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Acrylonitrile: A Reevaluation of the Database to Support an Inhalation Cancer Risk Assessment

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Acrylonitrile (ACN) is a monomer used extensively in the production of plastics, synthetic fibers, and rubber. In previous assessments conducted by IARC and the EPA, ACN was classified as a probable human carcinogen based on limited evidence in humans and sufficient evidence in laboratory animals. Specifically, EPA had determined that there was an association between ACN exposure and lung cancer based on a study by O'Berg (1980, *J. Occup. Med.* 22, 245–252). However, a follow-up of this cohort (O'Berg *et al.*, 1985, *J. Occup. Med.* 27, 835–840) shows no statistically significant excess of lung cancer mortality or incidence. Our evaluation of the more recent human database taken as a whole shows that there is not a clear association between ACN exposure and human cancer, yet the studies have insufficient power to be able to rule out a small increase. In laboratory rats, however, ACN has been shown to be clearly carcinogenic by the oral and inhalation routes. Applying the methodology of EPA's proposed 1996 cancer risk assessment guidelines to the rat tumor data, the estimated upper bound on the excess lifetime risk at continuous exposure to 1 $\mu g/m^3$ ACN is calculated to be in the range of 8.2×10^{-6} to 1.1×10^{-5}.

INTRODUCTION

Acrylonitrile (ACN) is a monomer used extensively in the production of plastics, synthetic fibers, and rubbers. The acute toxicity of ACN has been recognized for some time, but chronic effects including carcinogenicity have been less easily characterized for humans. Numerous epidemiologic studies and chronic rat bioassays have been conducted by various routes in an effort to better understand the potential for ACN to cause cancer in humans. While the epidemiologic studies do not provide evidence of a clear association between ACN exposure and human cancer, rat bioassays have shown a clear carcinogenic effect following both oral and inhalation exposures.

The International Agency for Research on Cancer (IARC, 1979) classified ACN in Group 2A (probable human carcinogen) based on sufficient evidence in laboratory animals and limited evidence in humans. Under the 1986 cancer guidelines of the U.S. Environmental Protection Agency (EPA, 1987), ACN was verified (August 15, 1991) as a Group B1 chemical (probable human carcinogen) based on a statistically significant increase in lung cancer in exposed workers and also based on tumors (primarily astrocytomas of the brain) in two strains of rat by multiple routes of administration (EPA, 1997). The EPA also developed quantitative cancer risk assessments for both the oral and the inhalation routes. The inhalation unit risk, based on the average relative risk of respiratory cancer (adjusted for smoking) in occupationally exposed workers reported in a study by O'Berg (1980) was calculated to be 6.8 E-5 per $\mu g/m^3$.

An update of the O'Berg cohort published in 1985 (O'Berg *et al.*, 1985) revealed that the increase in respiratory cancer which was noted in the 1980 publication was no longer statistically significant. Taken as a whole, additional studies published subsequent to the evaluations by EPA and IARC also do not support a causal association between cancer in humans and exposure to acrylonitrile. This led us to reevaluate the carcinogenicity database for both human and laboratory animals and update the assessment to include the more recent information. This document focuses on the cancer hazard characterization of ACN and the calculation of an inhalation risk estimate using the methodology described in EPA's 1996 proposed cancer risk assessment guidelines.

CANCER HAZARD ASSESSMENT OF ACN

Characterization of the cancer hazard posed by ACN is based on an evaluation of human and laboratory animal studies and mechanistic information. An overview of the weight-of-evidence for each of these areas follows; for a more in-depth analysis, the reader is referred to *TERA* (1997).

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Human Studies

At the time of the assessments published by U.S. EPA and IARC, there were more than a dozen epidemiological studies, but most were inadequate for use in cancer risk assessment because of limited exposure information, small cohort size, coexposures to other carcinogens, and weaknesses in study design and analysis. The EPA considered the O'Berg (1980) study to be the only one which was adequate for risk assessment purposes. Since that time, several additional epidemiological studies have been published which have added significantly to the weight-of-evidence for the human studies.

