Nineteenth Interim Report of the Committee on Acute Exposure Guideline Levels: Part B

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Committee on Acute Exposure Guideline Levels

Committee on Toxicology

Board on Environmental Studies and Toxicology

Division on Earth and Life Studies

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Preface

Extremely hazardous substances (EHSs)[2] can be released accidentally as a result of chemical spills, industrial explosions, fires, or accidents involving railroad cars or trucks transporting EHSs, or they can be released intentionally through terrorist activities. These substances can also be released by improper storage or handling. Workers and residents in communities surrounding industrial facilities where EHSs are manufactured, used, or stored and in communities along the nation's railways and highways are potentially at risk of being exposed to airborne EHSs during accidental or intentional releases. Pursuant to the Superfund Amendments and Reauthorization Act of 1986, the U.S. Environmental Protection Agency (EPA) has identified approximately 400 EHSs on the basis of acute lethality data in rodents.

As part of its efforts to develop acute exposure guideline levels for EHSs, EPA and the Agency for Toxic Substances and Disease Registry (ATSDR) in 1991 requested that the National Research Council (NRC) develop guidelines for establishing such levels. In response to that request, the NRC published *Guidelines for Developing Community Emergency Exposure Levels for Hazardous Substances* in 1993. Subsequently, *Standing Operating Procedures for Developing Acute Exposure Guideline Levels for Hazardous Substances* was published in 2001. It provided updated procedures, methods, and other guidelines used by the National Advisory Committee (NAC) on Acute Exposure Guideline Levels for Hazardous Substances and the NRC Committee on Acute Exposure Guideline Levels (AEGLs) in considering acute adverse health effects to develop AEGL values.

Using the 1993 and 2001 NRC guideline reports, the NAC—consisting of members from EPA, the Department of Defense (DOD), the Department of Energy (DOE), the Department of Transportation (DOT), other federal and state governments, the chemical industry, academia, and other organizations from the private sector—has developed AEGLs for approximately 200 EHSs.

In 1998, EPA and DOD requested that the NRC independently review the AEGLs developed by NAC. In response to that request, the NRC organized within its Committee on Toxicology the Committee on Acute Exposure Guideline Levels, which prepared this report.

At its meetings, the committee hears presentations from NAC staff and its contractor, Syracuse Research Cooperation, on draft AEGL documents. At some meetings, the committee also hears presentations from NAC's collaborators from other countries. The committee provides comments and recommendations on those documents in its interim reports to NAC, and NAC uses those comments to make revisions. The revised documents are presented by NAC to the committee at subsequent meetings until the committee concurs with the final draft documents. The revised documents are then published as appendixes in the committee's reports.

The present report is the committee's 19th interim report. It summarizes the committee's conclusions and recommendations for improving NAC's AEGL documents for 5 aliphatic nitriles: acetonitrile, isobutyronitrile, propionitrile, chloroacetontrile, and malonitrile.

[2]As defined pursuant to the Superfund Amendments and Reauthorization Act of 1986.

This report has been reviewed in draft form by individuals chosen for their diverse perspectives and technical expertise in accordance with procedures approved by the NRC Report Review Committee. The purpose of this independent review is to provide candid and critical comments that will assist the institution in making its published report as sound as possible and ensuring that the report meets institutional standards for objectivity, evidence, and responsiveness to the study charge. The review comments and draft manuscript remain confidential to protect the integrity of the deliberative process. We wish to thank the following individuals for their review of this report: Harvey Clewell, Hamner Institutes for Health Sciences; James McDougal, Wright State University; Judith Zelikoff, New York University.

Although the reviewers listed above have provided many constructive comments and suggestions, they were not asked to endorse the conclusions or recommendations, nor did they see the final draft of the report before its release. The review of this report was overseen by Robert Goyer, University of Western Ontario. Appointed by the NRC, he was responsible for making certain that an independent examination of this report was carried out in accordance with institutional procedures and that all review comments were carefully considered. Responsibility for the final content of this report rests entirely with the author committee and the NRC.

