj.	Rusch, G.M., et al, 1986. 403 ppm for 4 hours.	
05	BrCl ----	2860		Est. from HBr	Estimated, based on HBr data from Vernot et al, 1977.	
06	CO	3760		LC50 RAT time adj.	Rose, C.S., et al, 1970. 1880 ppm for 4 hours.	
07	COF2	360		LC50 RAT	Scheel, L.D., et al, 1968.	
08	COS	900	*	LCLO MUS time adj.	Berichte der Deutschen Chemischen Gesellschaft. 76,299,43. 1200ppm/35M	
09	Cl2 -----	293		LC50 RAT	Vernot, E.H., et al, 1977. No females, no observation time.	
10	ClF5	122		LC50 RAT	Darmer, K.I., et al, 1972. (no females used).	
11	ClF3	299		LC50 RAT	Darmer, K.I., et al, 1972. (no females used).	
12	C2N2	350		LC50 RAT	McNerney, J.M., and Schrenk, H.H., 1960. Calculated from graph.	
13	CNCl2	80	*	LC50 RAT time adj.	THICSM, ITI, Tokyo, 1977. 118 ppm for 30 minutes; unknown number, observation time.	
14	B2H6 ----	80	*	LC50 RAT time adj.	Adams, R.M., 1964. 40 ppm for 4 hours.	
15	SiH2Cl2	314		LC50 RAT	Chemical Hygiene Fellowship Report 49-112, UCC, 1986.	
16	(C2H5)2NH	8000		LC50 RAT time adj.	Smyth, H.F., et al, 1954. 4000 ppm for 4 hours on 6 rats, sex unknown.	
17	(CH3)2NH	11000	*	LC50 RAT time adj.	Steinhagen, W.H., et al, 1982. 4540 ppm for 6 hours; unknown number observed 2 days.	
18	C2H5NH2	16000		LC50 RAT time adj.	Smyth, H.F., et al, 1954. 8000 ppm killed 2/6 in 4 hours.	****
19	C2H4O ---	2900	*	LC50 RAT time adj.	Jacobson, K. H., et al, 1956. 1460 ppm for 4 hours; no females.	
20	C2H5F	>26%		LC50 RAT time adj.	Chemical Hygiene Fellowship Report 10-28, UCC, 1947.	
21	F2	185		LC50 RAT	Keplinger, M.L. and Suissa, L.W., 1968. 10 rats, sex unknown, 14 days.	
22	GeH4	20	*	Est. from AsH3	Levvy, 1947, from National Research Council, 1984. Should be ~26 ppm.	****
23	C3OF6	470	*	LC50 RAT time adj.	Borzella, J.F. and Lester, D., 1964. Number, sex, observation time unknown.	
24	HBr -----	2860		LC50 RAT	Vernot, E.H., et al, 1977. No females, no observation time.	
25	HCl	3120		LC50 RAT	Vernot, E.H., et al, 1977. No females or observation; more conservative than Darmer.	
26	HF	1276		LC50 RAT	Darmer, K.I. et al, 1972. No females. Confirmed by Rosenholtz (1307 ppm).	
27	HI	2860		Est. from HBr	Estimated, based on HBr data from Vernot et al, 1977.	
28	H2Se	2	*	LC50 GPG	Dudley, H.C. and Miller, J.W., 1941.	
29	H2S -----	712		LC50 RAT	Vernot, E.H., et al, 1977. No females or observation.	
30	CH3NH2	7000		LC50 MUS	Mezentseva, N.V., 1956.	
31	CH3Br	850	*	LC50 RAT time adj.	Toxicology and Applied Pharmacology. 81,183,85. 302 ppm for 8 hours.	
32	CH3Cl	8300	*	LC50 MUS time adj.	National Institutes of Health, Bulletin 191,1,49. 3146 ppm for 7 hours.	
33	SiClH2CH3	1200		Est. twice No. 34	Estimated, based on Marhold, J.V., 1972.	****
34	SiCl2HCH3	600		LC50 RAT time adj.	Marhold, J.V., 1972. [Czechoslovakia]	
35	CH3SH	1350		LC50 RAT time adj.	Tansy, M.F., et al, 1981. 675 ppm for 4 hours.	
36	NO	115		LC50 RAT for NO2	Estimated, based on NO2 data from Carson, R.T. et al, 1962.	
37	NO2	115		LC50 RAT	Carson, R.T. et al, 1962. No females.	
38	NF3	6700		LC50 RAT	Vernot, E.H. et al, 1973. No females.	
39	N2O3 ----	57		calc. N2O3=NO+NO2	Estimated, based on NO2 data from Carson, R.T. et al, 1962.	****
40	NOCl	115		Est. from NO2	Estimated, based on NO2 data from Carson, R.T. et al, 1962.	
41	OF2	2.6		LC50 RAT	Darmer, K.I. et al, 1972. No females.	
42	ClFO3	770		LC50 RAT time adj.	THICSM, ITI, Tokyo, 1977. 385 ppm for 4 hours; unknown number, sex, observation.	
43	COCl2	5		LC50 RAT time adj.	Based on 4 ppm/75 min [Rinehart and Hatch, 1964] and 12 ppm/30 min [Chasis, 1944].	
44	PH3 -----	20	*	LC50 RAT time adj.	Waritz, R.S. and Brown, R.M., 1975. 11 ppm for 4 hours; no females; unclear observ.	
45	PF5	250	*	Est. 1/5 of HF	Estimated, based on HF data from Darmer, K.I. et al, 1972.	
46	SeF6	50		LC50 RAT adj.	Kimmerle, G., 1959.	
47	SiF4	319		LC50 RAT for HF/4	Estimated, based on HF data from Darmer, K.I. et al, 1972.	
48	SbH3	90	*	LCLO GPG	Browning, E. Toxicology of Industrial Metals. London: Butterworths, 1961.	
49	SO2 -----	2520		LC50 RAT	NTIS publication AD-A148-952; still searching for document.	
50	SF4	319		LC50 RAT for HF/4	Estimated, based on HF data from Darmer, K.I. et al, 1972.	
51	SO2F2	3020		LC50 RAT	Vernot, E.H., et al, 1977. No observation; conservative female data used.	
52	TeF6	25		LC50 RAT adj.	Kimmerle, G., 1959.	
53	C2F3OCl	12		Est. as Trichloro..	Estimated, based on trichloroacetylchloride, RTECS.	****
54	WF6 -----	1276		Est. from HF	Estimated, based on HF data from Darmer, K.I. et al, 1972.	

