United States Environmental Protection Agency

EPA/690/R-14/002F
Final
3-4-2014

Provisional Peer-Reviewed Toxicity Values for

Azodicarbonamide
(CASRN 123-77-3)

Superfund Health Risk Technical Support Center
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Questions regarding the contents of this document may be directed to the U.S. EPA Office of Research and Development's National Center for Environmental Assessment, Superfund Health Risk Technical Support Center (513-569-7300).

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COMMONLY USED ABBREVIATIONS

BMC	benchmark concentration
BMCL	benchmark concentration lower confidence limit
BMD	benchmark dose
BMDL	benchmark dose lower confidence limit
HEC	human equivalent concentration
HED	human equivalent dose
IUR	inhalation unit risk
LOAEL	lowest-observed-adverse-effect level
$LOAEL_{ADJ}$	LOAEL adjusted to continuous exposure duration
$LOAEL_{HEC}$	LOAEL adjusted for dosimetric differences across species to a human
NOAEL	no-observed-adverse-effect level
$NOAEL_{ADJ}$	NOAEL adjusted to continuous exposure duration
$NOAEL_{HEC}$	NOAEL adjusted for dosimetric differences across species to a human
NOEL	no-observed-effect level
OSF	oral slope factor
p-IUR	provisional inhalation unit risk
POD	point of departure
p-OSF	provisional oral slope factor
p-RfC	provisional inhalation reference concentration
p-RfD	provisional oral reference dose
RfC	inhalation reference concentration
RfD	oral reference dose
UF	uncertainty factor
UF_A	interspecies uncertainty factor
UF_C	composite uncertainty factor
UF_D	database uncertainty factor
UF_H	intraspecies uncertainty factor
UF_L	LOAEL-to-NOAEL uncertainty factor
UF_S	subchronic-to-chronic uncertainty factor
WOE	weight of evidence

PEER-REVIEWED PROVISIONAL TOXICITY VALUES FOR AZODICARBONAMIDE (CASRN 123-77-3)

BACKGROUND

A Provisional Peer-Reviewed Toxicity Value (PPRTV) is defined as a toxicity value derived for use in the Superfund Program. PPRTVs are derived after a review of the relevant scientific literature using established Agency guidance on human health toxicity value derivations. All PPRTV assessments receive internal review by a standing panel of National Center for Environment Assessment (NCEA) scientists and an independent external peer review by three scientific experts.

The purpose of this document is to provide support for the hazard and dose-response assessment pertaining to chronic and subchronic exposures to substances of concern, to present the major conclusions reached in the hazard identification and derivation of the PPRTVs, and to characterize the overall confidence in these conclusions and toxicity values. It is not intended to be a comprehensive treatise on the chemical or toxicological nature of this substance.

The PPRTV review process provides needed toxicity values in a quick turnaround timeframe while maintaining scientific quality. PPRTV assessments are updated approximately on a 5-year cycle for new data or methodologies that might impact the toxicity values or characterization of potential for adverse human health effects and are revised as appropriate. It is important to utilize the PPRTV database (http://hhpprtv.ornl.gov) to obtain the current information available. When a final Integrated Risk Information System (IRIS) assessment is made publicly available on the Internet (www.epa.gov/iris), the respective PPRTVs are removed from the database.

DISCLAIMERS

The PPRTV document provides toxicity values and information about the adverse effects of the chemical and the evidence on which the value is based, including the strengths and limitations of the data. All users are advised to review the information provided in this document to ensure that the PPRTV used is appropriate for the types of exposures and circumstances at the site in question and the risk management decision that would be supported by the risk assessment.

Other U.S. Environmental Protection Agency (EPA) programs or external parties who may choose to use PPRTVs are advised that Superfund resources will not generally be used to respond to challenges, if any, of PPRTVs used in a context outside of the Superfund program.

QUESTIONS REGARDING PPRTVs

Questions regarding the contents and appropriate use of this PPRTV assessment should be directed to the EPA Office of Research and Development's National Center for Environmental Assessment, Superfund Health Risk Technical Support Center (513-569-7300).

INTRODUCTION

Azodicarbonamide (ADA), CASRN 123-77-3, is used in the rubber and plastic industries as a blowing agent in the expansion of several polymers including polyvinyl chloride, polyolefins, and other natural or synthetic rubbers. The World Health Organization (WHO) developed a Concise International Chemical Assessment Document (CICAD) for ADA (Cary et al., 1999). In that document, it was stated that at around 190−230°C, ADA decomposes into the gases nitrogen, carbon monoxide, carbon dioxide, and ammonia; solid residues; and sublimated substances. The U.S. Food and Drug Administration permits the use of ADA as an aging and bleaching ingredient in cereal flour and as a dough conditioner in bread making, provided that the total amounts of ADA do not exceed 2.05 g per 100 pounds of flour (0.0045% or 45 ppm) (NLM, 2011). ADA is poorly soluble in water and has a low vapor pressure, suggesting that it has low volatility. A table of physicochemical properties for ADA is provided below (see Table 1).