The committee gratefully acknowledges the valuable assistance provided by the following individuals: Iris Camacho, Ernest Falke, and Robert Benson (EPA); Gary Diamond, Mark Follansbee, Lisa Ingerman, and Julie Klotzbach (Syracuse Research Corporation); and George Rusch (Honeywell International, Inc.).

The committee acknowledges James J. Reisa, director of the Board on Environmental Studies and Toxicology, for his helpful guidance. Keegan Sawyer, project director, for her work in this project. Other staff members who contributed to this effort are Susan Martel (senior program officer for toxicology), Ruth Crossgrove (senior editor), Mirsada Karalic-Loncarevic (manager of the Technical Information Center), Radiah Rose (manager of editorial projects), and Tamara Dawson (program associate). Finally, we would like to thank all members of the committee for their expertise and dedicated effort throughout the development of this report.

Donald E. Gardner, *Chair*
Committee on Acute Exposure Guideline Levels

Contents

Nineteenth Interim Report of the Committee on Acute Exposure Guideline Levels

BACKGROUND

In 1991, the U.S. Environmental Protection Agency (EPA) and the Agency for Toxic Substances and Disease Registry (ATSDR) asked the National Research Council (NRC) to provide technical guidance for establishing community emergency exposure levels (CEELs) for extremely hazardous substances (EHSs) pursuant to the Superfund Amendments and Reauthorization Act of 1986. In response to that request, the NRC published *Guidelines for Developing Community Emergency Exposure Levels for Hazardous Substances* in 1993. Subsequently, *Standing Operating Procedures for Developing Acute Exposure Guideline Levels for Hazardous Substances* was published in 2001; it provided updated procedures, methods, and other guidelines used by the National Advisory Committee (NAC) on Acute Exposure Guideline Levels for Hazardous Substances for assessing acute adverse health effects.

NAC was established to identify, review, and interpret relevant toxicologic and other scientific data and to develop acute exposure guideline levels (AEGLs) for high-priority, acutely toxic chemicals. AEGLs developed by NAC have a broad array of potential applications for federal, state, and local governments and for the private sector. AEGLs are needed for emergency-response planning for potential releases of EHSs from accidents or terrorist activities.

AEGLs represent threshold exposure limits for the general public and are applicable to emergency exposure periods ranging from 10 minutes (min) to 8 hours (h). AEGLs 1, 2, and 3 will be developed when appropriate for each of five exposure periods (10 and 30 min and 1 h, 4 h, and 8 h) and will be distinguished by varying degrees of severity of toxic effects. It is believed that the recommended exposure levels are applicable to the general population, including infants and children and other individuals who may be susceptible. The three AEGLs have been defined as follows:

AEGL-1 is the airborne concentration (expressed as parts per million or milligrams per cubic meter [ppm or mg/m^3]) of a substance above which it is predicted that the general population, including susceptible individuals, could experience notable discomfort, irritation, or certain asymptomatic nonsensory effects. However, the effects are not disabling and are transient and reversible upon cessation of exposure.

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

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

THE CHARGE TO THE COMMITTEE

The NRC convened the Committee on Acute Exposure Guideline Levels to review the AEGL documents approved by NAC. The committee members were selected for their expertise in toxicology; medicine, including pharmacology and pathology; industrial hygiene; biostatistics; and risk assessment.

The charge to the committee is to (1) review the proposed AEGLs for scientific validity, completeness, internal consistency, and conformance to the NRC (1993) guidelines report; (2) review NAC's research recommendations and—when appropriate—identify additional priorities for research to fill data gaps; and (3) periodically review the recommended standing operating procedures for developing AEGLs.

This interim report presents the committee's conclusions and recommendations for improving the NAC's AEGL document for five selected aliphatic nitriles: acetonitrile, isobutyronitrile, propionitrile, chloroacetonitrile, and malonitrile.

A revised document should be submitted to the committee for review.

ALIPHATIC NITRILES

At its meeting held on Ocober 27-39, 2010, the committee reviewed the technical support document (TSD) on the five selected aliphatic nitriles. A presentation on the TSD was made by Gary Diamond, of Syracuse Research Corporation.