Of the greatest significance is a study which was recently completed by the National Cancer Institute (NCI) and the National Institute for Occupational Safety and Health (NIOSH) (Blair *et al.,* 1997). This is the largest study performed to date, with a cohort of 25,460 workers employed in eight U.S. plants which produce or use acrylonitrile. In addition to having a cohort with about 10 times as many workers as any other epidemiological study to date, the NCI/NIOSH study also developed quantitative estimates of historical exposures, which was a factor missing in many of the older studies. The study found no statistically significant increased relative risk for prostate cancer or other cancers of "a priori interest" (based on findings from other human or laboratory animal studies) including the stomach, brain, and breast and lymphatic and hematopoietic systems. There was some indication of increased incidence of lung cancer at the highest levels of acrylonitrile exposure, but the analyses of exposure–response did not provide strong or consistent evidence for a causal relationship.

Other studies published since the time of EPA's assessment include two updates of the O'Berg cohort which found that the incidence of lung cancer was no longer statistically significant when the cohort was followed for the longer period of time (O'Berg *et al.,* 1985; Wood *et al.,* 1997). In addition, retrospective cohort studies have been published by Benn and Taylor (1997), Swaen *et al.* (1992), Collins *et al.* (1989), and Chen *et al.* (1987). These studies are all of sufficient quality so as to contribute to the weight-of-evidence of the human studies and are summarized in chronological order in Table 1.

In addition to the retrospective cohort studies, some metaanalyses have been published. Rothman (1994) reviewed 12 published epidemiologic studies that reported cancer incidence or mortality among workers exposed to ACN. Rothman conducted a simple meta-analysis of the mortality results by adding together the observed and expected deaths, respectively, from all studies to obtain a summary measure that was weighted for study size. This analysis was performed for all cancer deaths as well as for respiratory cancer deaths in particular. The SMR for all cancer deaths was 1.03 with a 90% confidence interval of 0.92–1.15. The SMR for respiratory cancer deaths was 1.07 with a 90% confidence interval of 0.89–1.28. The author concluded that, in the aggregate, the body of human studies does not show a correlation between occupational exposure to ACN and subsequent death from respiratory cancer. It is noted, however, that many of the studies included in the metaanalysis had insufficient exposure characterization, so the usefulness of this meta-analysis can be questioned. The author noted that among workers heavily exposed to ACN, there may be a substantial effect of exposure on cancer risk that is attenuated in analyses that mix these workers with others who had smaller exposures. In addition, the author did not correct for inconsistency among the studies or evaluate cancer risk for other sites (i.e., prostate) for which there was limited reporting.

Collins and Aquavella (1997) have recently completed a metaanalysis of ACN-exposed workers, which includes data from several of the previously conducted major epidemiological studies. The metaanalysis focuses on combining information from multiple studies to look at cancer incidences specifically in the lung, brain, and prostate. No increase was found at any of these sites.

Summary of human weight-of-evidence. In the studies described above, some reports of increased mortality and/or incidence rates have been reported for lung cancer and prostate cancer; however, these findings have not been consistent across studies. Specifically, O'Berg (1980) had reported an increase in lung cancer incidence, but several other studies found that there was no indication of lung cancer risk related to ACN exposure including Chen *et al.* (1987), Collins *et al.* (1989), and Swaen *et al.* (1992). Preliminary results from Wood *et al.* (1997) also found no increase in lung cancer risk. The NCI/NIOSH study of over 25,000 workers found an increase in lung cancer in the highest exposure quintile, but analyses of the exposure–response relationship revealed inconsistent findings and the authors concluded that there was no strong evidence for a causal relationship between acrylonitrile exposure and lung cancer in humans (Blair *et al.,* 1997). In addition, a metaanalysis of combined data from 12 published studies on ACN indicated that workers exposed to ACN do not have an excess risk of mortality from all cancers or specifically from respiratory cancer. There have also been findings of an increased incidence or mortality rate for prostate cancer, but statistical significance was reported only in two of the studies (O'Berg *et al.,* 1985; Chen *et al.,* 1987). In summary, the epidemiological studies taken as a whole do not support the conclusion that exposure to ACN causes an increased risk of either lung or prostate cancer.