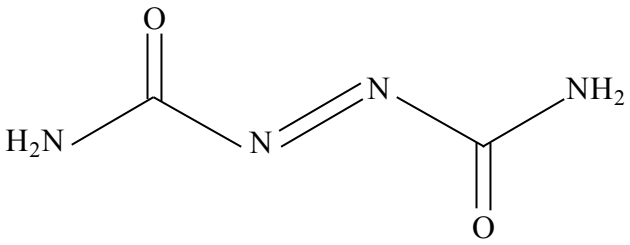

Figure 1. Chemical Structure of ADA (CASRN 123-77-3)

Table 1. Physicochemical Properties of ADA (CASRN 123-77-3)[a]

Property (unit)	Value
Boiling point (ºC)	ND
Melting point (ºC)	225
Density (g/cm^3 at 20ºC)	1.65
Vapor pressure (mmHg at 20°C)	1.88×10^{-10}
pH (unitless)	ND
Solubility in water (mg/L at 20°C)	35
Relative vapor density (air = 1)	ND
Molecular weight (g/mol)	116.08

[a]Source: NLM (2011).

ND = no data.

According to the WHO (Cary et al., 1999), both inhaled and ingested ADA are rapidly and completely converted to biurea (hydradicarbonamide, or HADA), the only breakdown product for ADA that has been identified. The WHO concluded that "it is likely that systemic

exposure is principally to this derivative rather than to the parent compound" (Cary et al., 1999). Because ADA is rapidly and completely converted to HADA (Cary et al., 1999), conversion of ADA to HADA is assumed to occur at a 1:1 ratio. In this PPRTV assessment, molecular weight adjustments were made in cases where dosimetry conversions from administered HADA to ADA were necessary.

There are a number of studies in the available literature on ADA that present strong evidence that ADA is a respiratory sensitizer in occupationally exposed humans (Kim et al., 2004; Normand et al., 1989; Whitehead et al., 1987; Ahrenholz et al., 1985; Malo et al., 1985; Slovak, 1981; Ferris et al., 1977). Two of these independent studies (Malo et al., 1985; Slovak, 1981) confirm cases of occupational asthma, with late-phase but not immediate reactions following exposure to ADA. A recent National Institutes of Health white paper listed several authoritative groups such as the European Union Health and Safety Executive, the New Jersey Department of Health and Senior Services, and the Association of Occupational and Environmental Clinics that have classified ADA as a respiratory sensitizer or asthmagen (NIH, 2011). However, the available animal studies do not provide supporting data for ADA-induced asthma. Several of the human occupational studies measure levels of ADA in the atmosphere (ranging from 0.01−12 mg/m^3), and these concentrations can be adjusted for continuous exposure to derive a provisional reference concentration (p-RfC) in the absence of suitable animal data. Because adequate human data are the most relevant for determining the health effects of a substance to humans and should be used to establish reference values when available, the occupational studies were used for derivation of the subchronic and chronic p-RfCs for ADA. Human data have been used on multiple occasions to derive reference values in IRIS, including a value for beryllium based on respiratory sensitization in exposed persons (U.S. EPA, 1998).

Table 2 provides a summary of available toxicity values for ADA from U.S. EPA and other regulatory agencies or organizations.

Table 2. Summary of Available Toxicity Values for ADA (CASRN 123-77-3)

Source/Parameter[a,b]	Value (Applicability)	Notes[c]	Reference	Date Accessed
Noncancer				
ACGIH	NV	NA	ACGIH (2013)	NA
ATSDR	NV	NA	ATSDR (2013)	NA
Cal/EPA	NV	NA	Cal/EPA (2014a, b)	1-28-2014[d]
NIOSH	NV	NA	NIOSH (2010)	NA
OSHA	NV	NA	OSHA (2011, 2006)	NA
IRIS	NV	NA	U.S. EPA	1-28-2014
Drinking Water	NV	NA	U.S. EPA (2012a)	NA
HEAST	NV	NA	U.S. EPA (2011a)	NA
CARA HEEP	NV	NA	U.S. EPA (1994a)	NA
WHO	NV	NA	WHO	1-28-2014
UK HSC/MEL	1 mg/m^3	Based on occupationally-induced asthma.	Cary et al. (1999)	NA
UK HSC/STEL	3 mg/m^3	Based on occupationally-induced asthma.	Cary et al. (1999)	NA
Cancer				
HEAST/WOE	NV	NA	U.S. EPA (2011a)	NA
IRIS	NV	NA	U.S. EPA	1-28-2014
HEAST	NV	NA	U.S. EPA (2011a)	NA
IARC	NV	NA	IARC (2013)	NA
NTP	NV	NA	NTP (2011)	NA
Cal/EPA	NV	NA	Cal/EPA (2014b, 2011)	NA