Two overarching issues regarding data from developmental toxicity studies are noted.

1. Selection of the point of departure (POD): Both the maternal and fetal effects from developmental studies should be considered for the POD selection. The maternal toxicities from those studies specifically reflect sensitivity during pregnancy. The developmental effects are pertinent systemic toxicity end points. The consideration for windows of susceptibility for fetuses supports the use of no-observed-effect levels (NOELs) from repeated dosing regimen during organogenesis for a single-day acute toxicity scenario (van Raaij et al. 2003, 2009). Fetal death can occur during a narrow developmental window and does not necessarily require repeated exposures. Additional support from chemical-specific data is presented separately for each chemical.

Throughout this TSD, it was stated on several occasions that no reproductive or developmental toxicity was noted in the absence of maternal toxicity (e.g., page III-10, line 21; page IV-12, line 2; page V-8, line 19). These observations are pertinent for identifying risk agents that have fetal effects not indicative of maternal toxicity. However, for the purpose of setting AEGLs, these emphases can appear dismissive or can be potentially confusing since both maternal and fetal effects are pertinent end points regardless of whether one has a lower threshold than the other.

One additional point of consideration for setting the AEGL when maternal toxicity is present concomitantly with fetal toxicity is the distinction between the reversibility of observed maternal effects and the irreversibility of the developmental effects. For example, Willhite (1983) reported that fetuses from hamster dams that survived excessive salivation of acetonitrile at 5,000 ppm after 1 h of exposure had severe malformations (exencephalyencephalocoele and rib fusions). (page II-17, lines 39-40). This reversibility distinction between maternal and fetal toxicity could affect the selection of the POD for the AEGL-2 and AEGL-3.

2. Uncertainty factors: Animal studies are almost exclusively relied upon for data on maternal sensitivity and developmental effects. Thus, care must be taken in considering deviation or reduction from the default uncertainty factors based on comparison to human data when they do not include the evaluation of the maternal and fetal end points.

Specific Comments and Other Comments are provided below for each of the five selected aliphatic nitriles.

Acetonitrile

The following is excerpted from the Executive Summary of the TSD:

> Slight chest tightness and cooling sensation in the lungs noted by one of three human male volunteers exposed to 40 ppm acetonitrile for 4 hours (Pozzani et al. 1959) were used as the basis for AEGL-1 values…. Slight pulmonary congestion or hemorrhage in rats exposed to 4000 ppm acetonitrile for 4 hours (Pozzani et al. 1959) was used as the basis for AEGL-2 values…. A calculated 4-h rat LC_{01} of 8421 ppm (Monsanto 1986) was used for derivation of AEGL-3 values.

AEGL-Specific Comments

AEGL-1

The committee approves the derivation of AEGL-1 values for acetonitrile; however, please see Other Comments regarding data quality and research needs.

AEGL-2

The 4-h exposure at 4,000 ppm taken from Pozzani et al. (1959) is probably too high of a POD because Union Carbide (1970) reported that 3 of 30 (10%) rats died at this time-concentration level (page II-13, line 2, Table II-3).

AEGL-3

A 4-h LC_{01} (concentration of a substance that is lethal to 1% of test organisms in a given time) of 8,421 ppm from the Monsanto (1986) study was selected as the POD. However, Pozzani et al. (1959) reported that 3 of 12 male rats died at 8,000 ppm (Table II-2). Union Carbide (1970) also reported that 10 of 30 rats died at 8,000 ppm (Table II-3). In fact, as noted above, Union Carbide reported that 10% of the rats died from a 4-h exposure at 4,000 ppm, a level slightly less than 50% of the POD.

Additional evidence that the POD should be substantially lower is also in the extrapolated 1-h and 8-h PODs. The estimated 1-h 19,976 ppm POD (page II-32, line 24) is 6-fold above the 3,800 ppm for 1 h at which Willhite (1983) reported pregnant hamsters died subsequent to dyspnea, tremors, hypersalivation, ataxia, and hypothermia (page II-17, lines 34-35). Regarding the estimated 8-h POD, it is noted that Pozzani et al. (1959) reported 1/12 female rats died from an 8-h exposure at 2,000 ppm (Table II-2), approximately 1/3 of the estimated 8-h 5,446 ppm POD (page II-32).