TABLE 1

Summary of Retrospective Cohort Studies on Acrylonitrile

Study	Cohort size	Findings	Comments
O'Berg (1980)	1345	A statistically significant increase was seen in lung cancer risk for some subgroups of the cohort (8 observed; 4.1 expected). There were also trends for increasing risk with increased cumulative exposure and latency. Three cases of prostate cancer were observed compared with 0.9 expected.	Workers were first employed between 1950 and 1966; mortality was followed until 1976. Exposure was classified as low, medium, or high.
O'Berg *et al.* (1985)	1345	Lung cancer incidence reported by O'Berg (1980) was no longer significant, although a slight excess remained in wage workers (10 observed; 6.0 expected. Relative risks were 1.4 for lung cancer incidence and 1.2 for mortality. Additional cases of prostate cancer were reported, making the excess statistically significant (6 observed; 1.5 expected). A trend was seen with increasing cumulative exposure and latency.	This study extended the follow-up period of O'Berg (1980) for an additional 7 years. Workers were first employed between 1950 and 1966; mortality was followed until 1981 and morbidity until 1983
Chen *et al.* (1987)	1083	No significant findings for cancer deaths; increased incidence of prostate cancer (5 observed, 1.9 expected; reported to be statistically significant). There was no increase in lung cancer incidence (5 cases observed and 6.9 expected).	Workers were first employed between 1940 and 1970; cancer morbidity and mortality were followed until 1983. No quantitative exposure data were available; jobs were classified as having "low, moderate or high" exposure
Collins *et al.* (1989)	1774	No significant findings. No increase in lung cancer or prostate cancer mortality was seen. There was also no linear trend of increasing lung cancer mortality with increasing exposure.	Workers were first employed between 1951 and 1973; mortality was followed until 1983. Exposure assessment was based on monitoring done in 1977. Categories were 0.01–0.7, 0.7–7.0, and >7.0 ppm/year.
Swaen *et al.* (1992)	2842	No significant findings for overall cancer mortality or mortality associated with any site. For prostate cancer, there were 2 deaths observed and 1.22 expected. There was a trend of increasing lung cancer mortality with increasing dose and latency, but it was not statistically significant at any exposure level.	Workers were first employed in 1979, and the cohort was followed until 1988. Exposure ranges of 0–0.5, 0.5–1, 1–2, and 2–5 ppm were based on 8-h TWA measurements and estimates based on job classification. Peak exposures were also estimated.
Blair *et al.* (1997)	25,460	No increased risk was found for cancer of the stomach, brain, breast, or prostate or lymphatic and hematopoietic system.[a] Although an excess of lung cancer was seen in the highest quintile of cumulative exposure, the authors indicate that the analyses of exposure–response do not provide strong or consistent evidence for a causal association between acrylonitrile exposure and lung cancer.	Workers were employed from the 1950s through 1983 and were followed through 1989. Quantitative estimates of historical exposure were calculated. Analyses were conducted by several indices of exposure including cumulative (ppm-years), average, peak, intensity, duration, and lagged exposure.
Wood *et al.* (1997)	2559	No increase of overall or specific site cancer mortality and incidence in employees exposed to acrylonitrile. There were no significantly associated increases nor consistent patterns suggestive of a dose response.	This is an update of the O'Berg and Chen cohorts. The increased risk of lung and colon cancer reported earlier by O'Berg did not persist. The study includes long-term follow-up of 75,009 person years. Analyses were conducted by several indices of exposure including latency, duration, highest peak, and cumulative (ppm-years).
Benn and Taylor (1997)	~3000	Overall, it was found that acrylonitrile workers had no increased risk for overall cancer mortality or lung cancer. There appeared to be an increased lung cancer mortality among younger men, but it was not confined to those workers with high exposure level, and the smoking history was not available, making it difficult to draw strong conclusions.	Workers were exposed for at least 1 year between 1950 and 1978; the cohort was followed until 1991. No quantitative exposure data were available; jobs were classified as having "high" exposure to ACN, "other possible ACN exposure," or "little/no possible ACN exposure."

[a] Emphasis was placed on evaluating cancer risk for these organs because these were the target organs in laboratory animal studies or previous epidemiological studies had suggested an increased risk.