Gas Comparison CGA/ISO

GASES ON BOTH LISTS	CGA ONLY	ISO ONLY
AMMONIA	BROMINE CHLORIDE	ANTIMONY PENTAFLUORIDE
BORON TRICHLORIDE	CARBONYL FLUORIDE	BIS-TRIFLUOROMETHYL PEROXIDE
BORON TRIFLUORIDE	DIETHYLAMINE	BROMINE PENTAFLUORIDE
CARBON MONOXIDE	METHYL CHLOROSILANE	BROMINE TRIFLUORIDE
CARBONYL FLUORIDE	METHYL DICHLOROSILANE	BROMOACETONE
CHLORINE SULFIDE	NITROGEN TRIFLUORIDE	1.3-BUTADIENE(INHIBITED)
CHLORINE	PERCHLORYL FLUORIDE	COAL GAS
CHLORINE PENTAFLUORIDE	SELENIUM HEXAFLUORIDE	CYCLOPROPANE
CYANOGEN	TELLURIUM HEXAFLUORIDE	DEUTERIUM CHLORIDE
CYANOGEN CHLORIDE	TRIFLUOROACETYLCHLORIDE	DEUTERIUM FLUORIDE
DIBORANE		DEUTERIUM SELENIDE
DICHLOROSILANE		DEUTERIUM SULFIDE
DIMETHYLAMINE		DIBROMODIFLUOROMETHANE
ETHYLAMINE		DICHLORO-2-CHLOROVINYL-ARSINE
ETHYLENE OXIDE		DIETHYLZINC
FLUORINE		DIMETHYLSILANE
GERMANE		DIPHOSGENE
HEXAFLUOROACETONE		ETHYLDICHLOROARSINE
HYDROGEN BROMIDE		HEPTAFLUOROBUTYRONITRILE
HYDROGEN CHLORIDE		HEXAFLUOROCYCLOBUTENE
HYDROGEN FLUORIDE		HYDROGEN CYANIDE
HYDROGEN IODIDE		IODINE PENTAFLUORIDE
HYDROGEN SELENIDE		IODOTRIFLUOROMETHANE
HYDROGEN SUFIDE		METHYLDICHLOROARSINE
METHYLAMINE		METHYL VINYL ETHER (INHIBITED)
METHYL BROMIDE		MUSTARD GAS
METHYL CHLORIDE		NICKEL CARBONYL
METHYL MERCAPTAN		OZONE
NITRIC OXIDE (+SOME N204)		PENTAFLUOROPROPIONITRILE
NITROGEN DIOXIDE		PERFLUORO-2-BUTENE
NITROGEN TRIOXIDE		PENTABORANE
NITROSYL CHLORIDE		PHENYLCARBYLAMINE CHLORIDE
OXYGEN DIFLUORIDE		PHOSPHORUS TRIFLUORIDE
PHOSGENE		PROPYLENE OXIDE
PHOSPHINE		SILANE
PHOSPHOROUS PENTAFLUORIDE		SILICON TETRACHLORIDE
SILICON TETRAFLUORIDE		TETRAETHYL LEAD
STIBINE		TETRAFLUOROHYDRAZINE
SULFUR DIOXIDE		TETRAMETHYL LEAD
SULFUR TETRAFLUORIDE		TRIETHYL ALUMINUM
STIBINE		TRIETHYL BORANE
SULFUR DIOXIDE		TRIFLUOROACETONITRILE
SULFUR TETRAFLUORIDE		TRIFLUOROETHYLENE
SULFURYL FLUORIDE		TRIETHYLAMINE
TUNGSTEN HEXAFLUORIDE		TRIMETHYSILANE
		TRIMETHYLSTIBINE
		URANIUM HEXAFLUORIDE
		VINYL BROMIDE (INHIBITED)
		VINYL CHLORIDE (INHIBITED)
		VINYL FLUORIDE (INHIBITED)