[a]Sources: ACGIH = American Conference of Governmental Industrial Hygienists; ATSDR = Agency for Toxic Substances and Disease Registry; Cal/EPA = California Environmental Protection Agency; CARA = Chemical Assessments and Related Activities; HEAST = Health Effects Assessment Summary Tables; HEEP = Health and Environmental Effects Profile; IARC = International Agency for Research on Cancer; IRIS = Integrated Risk Information System; NIOSH = National Institute for Occupational Safety and Health; NTP = National Toxicology Program; OSHA = Occupational Safety and Health Administration; UK HSC = United Kingdom Health and Safety Commission; WHO = World Health Organization.
[b]Parameters: MEL = maximum exposure limit; STEL = short-term exposure limit.
[c]Information might include details related to the principal study, critical effect, and POD. A discussion of uncertainty and/or modifying factor(s) is not included because these may differ among agencies/organizations, precluding comparison.
[d]The Cal/EPA Office of Environmental Health Hazard Assessment (OEHHA) Toxicity Criteria Database (http://oehha.ca.gov/tcdb/index.asp) was also reviewed and found to contain no information on ADA.

NA = not applicable; NV = not available.

Literature searches were conducted on sources published from 1900 through January 2014, for studies relevant to the derivation of provisional toxicity values for ADA, CASRN 123-77-3. The following databases were searched by chemical name, synonyms, or CASRN: ACGIH, ANEUPL, ATSDR, BIOSIS, Cal/EPA, CCRIS, CDAT, ChemIDplus, CIS, CRISP, DART, EMIC, EPIDEM, ETICBACK, FEDRIP, GENE-TOX, HAPAB, HERO, HMTC, HSDB, IARC, INCHEM IPCS, IPA, ITER, IUCLID, LactMed, NIOSH, NTIS, NTP, OSHA, OPP/RED, PESTAB, PPBIB, PPRTV, PubMed (toxicology subset), RISKLINE, RTECS, TOXLINE, TRI, U.S. EPA IRIS, U.S. EPA HEAST, U.S. EPA HEEP, U.S. EPA OW, and U.S. EPA TSCATS/TSCATS2. The following databases were searched for relevant health information: ACGIH, ATSDR, Cal/EPA, U.S. EPA IRIS, U.S. EPA HEAST, U.S. EPA HEEP, U.S. EPA OW, U.S. EPA TSCATS/TSCATS2, NIOSH, NTP, OSHA, and RTECS.

REVIEW OF POTENTIALLY RELEVANT DATA (CANCER AND NONCANCER)

Table 3 provides an overview of the relevant database for ADA and includes all potentially relevant, repeated short-term-, subchronic-, and chronic-duration studies. Principal studies are identified in bold. The phrase "statistical significance" used throughout the document indicates a *p*-value of <0.05 unless otherwise noted.

Table 3. Summary of Potentially Relevant Data for ADA (CASRN 123-77-3)

Category	Number of Male/Female per Dose Group, Strain, Species, Study Type, Study Duration	Dosimetry[a]	Critical Effects	NOAEL[a]	BMDL/ BMCL[a]	LOAEL[a]	Reference (Comments)	Notes[b]
Human								
			1. Oral (mg/kg-d)[a]					
Acute[c]	ND							
Short-term[d]	ND							
Long-term[e]	ND							
Chronic[f]	ND							
			2. Inhalation (mg/m^3)[a]					
Acute[c]	ND							
Short-term[d]	ND							
Long-term[e]	1/0, inhalation, occupational exposure, >10 yr	NV	Positive 1% ADA patch test; subject was diagnosed with ADA-induced occupational asthma	NV	DU	NV	Kim et al. (2004)	PR
	4/0, inhalation and/or dermal, occupational exposure ≥3 yr	NV	Shortness of breath; asthma attacks (at work or after provocation tests) or asthmatic bronchitis; decrements in 1-sec forced expiratory volume (FEV_1); eczema of the hands, forearms, or face	NV	DU	NV	Normand et al. (1989)	PR

Table 3. Summary of Potentially Relevant Data for ADA (CASRN 123-77-3)

Category	Number of Male/Female per Dose Group, Strain, Species, Study Type, Study Duration	Dosimetry[a]	Critical Effects	NOAEL[a]	BMDL/ BMCL[a]	LOAEL[a]	Reference (Comments)	Notes[b]
Long-term[e]	2/0, inhalation, occupational exposure, ≥3 yr	NV	Both cases: irritation of the eyes, cough, dyspnea, shortness of breath, and wheezing; decrements in FEV_1 (24% decrease 6 hr after exposure); case 1 diagnosed with late-onset asthma, case 2 with both immediate- and late-onset asthma reaction.	NV	DU	NV	Malo et al. (1985); results mirror effects in Whitehead et al. (1987) and Slovak (1981)	PR
	13/0, inhalation and/or dermal, occupational exposure; spirometry and exposure measurements taken on Monday, Friday, and the following Monday of a single wk; total exposure history unknown	Full-shift respirable mass concentrations were 0.25−0.75 on Mondays and 0.68 on Friday (adjusted from time weighted-average)	6 workers had no complaints; 7 had symptoms: 6 had productive cough, 5 had shortness of breath, 5 had nocturnal cough, 2 felt fatigued at the end of the work day, and 2 had leg cramps; decreases in FEV_1 and mean forced vital capacity (FVC) were reported between Monday and Friday with some recovery the following Monday after the weekend with no exposure	NV	DU	0.25−0.75 (adjusted)	Ferris et al. (1977)	PR