TABLE 2
Summary of Oral Bioassays of Acrylonitrile

Study	Species, sex, number	Route	Tumor types
Gallagher *et al.* (1993)	Sprague–Dawley rats	Drinking water	Zymbal gland; positive trend for forestomach
Quast *et al.* (1980a)	Sprague–Dawley rats	Drinking water	CNS, Zymbal gland, stomach, and mammary gland
Bio/dynamics Inc. (1980a)	Spartan rats	Drinking water	CNS, Zymbal gland, and stomach
Bio/dynamics Inc. (1980b)	Fischer 344 rats	Drinking water	CNS, Zymbal gland, and mammary gland
Bio/dynamics Inc. (1980c)	Spartan rats	Gavage (in water)	CNS, Zymbal gland, stomach, and mammary gland
Maltoni *et al.* (1977)	Sprague–Dawley rats	Gavage (in olive oil)	Mammary gland and stomach

Laboratory Animal Studies

Several chronic cancer bioassays have been conducted in rats by the oral and inhalation routes. A clear carcinogenic response has been shown by both routes, with target organs including the central nervous system, Zymbal gland, the forestomach, mammary gland, tongue, and small intestine. These studies are summarized below, with the inhalation studies in greater detail because they are used to support a quantitative assessment as well.

Oral studies. Several cancer bioassays of ACN have been conducted in rats in drinking water or by gavage administration. Increased incidences of tumors of the CNS and Zymbal gland and mammary gland tumors in females have been reported across most of these studies. In addition, increases in tumors of the forestomach have been reported, which likely reflect a portal-of-entry effect. These studies are summarized in Table 2; a more detailed description of the studies is provided in *TERA* (1997).

Inhalation studies. Cancer bioassays of ACN have also been conducted in the rat by the inhalation route, with only the study by Quast *et al.* (1980b) involving multiple exposure concentrations in a lifetime bioassay. Studies by Maltoni *et al.* (1977, 1988) involved varying exposure regimens, some of which were subchronic in duration or only one exposure concentration. Therefore, these studies are of limited use in quantitative risk assessment and are not discussed further.

In the study by Quast *et al.* (1980b), Sprague–Dawley rats (100/sex/group) were exposed to ACN vapors at concentrations of 0, 20, or 80 ppm for 6 h/day, 5 days/week, for 2 years. The human equivalent concentrations for this study were 0, 7.5, and 30 mg/m^3, respectively (calculations presented in the Appendix). Clinical signs of toxicity were most apparent in rats exposed to 80 ppm ACN. Significant early mortality also occurred in the 80 ppm males and females within the first year of exposure and in 20 ppm females during the last several months of the study.

Statistically significantly increased tumor incidences were observed in several organs of exposed rats, including the central nervous system (CNS, classified as astrocytomas); Zymbal gland; tongue; small intestine; and mammary gland. All tumors were statistically significantly increased at the highest concentration only, with the exception of the astrocytomas, the incidence of which was statistically significantly increased in female rats exposed to both 20 and 80 ppm. The authors also indicated that tumors of the stomach in 80 ppm males, and of the nasal turbinates of 80 ppm females, were treatment related although they were not statistically significantly increased.

Mode of Action

EPA's proposed cancer risk assessment guidelines (EPA, 1996) highlight the importance of mode of action as being a key factor in determining the most appropriate method for low-dose extrapolation. As summarized below, ACN has been shown to have genotoxic activity, which is believed to be mediated through its metabolism to cyanoethylene oxide (CEO). It is beyond the scope of this paper to provide a more in-depth description of the mutagenicity and genotoxicity studies on acrylonitrile; the reader is referred to *TERA* (1997) for additional information.

Both ACN and CEO have been found to bind covalently to DNA, although the level of adduct formation by CEO was very low. ACN has been found to be mutagenic in several systems, including several strains of *Salmonella typhimurium* and the TK6 human lymphoblast system (both only in the presence of a metabolic activating system). In contrast, CEO is a direct acting mutagen. ACN induced sister chromatid exchange in human lymphoblasts, human bronchial epithelial cells, and Chinese hamster ovary cells. However, ACN does not cause chromosomal abberations, nor does it have dominant lethal effects.

In addition to a genotoxic component, it is likely that other processes contribute to the carcinogenic outcome. Additional studies are currently underway to investigate possible mechanisms for ACN-induced carcinogenicity, including the ability of ACN to inhibit gap junction intercellular communication in rat liver and rat glial cells and to induce oxidative stress damage (Friedman, 1997).

Weight-of-Evidence Summary

The weight-of-evidence for the carcinogenicity of ACN in humans is based on nonpositive or equivocal findings in exposed humans; positive findings in rats of cancer induction by both the oral and the inhalation routes; and mechanistic data indicating a probable genotoxic component. At present, the determination that a quantitative assessment for ACN carcinogenicity should be conducted is based on findings in the rat bioassays. With regard to the most appropriate dose–response model to use for ACN, it appears that linear extrapolation should be used in the absence of a biologically based model.

