Center for Regulatory Effectiveness
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EXAMPLES OF RESEARCH ON HUMAN VOLUNTEERS WITH POTENTIALLY TOXIC CHEMICALS, PATHOGENS, AND RADIATION, CONDUCTED, SUPPORTED, OR RELIED ON BY U.S. FEDERAL AGENCIES (AND NAS/NRC)

Notes:

- The following information is not based on a systematic literature search and does not purport to be comprehensive.
- Examples given do not go back further than Jan. 1, 1990, although some of the examples from post 1990 reference many volunteer studies conducted prior to 1990.

INTER-AGENCY

MTBE and ethanol as gasoline additives

Interagency Assessment of Oxygenated Fuels (June1997)

-- Prepared under the auspices of the National Science and Technology Council at the request of EPA. The Interagency Steering Committee for the study included OSTP, EPA, CEQ, NOAA, DOI, USDA, HHS, and DOE. (P. xi) The study was peer reviewed by the National Research Council of the National Academy of Sciences.

-- The acute health effects data review portion of the study relied on three human volunteer studies (p. 4-11):

-- Cain WS, Leaderer BP, Ginsberg GL, Andrews LS, Cometto-Muniz, Gent JE, Buck JF, Beglund LG, Mohsenin V, Monahan E, and Kjaergaard S. 1996. Acute exposure to low-level methyl tertiary butyl ether (MTBE): human reactions and pharmacokinetic responses. *Inhal Toxicol* 8:21-48.

-- Johanson G, Nihlen A, and Lof A. 1995. Toxicokinetics and acute effects of inhaled MTBE and ETBE in male volunteers. *Toxicol Lett* 82-83:713-18.

-- Prah J, Goldstein G, Devlin R, Otto D, Ashley D, House D, Cohen K,

and Gerrity T. 1994. Sensory, symptomatic, inflammatory and ocular responses to and the metabolism of methyl tertiary butyl ether in a controlled human exposure experiment. *Inhal Toxicol* 6:521-538.

-- study supported by EPA

A number of other studies referenced below under individual agencies received funding from more than one agency, as indicated. Examples include the study by Luderer et al., 1999, on effects of toluene, which was funded in part by DOE, NIOSH, and NIEHS, the study by Emmen et al., 2000, on effects of CFC alternatives, which was sponsored in part by DOD and EPA, and the study by Vinegar et al. on effects of Halon and HFCs,which was co-sponsored by the Air Force and EPA.

See also the NAS/NRC section below regarding the FACA committee for AEGLs, which includes personnel from many federal agencies.

CPSC

phthalates (DINP)

– *Report to the U.S. Consumer Product Safety Commission by the Chronic Hazard Advisory Panel on Diisononyl Phthalate (DINP)*. (CPSC Directorate for Health Sciences, June 2001). Pp. 16-18 and Table IV-2.

– relied on the following studies of adult volunteers who chewed on plastic to calculate the amount of DINP likely to be extracted from plastic toys by youngsters who chewed on them.

– Chen SB. Laboratory Sciences Report on the migration of diisononyl phthalate from polyvinyl chloride children's products. U.S. Consumer Product Safety Commission, Oct. 27, 1998.

– Fiala F, Steiner I, Kubesch K. 2000. Migration of di-(2-ethylexy1) phthalate (DEHP) and diisononyl phthalate (DINP) from PVC articles. *Deutsche Lebensmittel-Rendschau* 96:51-57.

– Rijksinstituut voor Voksgesondheid en Milieu (National Institute of Public Health and Environment, "RIVM"). 1998. Phthalate release from soft PVC baby toys: Report from the Dutch Consensus Group. RIVM Report No. 61 3320 002 (Könemann WH ed., Bilthoven.)

DOD

carbon monoxide

-- McGrath JJ, Schreck RM and Lee PS. 1993. Effects of altitude on toxic gas uptake:

CO inhalation in healthy adult volunteers. Proc. U.S. Army Chemical Research Scientific Congress on Chemical Defense Research-ERDEC-SP-002.

– Kizakevich PN, McCartney ML, Hazucha MJ, Sleet LH, Jochem WJ, Hackney AC, and Bolick K. 2000. Noninvasive ambulatory assessment of cardiac function in healthy men exposed to carbon monoxide during upper and lower body exercise. *Eur J Appl Physiol* 83(1):7-16.

  – supported in part by U. S. Army Medical Research and Materiel Command.