Table 3. Summary of Potentially Relevant Data for ADA (CASRN 123-77-3)

Category	Number of Male/Female per Dose Group, Strain, Species, Study Type, Study Duration	Dosimetry[a]	Critical Effects	NOAEL[a]	BMDL/ BMCL[a]	LOAEL[a]	Reference (Comments)	Notes[b]
Long-term[e]	151 (sex not provided), inhalation, occupational exposure (duration unknown)	0.7−1.8 (adjusted from time weighted average)	18.5% (n = 28) of male subjects diagnosed with asthma after exposure; re-exposure caused worsening of symptoms; 7/13 sensitized participants still exposed 3 mo after onset of disease developed prolonged airway hyperreactivity to common irritants	NDr	DU	0.7−1.8 (adjusted)	Slovak (1981)	PR
	227 (80/147), inhalation, occupational exposure, average employment duration ≥2.9 yr	**Personal sampling ranged from trace (i.e., above detection limit, but below the quantifiable level) to 0.269 (mean of 0.00689) (adjusted from time-weighted average)**	**Lower respiratory effects and symptoms of chronic bronchitis correlated with work involving ADA supported by 17 workers given pre- and postpulmonary function tests exhibiting statistically significant, modest decreases in FVC and FEV_1 during work shift**	**NDr**	**DU**	**0.00689 (adjusted mean, 1984 sampling)**	**Whitehead et al. (1987); NIOSH (1985)**	**PS, PR**

Table 3. Summary of Potentially Relevant Data for ADA (CASRN 123-77-3)

Category	Number of Male/Female per Dose Group, Strain, Species, Study Type, Study Duration	Dosimetry[a]	Critical Effects	NOAEL[a]	BMDL/ BMCL[a]	LOAEL[a]	Reference (Comments)	Notes[b]
Long-term[e]	30 exposed/16 unexposed (sex not provided), inhalation, occupational exposure, average employment of 6.25 yr	0.054−4.3 (mean: 1.3) in those directly exposed and nondetectable to 0.036 in those indirectly exposed (mean: 0.0036) **(adjusted from time-weighted average)**	Increased (18/30, [60%]) lower respiratory tract symptoms (coughing, wheezing, and shortness of breath) compared with 1/16 (6%) unexposed workers; increased (26/30, [87%]) upper respiratory tract symptoms (nasal stuffiness, itchy or irritated eyes, and runny nose) compared with 5/16 (31%) unexposed workers	NDr	DU	0.0036−1.3, (adjusted mean, indirect and direct exposure)	Ahrenholz et al. (1985)	NPR
Chronic[f]	ND							
Animal								
			1. Oral (mg/kg-d)[a]					
Subchronic	10/10, strain not reported, mouse, gavage, 5 d/wk, 13 wk	M: 0.7, 56, 111, 223, 446, or 893 F: 0, 111, 223, 446, 893, or 1,786 (adjusted)	No observed effects	893 (adjusted)	DU	NDr	IRDC (1982a) in Cary et al. (1999); original study unpublished and unavailable	NPR
	10/10, strain not reported, rat, gavage, 5 d/wk, 13 wk	M: 0.7, 71, 357, or 1,786 F: 0, 143, 714, or 3,571 (adjusted)	Mortality and pyelonephritis with casts and crystalline deposits in renal tubules in males and females at 1,786 and 3,571 mg/kg-d, respectively	357 (adjusted)	DU	1,786 (FEL; adjusted)	IRDC (1982b) in Cary et al. (1999); original study unpublished and unavailable	NPR

Table 3. Summary of Potentially Relevant Data for ADA (CASRN 123-77-3)

Category	Number of Male/Female per Dose Group, Strain, Species, Study Type, Study Duration	Dosimetry[a]	Critical Effects	NOAEL[a]	BMDL/ BMCL[a]	LOAEL[a]	Reference (Comments)	Notes[b]
Subchronic	11−12/0 (12 in control group and 11 in treatment group), Sprague-Dawley rat, diet, 4 wk	0, or 8,600 (adjusted)	Significantly decreased 24-hr thyroidal ^{125}I uptake	NDr	DU	8,600 (adjusted)	Gafford et al. (1971)	PR
Chronic	25/25 (F0 generation), albino FDRL rat, diet, 2 yr[g]	M: 0, 53.3, 168.5, or 533.1 F: 0, 60.5, 191.1, or 604.7 (adjusted) M: 0, 7 F: 0, 8.20 (adjusted)	No observed effects	533.1 (adjusted)	DU	NDr	Oser et al. (1965a)	PR This chronic study is part of the reproductive study
	25/25 (10/10 in control group), albino FDRL rat, diet, 1 yr[g]	M: 0, 3,554, or 7,108 F: 0, 4,035, or 8,063 (adjusted)	No observed effects	7,108 (adjusted)	DU	NV	Oser et al. (1965b)	PR
	2/2, mongrel dog, diet, 2 yr[g]	M: 0, 15.33, 48.44, or 153.3 F: 0, 13.65, 43.14, or 136.5 (adjusted)	No observed effects	136.5 (adjusted)	DU	NV	Oser et al. (1965c)	PR