CANCER INHALATION DOSE–RESPONSE ASSESSMENT

The inhalation bioassay by Quast *et al.* (1980b) is the only one suitable for use in quantitative risk assessment. In this study, tumor incidences in four target organs were statistically significantly increased: astrocytomas, Zymbal gland tumors, and tumors of the small intestine and tongue. The astrocytomas and Zymbal gland tumors are the most clearly associated with ACN exposure as these tumor types were seen in each of the independently conducted bioassays. It is noted that none of the oral bioassays showed an increased incidence of tumors of the tongue or small intestine. The relevance of Zymbal gland tumors to human carcinogenesis is highly questionable, as there is no comparable target organ in humans. Therefore, this analysis has focused on modeling of the astrocytoma incidence data. Both benign and malignant tumors are included because there was a clear progression of this tumor type such that the benign tumors had the potential to become malignant. [*Note:* Additional modeling of the combined tumor incidences for all sites (CNS, Zymbal gland, tongue and small intestine) is described in *TERA* (1997)].

Quast *et al.* (1980b) noted that there was significant mortality in the bioassay. Therefore, animals dying before the first relevant tumor was observed are taken out of the analysis since they died before they were at risk for developing cancer. Table 3 provides a summary of the tumor incidence data for astrocytomas when the rats dying before the first tumor are excluded from the analysis.

Modeling of data in the observable range. We have modeled the astrocytoma tumor incidence data using a polynomial model, although it is noted that the outcome is not highly model dependent. The human equivalent concentrations (0, 7.5, and 30 mg/m^3) were used in the modeling. In accordance with EPA (1996), both the ED_{10} and the LED_{10} were calculated. For male rats, the ED_{10} and LED_{10} were calculated to be 14.6 and 9.1 mg/m^3, respectively. For female rats, the ED_{10} and LED_{10} were calculated to be 12.2 and 9.1 mg/m^3, respectively.

Extrapolation to low-dose range. The second step under EPA's 1996 proposed guidelines is to draw a straight line from the ED_{10} or the LED_{10} to the origin. The cancer potency (Table 4) is then reported as the slopes of these lines, which are calculated using the equation

$$\text{slope} = 0.1 \div \text{ED}_{10} \text{ or } \text{LED}_{10}. \quad (1)$$

The concentration of acrylonitrile associated with a specific risk level (e.g., one-in-a-million) can then be calculated from the slope(s) using the equation

$$\text{Excess Risk} = \text{slope} \times [\text{ACN}] \text{ in mg/m}^3. \quad (2)$$

The results of the assessment show that male and female rats have similar susceptibilities. Because the data from the female rats resulted in a slightly higher slope factor, these data were used to calculate the inha-

TABLE 3
Tumor Incidence Data for Astrocytomas, Adjusted for Early Mortality

Exposure concentration (ppm)	Tumor incidence					
	Male			Female		
	Benign	Malignant	Total	Benign	Malignant	Total
0	0/97	0/97	0/97	0/99	0/99	0/99
20	0/93	4/93	4/93	4/99	4/99	8/99
80	7/83	15/83	22/83	4/99	17/99	21/99

lation unit risk. The resulting risk specific concentrations and the unit risk (i.e., the lifetime risk at continuous exposure to 1 $\mu g/m^3$) are presented in Table 5.

Confidence statement. The inhalation cancer risk assessment for ACN presented in this document is based on a number of assumptions that have a bearing on the confidence that one can place on the calculated risk estimate. Because these assumptions are health protective in nature, it is not likely that the cancer potency has been underestimated and may, in fact, be an overestimation of actual risk to humans. These assumptions, which are described more fully in *TERA* (1997), are:

- The use of a rat bioassay to predict cancer risk from ACN is relevant to humans.
- It is appropriate to adjust the concentrations to which the rats were intermittently exposed by factors (i.e., 6/24 h and 5/7 days) to yield equivalent concentrations for a continuous exposure.
- It is appropriate to calculate cancer risk at low levels of exposure based on an assumption of low-dose linearity (which does not take into account the protective or adaptive mechanisms that humans have for dealing with exposures to xenobiotics (e.g., detoxifying metabolic reactions, DNA repair)).