Halon and HFCs

– Vinegar A, Cook R, McCafferty J, Caracci M, Jepson G. 1997. Human inhalation of Halon 1301, HFC-134a and HFC-227ea for collection of pharmacokinetic data. (Air Force Wright-Patterson Armstrong Laboratory publication).

  -- co-sponsored by Air Force and EPA

– Emmen HH, Hoogendijk EM, Klopping-Ketelaars WA, Juijser H, Duistermaat E, Ravensberg JC, Alexander DJ, Borkhataria D, Rusch GM, Schmit B. 2000. Human safety and pharmacokinetics of the CFC alternative propellants HFC 134a (1,1,1,3-tetrafluoroethane) and HFC 227 (1,1,1,2,3,3,3-heptafluoropropane) following whole-body exposure. *Regul Toxicol Pharmacol* 32(1):22-35.

  – sponsored in part by DOD and EPA

pyridostigmine

– The Army Medical Research and Materiel Command announced in December 1997 that it had funded, in cooperation with VA and HHS, two studies at Midwest Research Institute on the potential adverse neurobehavioral/cholinesterase effects of pyridostigmine bromide (PB).

  – PB is considered to be an anti-nerve agent, and was administered to troops in the Gulf War. Due to reports of adverse health effects, investigation was continued through the 90s.

DOE

toluene

-- Luderer U, Morgan MS, Brodkin CA, Kalman DA, and Faustman EM. 1999. Reproductive endocrine effects of acute exposure to toluene in men and women. *Occup Environ Med* 56(10):657-66.

  – funded in part by DOE, NIOSH, and NIEHS

EMF

– See material regarding EMF RAPID research program conducted in conjunction with NIEHS below in NIEHS section.

EPA

Air particulate matter

– ongoing experiments with healthy young and elderly volunteers and volunteers suffering from asthma or chronic obstructive pulmonary disease (COPD) in EPA's NHEERL (National Health and Environmental Effects Research Laboratory) air chamber facilities.

  – looking for heart rate variability, pattern of lung deposition, and lung inflammation

  – experiments described in summary form in NHEERL annual report for FY 2000

aldicarb, aldicarb sulfoxide, and aldicarb sulfone

-- reference dose in IRIS set on basis of "A Safety and Tolerability Study of Aldicarb at Various Dose Levels in Healthy Male and Female Volunteers. 1992. Inveresk Clinical Research Report No. 7786, MID No. 423730-01. HED Doc. No. 0010459" (unpublished).

barium and barium compounds

-- On July 1, 1991, EPA set a final drinking water MCLG for barium and barium compounds based on an RfD derived from a study in which barium chloride in drinking water was administered to volunteers (cited in the IRIS database as "Wones, RG,; Stadler, BL; Frohman, LA. (1990) Lack of effect of drinking water barium on cardiovascular risk factor. Environ Health Perspect 85:355-59", and cited in the EPA final drinking water rule as "Wones 1990".) An uncertainty factor of 3 was applied to the NOAEL. 56 Fed.Reg. 30266, 30272.

– The latest IRIS database entry for barium and barium compounds, last revised 1/21/99, continues to show the same RfD using an uncertainty factor of 3. Unlike the 1991 drinking water final rule (above), however, it does not state that the RfD is based solely on the Wones et al. 1990 human volunteer study; rather, it states: "No single study is appropriate as the basis for a lifetime RfD for barium. The RfD is based on a weight-of-evidence approach that focuses on four co-principal studies: the Wones et al. (1990) experimental study in humans, the Brenniman and Levy (1984) epidemiologic study, and the subchronic and chronic rat studies that employed adequate diets and investigated both cardiovascular and renal endpoints

(NTP, 1994)."

carbon monoxide

– In 1994, EPA completed another review of the CO ambient air quality standard (NAAQS) and determined that revisions were not appropriate. 59 Fed. Reg. 38906 et seq. (Aug. 1, 1994). The 1994 decision was based primarily on controlled human volunteer studies of patients suffering from angina pectoris, ischemic heart disease, and obstructive coronary artery disease. 59 Fed.Reg. at 38909-11. The data from those studies were also supported by numerous controlled human volunteer studies of the effects of carbon monoxide on oxygen uptake and exercise performance in healthy individuals. 59 Fed.Reg. at 38909, 38911. The notice of the final decision also discussed the findings from numerous controlled human volunteer studies for neurobehavioral effects such as changes in visual perception, hearing, motor performance, sensorimotor performance, and vigilance, but concluded that because the cardiovascular studies showed effects at lower levels, they should remain the primary focus. 59 Fed.Reg. at 38911.