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Subject: LC50 Value for ISO 10298

Dear Dr.Tissot,

Since the ISO10298 committee meeting of January 15, 2008, Air Products and Chemicals, Inc. has undertaken a review of the studies related to hydrogen fluoride acute inhalation exposures. We believe that the 966 ppm LC_{50} value for hydrogen fluoride, which is currently included in ISO10298, is not the most appropriate value to use.

Table 3-4 of the *2004 US National Advisory Committee AEGL review for Hydrogen Fluoride*[1] lists the relevant 1-hour rat studies as follows:

Concentration (ppm)	Effect	Reference
2,300	LC_{50}	Haskell Laboratory 1990
2,039	LC_{10}	Dalbey et al. 1998
1,395	LC_{50}	Wohlslagel et al. 1976
1,307	LC_{50}	Rosenholz et al. 1963
1,276	LC_{50}	MacEwen and Vernot 1970
966	LC_{50}	Vernot et al. 1977

As agreed to in the ISO 10298 committee, the most appropriate LC_{50} value to adopt for hydrogen fluoride is the value from the most technically sound study. The more recent hydrogen fluoride studies, which were not publicly available when the 1995 ISO10298 was adopted, are technically better than the older studies for the following reasons:

- They employed a better exposure method (head-only vs. whole body). With wholebody exposures it is much more difficult to achieve accurate and reproducible concentrations in the breathing zone. Furthermore, the total exposure is often under estimated because the animals are simultaneously exposed via the dermal and oral routes (via grooming). The new OECD inhalation test guidelines support this position:

  For acute inhalation toxicity studies the preferred mode of exposure is the head/nose-only exposure technique. This type of exposure minimises exposure or uptake by non-inhalation routes. Additionally, it allows testing of high concentrations as required to meet the limit concentration. The instability of test compounds (e.g., reactivity with excreta or humidity) and the possible heterogeneity of the test atmosphere in inhalation chambers are of less concern when head/nose-only inhalation chambers are used. The duration required to attain the inhalation chamber equilibration is minimal in head/nose-only chambers. However, the test performer has the option of using other systems (e.g., whole-body inhalation chambers) when justification can be made.[2,3]

- The more recent studies used improved analytical methods:

  Sampling and analytical methods used in the human and animal studies conducted in the 1960s and 1970s were not as sensitive as those perfected by the late 1980s and 1990s and may have under- or overestimated concentrations. An improved sampling/analytical methodology developed by Haskell Laboratory (1990) indicates that HF may have collected on glassware in the exposure apparatus. That factor would indicate that exposure concentrations in the early studies may have been underestimated.[1]

- The newer studies are more likely to have been conducted in accordance with GLPs.