The presentation of developmental toxicity in Section II.3.3 (page II-17) should be expanded to lend support for considering maternal and fetal toxicity. Maternal death (40%) and fetal implantation loss and resorption in rats occurred at 6 h/day exposure at 1,800 ppm during gestation days 6 through 20 (Saillenfait et al. 1993). Although the days on which maternal deaths were not reported, these data from a repeated exposure regimen may indicate higher sensitivity during pregnancy. In fact, a NOEL based on the Saillenfait et al. (1993) study on isobutyronitrile for maternal and fetal toxicity was used as the POD for AEGL-2 (page III-11, lines 28-29). The potentially higher sensitivity to acetonitrile during pregnancy is also indicated in the study by Willhite (1983), which showed death in hamsters after 1 h exposure at 3,800 ppm (page II-17, lines 34-35).

Regarding fetal toxicity, Saillenfait and Sabate (2000) reported high incidence of fetal morphogenic alterations in rats from a single maternal oral exposure at 2,000 mg/kg on gestation day 10. It may be that this study was not included in the TSD because it is not through the inhalation route. However, the systemic toxicity to the fetuses is a pertinent end point, and this study showed that it can result from a single exposure. Data on exposure routes other than inhalation are rightly included in the database for other nitriles throughout the TSD. A systemic toxicity is of concern especially since "aliphatic nitriles are readily absorbed from the lung and gastrointestinal tract, resulting in systemic

toxicity" (page I-4, lines 5-6). Specific to acetonitrile, human poisoning cases "… suggest that acetonitrile is well absorbed by both inhalation and dermal routes." (page I-4, line 19).

Other Comments

Page II-26, Section II.7.3: Since the POD for AEGL-1 was based on a single human experiment (Pozzani et al. 1959) with only three subjects at the lowest concentration and only two of the previous three subjects for the middle and highest concentrations and no supporting animal data, it seems excessive to characterize the data as "adequate". At the very least, there should be a stated research need to develop supporting data for the AEGL-1, whether animal or human. This is especially valid given that a modifying factor was used because of the sparse database.

Isobutyronitrile

The following is excerpted from the Executive Summary of the TSD:

> Data were insufficient for derivation of AEGL-1 values for isobutyronitrile. The AEGL-2 was based on a no-effect-level for maternal and fetal toxicity from a developmental toxicity study in rats (100 ppm, 6 hour/day, days 6-20 of gestation) (Saillenfait et al. 1993)…. The AEGL-3 was based on a calculated 1-hour LC_{01} of 677 ppm in rats (Eastman Kodak Co. 1986).

AEGL-Specific Comments

AEGL-1

The committee agrees that data are insufficient at this time to derive AEGL-1 values.

AEGL-2

The 6-h POD of 100 ppm was selected based on maternal and fetal death at 200 ppm during gestation day 6 through 20 reported by Saillenfait et al. (1993). As presented under Section I of this document, developmental effects are pertinent systemic toxicity end points, and the consideration for windows of developmental susceptibility supports the use of NOELs from repeated dosing during organogenesis for single-day acute toxicity scenarios (van Raaij et al. 2003, 2009). Most important, because death is the maternal and fetal end point, this POD should be pertinent to AEGL-3 rather than AEGL-2.

An interspecies uncertainty factor of 3 instead of the default 10 is used to prevent inconsistency between AEGL-2 values and the report of no effects for an estimated 20-25 ppm in humans for a "few minutes" as reported by American Industrial Hygiene Association (AIHA 1992). However, the source of this information in the AIHA report is a 1986 personal communication from an accidental spill (cited in AIHA as "Texas Eastman Company: [Personal Communication] 1986"). No data are available for either the concentration estimation method or details for the "no symptoms of cyanide exposure" notation. Given the lack of data, it is prudent that this piece of information not be used as the basis for adjusting the interspecies uncertainty factor, especially since the TSD notes that rats are not the most sensitive laboratory animal species (page III-19).