-- Air quality standards, and reviews of those standards, are based on "Criteria Documents", followed by "Staff Papers", and supplemented by CASAC evaluation of those two documents. The most recent Criteria Document for carbon monoxide was published in June 2000. AIR QUALITY CRITERIA FOR CARBON MONOXIDE. USEPA EPA 600/P-99/001F. 01, June 2000. That CD states that the "[h]ealth assessment provided in this document supports and substantiates the conclusions drawn in the previous [criteria] document." (Abstract.) The previous criteria document was completed in 1991 and was one of the source documents for the review discussed above that was completed in 1994. The 2000 CD goes on to state: "Although the scientific data have changed little since 1991, controlled-exposure studies continue to provide the most quantitative evidence on low-level CO effects in humans. *Id.*, section 6.1 ("Health Effects of Exposure to Carbon Monoxide"), p. 6-1.

chlorpyrifos

– until June 2000 (when it published a revised risk assessment that rejected human volunteer data on the basis of the Agency's "interim" policy), EPA used a human volunteer study to set the RfD

  – Dow Chemical Company. 1972. Accession No. 112118 (unpublished).

cryptosporidium

– EPA/NCEA is currently funding a large volunteer project at the Univ. of Texas Health Science Center, Houston, titled "Infectivity and Virulence of Cryptosporidium Genotype H Oocysts in Healthy Adult Volunteers" under Grant No. R828035. The purpose of the study is to determine infectious dose and biologic responses and markers. The study has already resulted in diarrheal illness in a

number of the volunteers, apparently severe in some cases. The list of references given for this grant under "Publication Details" also lists a number of journal articles that indicate studies of volunteers.

ethephon

– EPA's online IRIS database RfD currently shows it was last revised on 03/01/1991. The RfD was set using a LOEL derived from a controlled human volunteer study. The study is cited as "Union Carbide Agricultural Products Company, Inc. 1977a. MRID 00066931." The RfD determination also took into account as a non-principal study another human volunteer study ("Union Carbide, 1972").

ethion

– EPA's online IRIS database currently shows that its oral RfD was last revised 09/01/1989. A NOEL and a LOEL for plasma cholinesterase inhibition were based on a human volunteer study. (Cited as FMC Corporation. 1970. MRID No. 00073157.) EPA issued a revised Human Health Risk Assessment for ethion on July 14, 1999. The revised risk assessment relied principally on animal studies, and the result was that the acute RfD was raised.

Halon and HFCs

– See Vinegar A et al. and Emmen et al. studies under DOD section, above.

malathion

– The IRIS database currently shows that the oral RfD was last revised on 01/01/1992. At that time, the "principal study" supporting the RfD was a subchronic human volunteer feeding study, cited as "Moeller, H.C. and J.A. Rider, 1962. Plasma and red blood cell cholinesterase activity as indication of the threshold of incipient toxicity of ethyl-p-netrophenyl thiononobenzenephosphorate (EPN) and malathion in human beings. Toxicol. Appl. Pharmacol. 4:123-30."

mercury and mercury compounds (methylmercury)

– EPA's current IRIS oral RfD for methylmercury was last revised on 07/27/2001. Instead of employing a LOAEL/NOAEL approach, the RfD is based on a Benchmark Dose approach (BMD), with a "critical effect" of developmental neuropsychological impairment. While the "principal study" cited is a Faroe Islands epidemiologic study, employment of the BMD approach necessarily required dose conversion data, including data on human absorption, distribution, and excretion, and for these types of necessary data the Agency relied on at least five controlled human volunteer studies involving ingestion of fish contaminated with specific quantities of methymercury.

– The methylmercury RfD summary shows that it relied substantially for its data on

the Agency's mandated 1997 Mercury Study Report to Congress. (EPA-452/R-97-007, Dec. 1997.) That study also shows that substantial reliance was placed on human volunteer studies for determining absorption and elimination rates in humans of elemental mercury, inorganic mercury, and methylmercury. *Id* at 2-1, 2-2, 2-3, 2-7, 2-8, 2-13, 2-14, 6-23, 6-24, 6-48, B-38, B-39 and B-43.