Table 3. Summary of Potentially Relevant Data for ADA (CASRN 123-77-3)

Category	Number of Male/Female per Dose Group, Strain, Species, Study Type, Study Duration	Dosimetry[a]	Critical Effects	NOAEL[a]	BMDL/ BMCL[a]	LOAEL[a]	Reference (Comments)	Notes[b]
Chronic	2/2, mongrel dog, diet, 1 yr[g]	M: 1,022 or 2,044 F: 910 or 1,820 (adjusted)	Most of the treated dogs became moribund; multiple renal calculi, bladder calculi, and chronic pyelonephritis	NDr	DU	NDr	Oser et al. (1965d); frank effects and lack of control prevent establishment of NOAEL/ LOAEL	PR
Developmental	ND							
Reproductive	**25/25 in F0 generation, 10/10 in F1, F2, and F3 generations, albino FDRL rat, diet, administered HADA or ADA**	**M: 0, 53.3, 168.5, or 533.1 F: 0, 60.5, 191.1, or 604.7 (adjusted and converted from HADA to ADA dose) or M: 0, 7 F: 0, 8.20 (adjusted ADA dose)**	**No observed effects**	**Systemic: 533.1 (adjusted) Reproductive: 604.7 (adjusted)**	**DU**	**NDr**	**Oser et al. (1965e)**	**PS, PR**
Carcinogenicity	ND							
2. Inhalation (mg/m^3)[a]								
Subchronic	10/10, F344 rat, inhalation, 6 hr/d, 5 d/wk, 13 wk	M: 0, 29.7, 60.6, or 121 F: 0, 30.6, 62.7, or 125 (adjusted, extrarespiratory RDDR used for all concentration groups)	T3 and T4 levels in the highest male exposure group significantly elevated (50% and 40%, respectively) compared with controls	60.6	DU	121	Medinsky et al. (1990)	PR

Table 3. Summary of Potentially Relevant Data for ADA (CASRN 123-77-3)

Category	Number of Male/Female per Dose Group, Strain, Species, Study Type, Study Duration	Dosimetry[a]	Critical Effects	NOAEL[a]	BMDL/ BMCL[a]	LOAEL[a]	Reference (Comments)	Notes[b]
Subchronic	10/10, B6C3F$_1$ mouse, inhalation, 6 hr/d, 5 d/wk, 13 wk	M: 0, 49.9, 99.4 or 202 F: 0, 47.9, 96.3 or 196 (adjusted; extrarespiratory RDDR used for all concentration groups)	No observed effects	196	DU	NDr	Medinsky et al. (1990)	PR
	10/0, Hartley guinea pig, inhalation, 6 hr/d, 5 d/wk, 4 wk	0, 14.4, or 52.8 (adjusted; extrarespiratory RDDR used for all concentration groups)	No observed effects	52.8	DU	NDr	Gerlach et al. (1989)	PR
Chronic	ND							
Developmental	ND							
Reproductive	ND							
Carcinogenicity	ND							

[a]Dosimetry: For animal studies, LOAEL, BMDL/BMCL, and LOAEL values are converted to an adjusted daily dose (ADD in mg/kg-d) for oral noncancer effects and a human equivalent concentration (HEC in mg/m^3) for inhalation noncancer effects unless otherwise noted. All long-term exposure values (4 wk and longer) are converted from a discontinuous to a continuous exposure. Values from animal developmental studies are not adjusted to a continuous exposure.
RDDR = Regional Deposited Dose Ratio.
[b]Notes: IRIS = utilized by IRIS, date of last update; PS = principal study; PR = peer reviewed; NPR = not peer reviewed; NA = not applicable.
[c]Acute = exposure for ≤24 hr (U.S. EPA, 2002).
[d]Short-term = repeated exposure for >24 hr ≤30 d (U.S. EPA, 2002).
[e]Long-term = repeated exposure for >30 d ≤10% lifespan (based on 70-yr typical lifespan) (U.S. EPA, 2002).
[f]Chronic = repeated exposure for >10% lifespan (U.S. EPA, 2002).
[g]= studies were conducted by treating animals with HADA (all the doses in this table have been converted from HADA to ADA).