In light of the lack of data, the AEGL-2 can alternatively be set at a fraction of the AEGL-3. If necessary, this approach can be further supported by an estimate of the time-air concentration equivalent

to the oral dose of 38.6 mg/kg noted for having parenchymous liver degeneration (page III-9, line 31). A method is provided in the reference concentration methodology by EPA (1994) that uses default coefficients in equations for minute volumes of laboratory animals (Table 4-6 in EPA 1994, citing a 1988 EPA documentation of biologic values for use in risk assessment).

AEGL-3

As stated in comments under AEGL-2, the 6-h 100 ppm based on maternal and fetal death is appropriate for an AEGL-3 POD. This value will result in a slightly lower POD than the 1-h POD at 677 ppm in the TSD.

As stated in comments under AEGL-2, the personal communication noting no symptoms of cyanide exposure for a "few minutes" at 20-25 ppm in an accidental spill is insufficient to support deviation from the default interspecies uncertainty factor of 10, especially since the TSD notes that rats not being the most sensitive laboratory animal species (page III-20).

The similarity between AEGL-2 and AEGL-3 values are noteworthy. One likely reason is because both PODs are based on death as an end point. The 6-h 100 ppm POD for AEGL-2 is based on maternal and fetal death in rats from the study by Saillenfait et al. (1993), while the 1-h LC_{01} of 677 ppm POD for AEGL-3 is based on death in rats from the study by Eastman Kodak Company (1986a).

Another observation is that the 8-h AEGL-3 value is practically the same as the 8-h recommended exposure limit–time-weighted average (REL-TWA) (Table III-6). Further investigation is needed to understand this anomaly, with careful considerations for the POD, the most relevant end point, and the uncertainty factors, all in light of the existing data gaps. Until then, it is advisable not to set an 8-h AEGL-3.

Propionitrile

The following is excerpted from the Executive Summary of the TSD:

> Chemical-specific data are insufficient for the derivation of AEGL-1 values for propionitrile. The AEGL-2 was based on headache, nausea, dizziness, vomiting, confusion, and disorientation in a 34-year-old male worker exposed to approximately 34 ppm propionitrile for 2 hours)… The AEGL-3 was based on the highest concentration (690 ppm) causing no mortality in rats exposed to propionitrile for four hours.

AEGL-Specific Comments

AEGL-1

The committee agrees that data are insufficient at this time to derive AEGL-1 values for propionitrile.

AEGL-2

A modifying factor of 2 is used to account for the sparse data; the POD is based on the response of two workers reported by Scolnick et al. (1993). A separate concern that warrants the use of a modifying factor for the 2-h POD of 34 ppm is the severity of response experienced by one worker—headache, nausea, dizziness, and vomiting. This response indicates that the 34-ppm POD is not a NOEL.

Accordingly, the modifying factor is justified not only by the scarcity of data but also by ensuring protection against these effects that may impair escape.

AEGL-3

A 4-h exposure at a 690-ppm POD was selected based on no deaths reported in rats by Younger Labs (1978). However, other data indicate that this POD is not sufficient for protecting against death and toxicities in pregnant animals and their fetuses. Saillenfait et al. (1993) reported maternal death and fetal implantation loss and resorption in rats from exposures for 6 h/day at 200 ppm during gestation day 6 through 20 (page IV-10, lines 41-46). The NOEL for maternal and fetal toxicity is 150 ppm. Similarly, maternal death and fetal resorption in rats was also reported by Johannsen et al. (1986) at an oral dose of 80 mg/kg during gestation days 6 to 19 (page IV-11, lines 19-23). The corresponding NOEL is 40 mg/kg. Moreover, Willhite et al. (1981a) also reported maternal and fetal toxicity in hamsters after a single intraperitoneal (i.p). injection at 0.54-1.51 mmol/kg (30-83 mg/kg) (page IV-11, lines 4-11).