– In January 2000, EPA issued final "Water Quality Criterion for the Protection of Human Health: Methylmercury". (EPA-823-R-01-001, Jan. 2001.) The criterion is not a binding regulation, but is intended to provide guidance to States and Tribes in setting water quality standards. (66 Fed.Reg. 1344 et seq., Jan. 8, 2001.) The criterion document states that it relies primarily on the information contained in the 1997 report to Congress, and briefly summarizes several human volunteer studies which provided human oral absorption and distribution data. *Id.* at 2-1 and 2-2.

methyl parathion

– The current IRIS oral RfD was last revised 03/01/91. The RfD was based on a NOEL of observed in a rat feeding study. Although treated as a "principal study", this rat feeding study was classified as only "supplementary". The portion of the RfD Summary under "Additional Studies/Comments" contains the following explanation regarding a human volunteer study for which only an abstract was available:

> In a subchronic study (30 days) with methylparathion in humans (Rider et al., 1971), RBC cholinesterase depression was reported, with a NOEL of approximately 0.3 mg/kg/day. Using a UF of 100 to adjust for chronic exposure and intraspecies sensitivity, an RfD based on this study would be 0.003 mg/kg/day. Adequate supporting data for human studies are not available. Nevertheless, even anecdotal data directly relating to human exposure should not be dismissed. Therefore, an RfD based on animal studies should not exceed 0.003 mg/kg/day unless additional data for humans can be found to support such a determination.

MTBE (methyl tertiary butyl ether, a gasoline additive)

– see study by Prah JD, et al., 1994, cited above in the "Interagency" section.

  – funded by EPA

– EPA research scientists reported verbally in May 2000 that they were conducting a new study of MTBE administered in drinking water to volunteers, on behalf of EPA's drinking water program (personal communications to W. Kelly of CRE).

nitrogen dioxide

-- EPA published a final rule on October 8, 1996 determining not to change the existing national ambient air quality standards for nitrogen dioxide. 61 Fed.Reg. 52852 et seq. The final rule relied on the health effects assessment presented in the Oct. 11, 1995 notice of proposed rulemaking. 60 Fed.Reg.52874 et seq. The standards decision relied substantially on human volunteer clinical studies of asthmatics (including adolescent asthmatics) for changes in, and absence or reversibility of, health effects (pulmonary function or airway responsiveness). 60 Fed.Reg. at 52878, 52879 3d col. Additional information supporting the decision was presented in the 1993 "Air Quality Criteria for Oxides of Nitrogen" (EPA/600/8-91/049aF, Aug. 1993). The controlled human volunteer studies were discussed at 1-19 (Executive Summary), Chapter 15 (pp. 15-1 to 15-105 ("Controlled Human Exposure Studies of Nitrogen Oxides"), and Chapter 16, pp. 16-1 to 16-2 ("Health Effects Associated with Exposure to Nitrogen Dioxide", referring back to Chapter 15). The OAQPS Staff Paper supporting the decision not to revise the standard contains extensive discussion of the findings from the controlled human volunteer studies assessed in the Criteria Document. "Review of the National Ambient Air Quality Standards for Nitrogen Dioxide – Assessment of Scientific and Technical Information", pp. vii-viii, 16, 33-38, 43-46, 49-50, EPA-452/R-95-005, Sept. 1995.

ozone

-- On July 18, 1997, EPA issued a final rule containing its decision to revise the national ambient air quality standard (NAAQS) for ozone and replace the 1-hr. standard with an 8-hr. standard. 62 Fed.Reg. 38856 *et seq*. The decision was based substantially on controlled human studies of healthy and asthmatic subjects for lung function decrements, respiratory symptoms (e.g., cough, pain on deep inspiration), non-specific bronchial responsiveness, biochemical indicators of pulmonary inflammation, and exercise response. *Id*. at 38863-64, 38872, and 38873 and Criteria Document. Most, if not all, of the studies relied on were conducted by EPA. *Id*. at 38867. See also the Criteria Document at 1-23 to 1-26 (Executive Summary).

pirimiphos-methyl

-- The IRIS database currently shows that the oral RfD was last revised 0l/01/1992. The principal studies supporting the RfD are two human volunteer feeding studies, cited as ICI Americas Inc. 1976a. MRID No. 00080732; HED Doc. No. 005105, and ICI Americas Inc. 1974a. MRID No. 00080747; HED Doc. No. 005105.

propoxur (Baygon)

– EPA's online IRIS database currently shows that the RfD, last revised 07/01/1992, was based on a single human volunteer study, cited as "Vandekar, M., R. Plestina and K. Wilhelm. 1971. Toxicity of carbamates for mammals. Bull. World. Health Org. 44:241-249."