DU = data unsuitable; DUB = data unamenable to BMDS; NA = not applicable; NV = not available; ND = no data; NDr = not determined; NI = not identified; NP = not provided; NR = not reported; NR/Dr = not reported but determined from data; NS = not selected.

HUMAN STUDIES

Oral Exposures

The effects of oral exposure to ADA have not been evaluated in humans.

Inhalation Exposures

The effects of inhalation exposure of humans to ADA have been evaluated in seven long-term-duration studies (Kim et al., 2004; Normand et al., 1989; Whitehead et al., 1987; Ahrenholz et al., 1985; Malo et al., 1985; Slovak, 1981; Ferris et al., 1977). Due to a small sample size, lack of proper controls, and/or lack of dosimetry information in the studies conducted by Kim et al. (2004), Normand et al. (1989), Malo et al. (1985), and Ferris et al. (1977), only three studies (Whitehead et al., 1987; Ahrenholz et al., 1985; Slovak, 1981) were considered as potential principal studies and are summarized in this document.

Acute

No acute inhalation studies in humans were identified.

Long-term Studies

Slovak (1981)

Slovak (1981) published a peer-reviewed occupational study of 151 employees (sex of all employees not provided) that had been or were currently engaged in manufacture, servicing, and quality control at an ADA plant since it opened in 1966. Slovak (1981) reported that because ADA had a low acute toxicity, the plant was not designed to appropriately contain and ventilate air contamination. Dust levels were measured following "standard techniques of industrial hygiene with personal sampling by Casella pump followed by gravimetric analysis." Time-weighted average concentrations of 2−5 mg/m^3 ADA were reported; however, no individual, raw exposure data were available. Adjusting for continuous exposure (from 5 working days to a full week) and minute volume, this range is 0.7−1.8 mg/m^3. No data were available for historical measured concentrations. An objective, nurse-administered questionnaire and a structured, clinical occupational history collected by the study author were used to determine any medical history of asthma. Workers exposed to ADA with a history of repeated episodes of wheezing or chest tightness with or without cough were considered to have asthma. Prick tests were also conducted in asymptomatic and ADA-sensitized exposed workers using 0.1, 1.0, or 5.0% ADA dissolved in dimethylsulfoxide. Spirometry was conducted before and after shifts for three groups of workers: (1) workers diagnosed with ADA-induced asthma, (2) all asymptomatic workers employed for at least 1 year in the plant, and (3) control process workers without any contact to ADA or other lung sensitizers. Eleven workers with ADA-induced asthma were provided with Wright mini-peak flow meters to self-record readings every 2 hours during waking hours. Challenge tests were not conducted because such tests were not considered justified in the occupational setting. It does not appear that study authors used statistical methods to measure differences (and there were no unexposed workers to use as a reference population for comparison) although the age and smoking habits of participants with asthma were reported for the workers included in the study.

Twenty-eight men of 151 (18.5%) participants were diagnosed as having developed asthma following exposure to ADA. Among these 28 male participants, more than 50% developed asthma within 3 months of the initial exposure, and 75% developed it within the first year. Furthermore, 56% had late-onset asthma, 22% had immediate-onset asthma, and 22% had dual-onset asthma. Approximately 46% (13 participants) reported worsening symptoms and a

shorter time between exposure at the plant and the reappearance of symptoms over the course of their ongoing exposure. Based on medical notes taken during past asthma attacks, 12 out of 28 participants that experienced episodes of asthma were confirmed to have had asthma attacks as a result of ADA exposure. About 44% of the participants reported their condition to the occupational health department and were transferred to other work. Of the 13 participants that continued working for more than 3 months, 7 developed subjective airway hyperactivity that persisted for more than 1 month after cessation of exposure. Of these, 5 of the 8 male participants exhibited persistent hyperactivity to general irritants such as sulfur dioxide and tobacco smoke for over 3 years after removal from ADA exposure. The 28 participants whose exposure ceased within the first 3 months did not exhibit persistent subjective airway hyperactivity. Prick tests were negative for all concentrations in both asymptomatic and ADA-sensitized exposed workers. Pre- and postshift spirometry readings were unremarkable during the study; reversible airflow obstruction was not observed, and no asthma attacks were observed. Peak flow measurements in sensitized individuals no longer exposed to ADA were not different during holiday periods and times at work, confirming there was no occupational exposure still affecting these individuals. Finally, atopy did not differ among ADA-sensitized workers and unsensitized, asymptomatic workers who worked more than 1 year at the plant, suggesting that atopy is not predictive of predisposition to ADA sensitivity.

Based on the development of asthma following exposure to ADA and the fact that subjective airway hyperactivity persisted for at least 1 month following exposures of more than 3 months, Slovak (1981) concluded that ADA is a respiratory sensitizer. A LOAEL of 0.7−1.8 mg/m^3 is established based on the respiratory symptoms reported in exposed workers; the data preclude establishing a NOAEL. Although this study provides support that ADA is a respiratory sensitizer, the subjects were exposed to a much higher concentration of ADA than the Whitehead et al. (1987) study (0.00689 mg/m^3) which is discussed below.