Page IV-11, lines 16-17, states, "There was no evidence that propionitrile was a selective developmental toxicant." Nevertheless, as presented under Section I of the TSD, developmental effects are pertinent systemic toxicity end points, and the consideration for windows of developmental susceptibility supports the use of NOELs from repeated dosing during organogenesis for single-day acute toxicity scenarios (van Raaij et al. 2003, 2009). Specific to propionitrile, this conclusion is supported in a study by Saillenfait and Sabate (2000), a study not included in the TSD. Fetal morphogenic alterations occurred from a single maternal oral exposure of 180 mg/kg on gestation day 10. Maternal toxicity included piloerection, prostration, and tremors. It is important to note that although maternal and fetal toxicity occurred at the same dose, maternal toxicity can be reversible while fetal toxicity is irreversible. See Section I of the TSD for a general discussion on related issues.

Other Comments

Page IV-14, line 25: The "AEGL-1 values were derived by analogy to acetonitrile" should be deleted since AEGL-1 values were not derived for propionitrile.

Chloroacetonitrile

The following is excerpted from the Executive Summary of the TSD:

> Chemical-specific data were insufficient for the derivation of AEGL-1, AEGL-2, or AEGL-3 values for chloroacetonitrile. In the absence of relevant chemical-specific data for chloroacetonitrile, a modification of the AEGL values for acetonitrile was utilized to derive AEGL-2 and AEGL-3 values for chloroacetonitrile…. AEGL-1 values were not derived by analogy due to the uncertainty of extrapolating from lethality to effects defined by AEGL-1. Therefore, AEGL-1 values for chloroacetonitrile are not recommended.

AEGL-Specific Comments

AEGL-1

The committee agrees that data are insufficient at this time to derive AEGL-1 values for chloroacetonitrile.

AEGL-2

AEGL-2 and AEGL-3 are derived as 10-fold reductions of the values for acetonitrile. Given that the 10-fold greater toxicity is derived from i.p. administration, it is prudent to apply a factor greater than 10.

AEGL-3

See comment above regarding AEGL-2 and AEGL-3.

Other Comments

Given the relatively sparse data, the literature review should be expanded to include other available data, for example, Lin et al. (1986), Jacob et al. (1998), Abdel-Naim and Mohamadin (2004), and Ahmed et al. (2008).

Malonitrile

The following is excerpted from the Executive Summary of the TSD:

> Chemical-specific data were insufficient for the derivation of AEGL-1, AEGL-2, or AEGL-3 values for malononitrile. In the absence of relevant chemical-specific data for malononitrile, a modification of the AEGL values for acetonitrile was used to derive AEGL-2 and AEGL-3 values for malononitrile. … AEGL-1 values were not derived by analogy due to the uncertainty of extrapolating from lethality to effects defined by AEGL-1.

AEGL-1

The committee agrees that data are insufficient at this time to derive values for AEGL-1.

AEGL-2

Given that AEGL-2 and AEGL-3 values were derived based upon those for acetonitrile, please review the comments for acetonitrile, as they may change the values derived for malonitrile.

AEGL-3

Please see comment above for AEGL-2.

REFERENCES

Abdel-Naim, A.B., and A.M. Mohamadin. 2004. Myeloperoxidase-catalyzed oxidation of chloroacetonitrile to cyanide. Toxicol. Lett. 146(3):249-257.

Ahmed, A.E., H.M. El-Mazar, A.A. Nagy, and A.B. Abdel-Naim. 2008. Chloroacetonitrile induces intrauterine growth restriction and musculoskeletal toxicity in fetal mouse. Toxicol. Ind. Health. 24(8):511-518.

AIHA (American Industrial Hygiene Association). 1992. Emergency Response Planning Guidelines: Isobutyronitrile. AIHA, Acron, OH.

Eastman Kodak Company. 1986a. Acute Inhalation Toxicity and One-Hour LC_{10} Value of Isobutyronitrile in the Rat. Study No. TX-86-193. Eastman Kodak Company, Rochester, NY.

EPA (U.S. Environmental Protection Agency). 1988. Recommendations for and Documentation of Biological Values for Use in Risk Assessment (Final). EPA/600/6-87/008. Environmental Criteria and Assessment Office, Office of Health and Environmental Assessment, Office of Research and Development, Cincinnati, OH. February 1988 [online]. Available: http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=34855 [accessed Dec. 20, 2010].