CONCLUSIONS

Previous assessments by IARC and EPA have classified ACN as a probable human carcinogen based on limited evidence in humans and sufficient evidence in laboratory animals. EPA based a quantitative risk estimate on the increase in lung cancer incidence reported in the epidemiological study by O'Berg (1980). The human weight-of-evidence appears to be insufficient to draw any strong conclusions. However, an evaluation of the more recent literature, including an update of the O'Berg cohort and a large study by the National Cancer Institute, indicates that the weight-of-evidence of the human studies does not support the conclusion that there is a causal association between exposure to humans and lung cancer. At the same time, the human studies are of insufficient power to rule out a small increase in cancer. ACN has been shown to be carcinogenic in the rat by both oral and inhalation routes of administration. Therefore, a quantitative risk estimate for inhalation exposures has been calculated based on the rat inhalation bioassay by Quast *et al.* (1980b). Tumor incidence data for astrocytomas (benign and malignant combined) were modeled in the observable range using a polynomial model. From this model, the ED_{10} and the LED_{10} were determined, and linear extrapolation from these two points to the origin was done to estimate risk levels at lower concentrations. Based on the animal model, the lifetime risk from continuous exposure to 1 $\mu g/m^3$ ACN was determined to be in the range of 1.1×10^{-5} (based on the LED_{10}) to 8.2×10^{-6} (based on the ED_{10}). These risk estimates are about six- and eightfold lower, respectively, than EPA's previous estimate of an inhalation unit risk.

TABLE 4
Low-Dose Slopes for the Astrocytoma Incidences of Quast *et al.* (1980b)

	Male rats		Female rats	
	Based on the ED_{10}	Based on the LED_{10}	Based on the ED_{10}	Based on the LED_{10}
Slope $(mg/m^3)^{-1}$		0.011	0.0082	0.011

TABLE 5
Summary of Risk-Specific Concentrations (RSC) and Unit Risks (UR) for ACN

	Based on the ED_{10}	Based on the LED_{10}
10^{-4} risk level	12 $\mu g/m^3$	9 $\mu g/m^3$
10^{-6} risk level	0.12 $\mu g/m^3$	0.09 $\mu g/m^3$
Lifetime risk at continuous exposure to 1 $\mu g/m^3$	8.2×10^{-6}	1.1×10^{-5}

APPENDIX

Calculation of Human Equivalent Concentrations

In the derivation of RfCs, EPA (1990)[1] calculates an HEC from an adjusted experimental concentration and an animal to human lambda ratio (the default for which is 1) (this ratio is the blood to air partition coefficient of the chemical for the animal species to the human value assuming that periodicity is attained since the model for the RfC being used is for a gas and extrarespiratory effect). The equation for this dosimetric adjustment can be found in EPA (1990) as

$$NOAEL_{HEC}(mg/m^3) = NOAEL_{ADJ}(mg/m^3) \times \lambda_A/\lambda_H,$$

where $NOAEL_{ADJ}$ is the experimental NOAEL adjusted for continuous lifetime exposure and λ_A/λ_H is the ratio of the blood to gas air partition coefficient of the chemi-

[1] Under EPA's 1994 guidance for the development of RfCs, ACN would be a category 2 gas. However, the equations presented in EPA (1994) for the calculation of extrarespiratory effects for category 1 and 2 gases are problematical and result in a nonsensical answer. Therefore, until the problems with these equations is solved, the interim methods of 1990 are used instead of the 1994 version.

TABLE A-1

Calculation of Human Equivalent Concentrations for the Experimental Acrylonitrile Concentrations Utilized by Quast *et al.* (1980b)

Experimental concentration (ppm)	Converted to mg/m^3 ($\times$ 2.1 mg/m^3 per ppm)	Adjusted for continuous exposure[a] (mg/m^3) ($\times$ 6/24 $\times$ 5/7)	Human equivalent concentration (mg/m^3) ($\times$ λ_A/λ_H (=1))
0	0	0	0
20	42	7.5	7.5
80	168	30	30

[a] Exposure regimen was for 6 h/day, 5 days/week.

cal for the laboratory animal species to the human value.

There are no data for ACN to support a value other than the default of 1 for the ratio of λ_A/λ_H.

The experimental concentrations and calculation of HECs for the bioassay by Quast *et al.* (1980b) were determined as described in Table A-1.

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