Whitehead et al. (1987) and NIOSH (1985)

Whitehead et al. (1987) is selected as the principal study for the derivation of the subchronic and chronic p-RfCs. In this occupational cross-sectional study, the study authors evaluated a population of 227 employees (80 men and 147 women) at the Leon Plastics plant in Grand Rapids, Michigan. The plant performed injection molding of a polyphenylene oxide resin with ADA as a foaming agent. However, due to changes in plant operations, the use of ADA decreased dramatically in the 4−5 months prior to this cross-sectional study. Current workers in injection molding had worked at that job for an average of 3.1 years, compared to 2.9 years in all other departments. The study authors administered pulmonary function tests (simple spirometry) to 223 of the 227 workers, and pre- and postshift pulmonary function tests were administered to 17 workers currently working in injection molding to assess short-term pulmonary function effects. Trained interviewers administered questionnaires that collected information on occupational history (including departments worked at the Grand Rapids plant); smoking status; past illness; and respiratory, nasal, eye, and skin symptoms. Pulmonary function values from employees currently working in injection molding (currently exposed) were compared to those from employees formerly working in injection molding (formerly exposed) and those of employees who had never worked in injection molding (never exposed). With respect to the prevalence of respiratory, nasal, eye, and skin symptoms, the following comparisons were made: (1) employees currently working in injection molding were compared to employees currently working in other departments, (2) employees formerly working in injection molding were compared to employees formerly working in other departments, and (3) employees currently and

formerly working in injection molding with known exposure to ADA were compared to employees currently and formerly working in injection molding with no known exposure to ADA. Logistic regression was used to analyze symptoms by presence or absence of exposure to ADA as well as sex, age, pack-years smoked, current smoking status, and potential confounding terms. A best model was found by backward elimination of nonsignificant terms using a *p*-value <0.10 criterion of significance.

NIOSH (1985) conducted three surveys at Leon Plastics in Grand Rapids, Michigan. However, in the initial survey conducted on March 24, 1983, exposures (personal and area) were not measured. In the second and the third surveys conducted on May 2−6, 1983, and March 11−12, 1984, respectively, NIOSH investigators gathered personal exposure information and area concentrations of ADA, polyphenylene oxide (not an irritant), and thermal decomposition products (i.e., styrene, benzene, phenol, xylene, and toluene). Samples were analyzed using high-performance liquid chromatography (HPLC). During the May 1983 survey, investigators detected benzene (0.02 mg/m^3), styrene (0.09 mg/m^3), toluene (1.5 mg/m^3), xylene (0.03 mg/m^3), and phenol (0.5−1.9 mg/m^3). In this survey, ADA concentrations of personal samples ranged from nondetectable to 0.280 mg/m^3 (reported as 280 $\mu g/m^3$) with a geometric mean value of 0.0039 ± 0.0063 mg/m^3 (reported as 3.9 ± 6.3 $\mu g/m^3$). Anecdotal interviews with a focus on respiratory problems were conducted among 16 injection molding workers. In the third survey in 1984, benzene was not detectable, styrene ranged from 0.1−0.3 ppm, and toluene ranged from 0.03−0.1 ppm; xylene and phenol were not analyzed. Thirty-two personal sampling results taken in the March 1984 survey, including 16 of the 17 workers given pre- and postshift pulmonary function tests, showed that the concentration of ADA ranged from trace amounts (above the detection limit, but below the quantifiable level) to 0.752 mg/m^3 (reported as 752 $\mu g/m^3$) with a geometric mean value of 0.0193 ± 0.0065 mg/m^3 (reported as 19.3 ± 6.5 $\mu g/m^3$, cited from the study). It should be noted that all but 2 of the 32 samples fell below 0.057 mg/m^3. The two highest concentration values (0.368 and 0.752 mg/m^3) occurred in instances where a higher exposure would be expected—in one case, the worker's station was located directly across from the resin mixing area; in the other case, the worker was a mixer of ADA (NIOSH, 1985). After adjusting for continuous exposure (from 5 working days to the full week) and minute volume, the exposure concentrations were ranged from trace to 0.269 mg/m^3 with a mean of 0.00689 mg/m^3 (geometric mean; 1984 sampling). Table B.1 provides the 1984 personal ADA sample results for the 32 workers. Whitehead et al. (1987) was an extended analysis of the third survey from NIOSH (1985). The dosimetry data from March 1984 were used for consideration of a study LOAEL because (1) the health study by Whitehead et al. (1987) was conducted in conjunction with this March 1984 sampling period (and not during 1983 sampling), (2) the Whitehead et al. (1987) study has a relatively larger sample size and complete health effect data, and (3) personal sampling from March 1984 provides a better estimate of worker exposure levels.