Based on these technical points, the most appropriate value for hydrogen fluoride is the Haskell (1990) LC_{50} value of 2,300 ppm. This is also supported by the Dalbey et al. (1998) work showing the LC_{50} to be >2,039 ppm.

A statistical approach applying equal weight to all of the available studies could also be used to select the LC_{50} value to adopt. There are five 1-hour rat LC_{50} values in the AEGL document to consider. Three of these values are virtually identical as indicated in the 2004 AEGL report:

> *Similar 60-min LC_{50} values for the rat were found by Wohlslagel et al. (1976), Rosenholtz et al. (1963), and MacEwen and Vernot (1970); 1,395, 1,307, and 1,276 ppm, respectively.* [1]

The mean of the five LC_{50} values is 1,449 ppm, and the median LC_{50} value is 1,307 ppm. The median LC_{50} of 1,307 ppm could be adopted for hydrogen fluoride as a reasonable value.

Based on the above information, we propose adopting the median 1-hour rat LC_{50} value of 1,307 ppm. As noted at the meeting of January 15, 2008 in Paris, the value that is adopted for hydrogen fluoride will have a significant impact on the classification of the other hydrolyzable fluoride gases such as phosphorus trifluoride and tungsten hexafluoride. Tungsten hexafluoride has an estimated LC_{50} value of 160 ppm based on a 966 ppm 1-hour LC_{50} for hydrogen fluoride. This value would result in the classification of tungsten hexafluoride as a highly toxic gas, and severely restrict packaging and transportation options. If the 1,307 ppm 1-hour LC_{50} is adopted, tungsten hexafluoride would have an estimated LC_{50} value of 218 ppm which would cause tungsten hexafluoride to be classified as toxic rather than highly toxic. This approach would also make it easier to harmonize ISO10298 with CGA P-20.

We would be happy to discuss this with you further by telephone. We are anxious to reach agreement on this for the final draft of ISO10298, which is due January 25, 2008.

Sincerely,

Eugene Y. Ngai
Director of ER & Disposal Technology

Carrie E. Hamilton
Product Safety Specialist - Toxiciology

cc: Hervé Barthélémy
Nicole Legent

References

1. "Acute Exposure Guideline Levels for Selected Airborne Chemicals, Volume 4", Subcommittee on Acute Exposure Guideline Levels, Committee on Toxicology Board on Environmental Studies and Toxicology, The National Academy Press, Washington DC, 2004
2. "OECD Guideline for the Testing of Chemicals", Draft Proposal for New Guideline: #433 (2004)
3. "OECD Guideline for the Testing of Chemicals", Draft Proposal for New Guideline: #436 (2005)

Feel the Heat

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Jan 17, 2013

To: ISO/TC 58/SC 2/WG 7
Jack Wert-CGA

Re: ISO/NP 14456 "Gas properties and associated classification (FTSC) codes"

As noted, the FTSC should be updated with the data from ISO 10298. Changes to ISO 10298 were noted in my letter dated Oct 18, 2011 **"**New standard on "Gas properties". Please note the following edits

Table 5:Tungsten Hexafluoride T changed from 3 to 2 based on item 3 of my letter

> A key revision was establishment of the LC_{50} for hydrogen fluoride at 1307 ppm which was the value from the most technically sound study. (E. Ngai & C. Hamilton letter "LC_{50} Value for ISO 10298" to Dr. S Tissot, dated Jan 24, 2008) "The more recent hydrogen fluoride studies, which were not publicly available when the 1995 ISO10298 was adopted, are technically better than the older studies The mean of the five LC_{50} values is 1,449 ppm, and the median LC_{50} value is 1,307 ppm. This revision affected the values estimated for the hydrolyzable fluoride gases such as tungsten hexafluoride which do not have actual toxic studies.

Table 8: Germane T changed from 3 to 2 based on updated study

Table 9: Dimethylzinc and Trimethylaluminum T changed from 3 to 1 based on Item 7 of my letter

> Table A.2 lists the metal alkyls such diethylzinc as having an LC_{50} of 10 ppm which would suggest that they are more toxic than phosphine and arsine. There is no data to support this. In transportation they are classified as pyrophoric water reactive liquids not toxic.

Should there be any questions, please contact me

Eugene Ngai

Eugene Ngai