sulphur dioxide

-- On May 22, 1996, EPA published a final decision not to revise the NAAQS for

sulphur oxides. 61 Fed.Reg. 25566. The decision relied substantially on controlled human volunteer studies of mild, moderate, and moderate/severe asthmatic subjects exposed via mouthpiece or in chamber. *Id*. at 25570-73. Those studies were discussed in detail and evaluated in the *Supplement to the Second Addendum (1986) to Air Quality Criteria for Particulate Matter and Sulfur Oxides (1982): Assessment of New Findings on Sulfur Dioxide Acute Exposure Health Effects in Asthmatic Individuals (1994)*(EPA-600/FP-93/002).

zinc and zinc compounds

– The IRIS database currently shows that the oral RfD was last revised on 10/01/92. The RfD was based on a human clinical study which investigated the effects of oral zinc supplements on copper and iron balance in volunteers. (Yadrick et al., 1989.) The effects on copper and iron biochemistry are stated to be a concern because long-term iron or copper deficiency could result in significant adverse effects--for example, anemia and increased risk of coronary artery disease.

See info on NAC/AEGL below under National Research Council (NAC/AEGL is a FACA committee chartered by EPA/OPPTS and comprised of scientists from many other federal agencies)

HHS

ATSDR

formaldehyde

– *Toxicological Profile for Formaldehyde (July 1999)* considers numerous human volunteer studies.

methylene chloride

– *Toxicological Profile for Methylene Chloride* (Sept. 2000) relies on numerous human volunteer studies.

tetrachloroethylene (PERC)

-- *Toxicological Profile for Tetrachloroethylene (PERC)* (Sept.1997) relies on numerous human volunteer studies conducted between 1952 and 1994 to arrive at a MRL (minimal risk level).

trichloroethylene (TCE)

– *Toxicological Profile for Trichloroethylene (TCE)* (Sept. 1997) relies on numerous human volunteer studies to arrive at MRL.

xylenes

– *Toxicological Profile for Xylenes* (August 1995) relies on volunteer studies

to derive MRL.

CDC/NIOSH

toluene

-- see info above on funding of Luderer et al. research on toluene in male and female volunteers, under DOE section, above.

– See also reference to NIOSH participation in NAC/AEGL under sections on National Research Council and EPA

FDA/CFSAN

pathogens in shellfish

-- The agency's Jan. 2001 "Draft Risk Assessment on the Public Health Impact of *Vibrio parahaemolyticus* in Raw Molluscan Shellfish" states (in section on Dose-response data) that FDA is currently funding a human volunteer study in which they will be fed raw oysters containing V. cholerae non-O1 at varying doses to determine dose-response. The CFSAN Foodborne Pathogenic Microorganisms and Natural Toxins Handbook states that this organism can cause severe gastroenteritis, which is usually self-limiting and treated with antibiotics, although it can rarely cause septicemic infections and deaths.

NIH

1,3-butadiene

– Lin YS, Smith TJ, Kelsey KT, 2001. Wypij D. Human physiologic factors in respiratory uptake of 1,3-butadiene. *Environ Health Perspect* 109(9):921-26.

-- funded by NIEHS

chloroform and trichloroethene

– Weisel Cp, Jo WK. 1996. Ingestion, inhalation, and dermal exposures tochloroform and trichloroethene from tap water. Environ Health Perspect 104(1):48-51.

-- partially funded by NIEHS

electromagnetic fields (EMF)

– The EMF RAPID (Research and Public Information Dissemination) program is conducted in conjunction with DOE (with most of the funding coming

from DOE). NIEHS has given grants to Midwest Research Institute to conduct human volunteer experiments exposing them to EMF and ELF and measuring melatonin and reproductive hormone levels.

– Graham C, Cook MR, Gerkovich MM, and Sastre A. 2001. Examination of the melatonin hypothesis in women exposed at night to EMF or bright light. *Environ Health Perspect* 110(2):A72-73; Graham C, Sastre A, Cook MR, and Gerkovich MM. 2001. *J Pineal Res* 31(2):109-13. (Also, Graham C, Cohen HD, Cook MR. Immunological and biochemical effects of 60-Hz electric and magnetic fields in humans. MRI Project No. RA-338-C. Kansas City: Midwest Research Institute, 1990. Referenced in report to Congress below.)

– See also NIEHS Report on *Health Effects from Exposure to Power-Line Frequency Electric and Magnetic Fields,* a report to Congress in May 1999, which reviews and relies on human volunteer studies both in the U.S. and in many other countries, and refers to such studies as "currently under way in many of these facilities." P. 18 in pdf version.