EPA (U.S. Environmental Protection Agency). 1994. Methods for Derivation of Inhalation Reference Concentrations and Application of Inhalation Dosimetry. EPA/600/8-90/066F. Office of Research and Development, Office of Health and Environmental Assessment, U.S. Environmental Protection Agency, Washington, DC. October 1994 [online]. Available: http://www.epa.gov/raf/publications/pdfs/RFCMETHODOLOGY.PDF [accessed Dec. 20, 2010].

Jacob, S., A.A. Abdel-Aziz, S.A. Shouman, and A.E. Ahmed. 1998. Effect of glutathione modulation of the distribution and transplacental uptake of 2-[14C]-chloroacetonitrile (CAN) quantitative whole-body autoradiographic study in pregnant mice. Toxicol. Ind. Health 14(4):533-546.

Johannsen, F.R., G.J. Levinskas, P.E. Berteau, and D.E. Rodwell. 1986. Evaluation of the teratogenic potential of three aliphatic nitriles in the rat. Fundam. Appl. Toxicol. 7(1):33-40.

Lin, E.L., F.B. Daniel, S.L. Herren-Freund, and M.A. Pereira. 1986. Haloacetonitriles: metabolism, genotoxicity, and tumor-initiating activities. Environmental Health Perspectives 69:67-71.

Monsanto. 1986. A Study of the Acute Inhalation Toxicity (4 Hour LC_{50}) of Acetonitrile in Rats. Document No. 87820016405. Microfiche No. OTS0510333. Submitted to U.S. Environmental Protection Agency, Washington, DC.

Pozzani, U.C., C.P. Carpenter, P.E. Palm, C.S. Weil, and J.H. Nair. 1959. An investigation of the mammalian toxicity of acetonitrile. J. Occup. Med. 1:634-642.

Saillenfait, A.M., and J.P. Sabaté. 2000. Comparative developmental toxicities of aliphatic nitriles: In vivo and in vitro observations. Toxicol. Appl. Pharmacol. 163(2):149-163.

Saillenfait, A.M., P. Bonnet, J.P. Guenier, and J. de Ceaurriz. 1993. Relative developmental toxicities of inhaled aliphatic mononitriles in rats. Fundam. Appl. Toxicol. 20(3):365-375.

Scolnick, B., D. Hamel, and A.D. Woolf. 1993. Successful treatment of life threatening propionitrile exposure with sodium thiosulfate followed by hyperbaric oxygen. J. Occup. Med. 35(6):577-580.

Union Carbide. 1970. Toxicology Studies-Acetonitrile. Union Carbide Corp., Industrial Medicine and Toxicology Department, New York. 2 pp.

van Raaij, M.T.M, P.A.H. Janssen, and A.H. Piersma. 2003. The Relevance of Developmental Toxicity Endpoints for Acute Limit Setting. RIVM Report 601900004/2003. RIVM (National Institute of Public Health and the Environment), Bilthoven, the Netherlands [online]. Available: http://www.rivm.nl/bibliotheek/rapporten/601900004.pdf [accessed Dec. 14, 2010].

van Raaij, M., P. Janssen, J. Nijhof, P. Bos, and A. Piersma. 2009. The Relevance of Endpoints in Developmental Toxicity Studies for Acute Limit Setting. AEGL June 2007 Update. RIVM (National Institute of Public Health and the Environment), Bilthoven, The Netherlands. (Presented to NAS/AEGL Committee on October, 2009).

Willhite, C.C. 1983. Developmental toxicology of acetonitrile in the Syrian golden hamster. Teratology 27(3):313-325.

Willhite, C.C., V.H. Ferm, and R.P. Smith. 1981a. Teratogenic effects of aliphatic nitriles. Teratology 23(3):317-323

Younger Labs. 1978. Initial Submission: Toxicological Investigation of Propionitrile with Cover Letter Dated 081992. Document No. 88920008153. Microfiche No. OTS0546148. Submitted to U. S. Environmental Protection Agency, Washington, DC.