– The U.S. also participates in the WHO research agenda recommended by the European Commission Expert Group. (See www.who.int/peh-emf/research/agenda/en/ and background paper which is Attachment B.) The Agenda (as last updated in May 2002) recommends additional volunteer research to test for effects on hormone levels, effects on the eye, inner ear and cochlea, memory loss, neurodegenerative diseases and neurophysiological effects, headache, sleep disorders, and immunological effects.

perchlorate

– Lawrence JE, Lamm SH, Pino S, Richman K, Braverman LE. 2000. The effect of short-term low-dose perchlorate on various aspects of thyroid function. Thyroid 10(8):659-63.

  – partially funded by NIH

toluene

– See reference to study by Luderer et al. under DOE section, above.

NASA

Halon

-- Calkins DS, Degioanni JJ, Tan MN, Davis JR, Pierson DL. 1993. Human performance and physiological function during a 24-hr exposure to 1% bromotrifuoromethane (Halon 1301). *Fundam Appl Toxicol* 20(2):240-47.

  -- funded by NASA

TCE, freons, fluorocarbons

– see material below under NRC/NAS section, below, on Spacecraft Maximum Allowable Concentrations

National Research Council of National Academy of Sciences

***Acute Exposure Levels for Selected Airborne Chemicals* (vols.1 and 2). 2002. National Research Council of the National Academies.**

– relies on numerous human volunteer studies for setting AEGLs for various chemicals

  – monomethyhydrazine
  – propylene glycol dinitrate
  – 1,1,1,2-tetrafluorethane (HFC-134a)
  – 1,1-cichlor-1-fluoroethane (HCFC-141b)

-- AEGL Subcomm. of BEST and the National Advisory Committee on Acute Exposure Guideline Levels (NAC/AEGL) peer reviews the recommendations of the National Advisory Committe on Acute Exposure Guideline Levels (NAC/AEGL) before publication of the AEGLs by the National Research Council.

– NAC/AEGL is chartered and managed under FACA (the Federal Advisory Committee Act) by EPA (OPPTS), and the committee includes representatives from EPA, ATSDR, DOE, NIOSH, OSHA, DOT, DOD, CDC, FDA and FEMA.

  – Federal agencies such as the U.S. Army (Chemical and Biological Defense Command, Aberdeen Proving Ground, MD, Edgewood Research, Development & Engineering Center), provide input and recommendations for the AEGL process (see, e.g, Miodustewski RJ, Reutter SA, Miller LL, Olajos EJ, Thomson SA. 1998. Evaluation of airborne exposure limits for G-Agents: Occupational and general population exposure criteria. U.S. Army Chemical and Biological Defense Command, Aberdeen Proving Ground)

    – relies on early volunteer studies

– Proposed AEGLs are promulgated for public notice and comment by EPA in the Federal Register prior to review by NRC and finalization.

  – See, e.g., 65 Fed.Reg. 14186, 14189 (Mar. 15, 2000), statement that the AEGL-2 for sulphur mustard (Agent HD, a chemical warfare agent) "is based upon human [volunteer] data precludes the use of an interspecies UF."

  – See, e.g., 65 Fed.Reg. 39264, 39266 (June 23, 2000): 1992 publication by Stevens B et al. on study of hydrogen chloride in human volunteers,

"Respiratory effects from the inhalation of hydrogen chloride in young adult asthmatics", *J Occup. Med* 34:923-29, used to set AEGL based on NOAEL. (Note: Hydrogen chloride, HCl is equated with Dimethyldichlorosilane for AEGL purposes.)

***Submarine Exposure Guidance Levels for Selected Hydrofluorocarbons*. 2000. National Research Council of the National Academies.**

– see discussion of volunteer studies in chapter on HFC-404a

***Spacecraft Maximum Allowable Concentrations for Selected Airborne Contaminants* (vols. 3 and 4). 1996. National Research Council of the National Academies.**

– See, e.g., vols. 3 and 4 (1997 and 2000) for reliance on numerous human volunteer studies (e.g., TCE, various freons and fluorocarbons).

  – In vol. 3, see ch. B1, *Bromotrifuoromethane (Halon 1301)*, for extensive reliance on human volunteer studies. Pp. 22-28, 43-46.

  – See NASA section, above.

VA

— See info above under DOD re studies by Midwest Research Institute on PB