The results from the Whitehead et al. (1987) study were summarized as follows. No statistically significant differences in pulmonary function in the total population of workers were observed when analyzed by departmental status (i.e., former-injection molding workers, current injection molding workers, and never injection molding workers). However, modest, statistically significant decrements in mean FVC and one-second FEV_1 over the work shift in the pre- and postshift study of 17 injection mold operators were observed. No consistent dose-response trends were observed in these 17 workers when stratified by measured ADA concentration level (0−0.02 mg/m^3, 0.02−0.04 mg/m^3, or ≥0.04 mg/m^3), years on current job, or the product of both

measures (concentration × years on job). The respiratory symptoms reported in workers currently working in injection molding were significantly more prevalent compared with workers in all other departments. For current injection molding workers, the study authors reported increased incidences of irritation (burning of the eyes, nose, or throat at least once per month; odds ratio [OR]: 1.77, $p = 0.04$), coughing (OR: 1.98, $p = 0.02$), wheezing (OR: 2.75, $p = 0.004$), and headache (OR: 1.82, $p = 0.04$) (no confidence intervals for odds ratios were reported, see Table B.2). The logistic regression analysis of these data yielded even more significant results when results were adjusted for age, sex, pack-years smoked, and smoking status. In this case, the study authors reported increased incidences of coughing (OR: 2.61, $p = 0.002$), wheezing (OR: 3.86, $p < 0.001$), and headache (OR: 2.62, $p < 0.001$). The comparison of symptoms between employees formerly working in injection molding and employees formerly working in other departments also indicated significantly increased incidences of irritation, coughing, shortness of breath, and headache (see Table B.2). Similarly, the comparison between employees currently and formerly working in injection molding with known exposure to ADA and employees currently and formerly working in injection molding with no known exposure to ADA showed significant differences in the exposed employees that included increased incidences of wheezing associated with shortness of breath (based on symptoms established from American Thoracic Society guidelines; OR: 7.8, $p = 0.01$), chronic bronchitis (OR: 3.47, $p = 0.02$), wheezing (based on symptoms reported by workers; OR: 16.32, $p = 0.0001$), and chest tightness (OR: 6.72, $p = 0.02$) (see Table B.3).

The study authors concluded that there was "convincing evidence" that work in injection molding was associated with respiratory symptoms including irritation, coughing, and wheezing; however, the prevalence did not appear to be associated with the amount of time on the current job (an average of 3.1 years in injection mold workers compared with 2.9 years in other departments). The NIOSH report concludes that based on the exposure data and the study, exposure to ADA is "considered the probable cause for the reported symptoms" (NIOSH, 1985). One factor obscuring the relationship between ADA and health effects was the presence of other contaminants. However, Whitehead et al. (1987) stated that polyphenylene oxide would not be an irritant, and the thermal decomposition products were all measured at relatively low levels (<0.1 mg/m^3). Based on the increase in respiratory symptoms in injection molding workers, the geometric mean exposure concentration of 0.00689 mg/m^3 is considered a LOAEL. The data preclude establishing a NOAEL.

Ahrenholz et al. (1985)

In a NIOSH Health Hazard Evaluation Report, Ahrenholz et al. (1985) conducted an occupational survey of exposure and symptoms in a group of workers (sex not provided) at the Armstrong World Industries Floor plant in Lancaster, Pennsylvania. The plant manufactured resilient flooring and officially began using ADA powder as a raw material in production during 1970. The initial NIOSH survey took place over November 30 and December 1, 1983, with an in-depth, follow-up study completed January 8−11, 1984. In 1984, the study authors collected ADA personal air concentrations using battery-operated sampling pumps for both full-shift and short-term sampling. Exposure measures were collected from three groups: a directly exposed group (working directly with ADA over a short period of time), an indirectly exposed group (working in the vicinity where ADA was used), and an unexposed group (no expected exposure for full-shift). A total of 30 ever-exposed (indirectly or directly) workers were included in the study. Sixteen unexposed workers out of 44 total unexposed interviewees (i.e., full-shift with no expected exposure) were also assessed for exposure and health-related symptoms. The study

authors reported that the average employment duration for ever-exposed and unexposed workers was 6.25 years. Health was assessed using a health interview and lung function tests. In the initial survey, NIOSH investigators conducted brief interviews with employees, reviewed their medical records, and conducted a medical evaluation to assess whether any reported health effects were associated with work in departments using ADA. The medical evaluation consisted of an in-depth questionnaire interview; pre- and postshift auscultation of the chest (listening to the chest with a stethoscope); pre- and postshift pulmonary function tests (i.e., spirometry measures of FVC, FEV_1, and average rate of flow over the middle two quarters of the effort [$FEF_{25–75}$]); and blood serum sampling to analyze antibodies for ADA. The pulmonary function tests were conducted in 15 of the 30 ever-exposed workers and 11 of the 16 unexposed workers. Interviews were structured questionnaires designed to collect information about occupational history, smoking status, and symptoms associated with upper and lower respiratory disease and hypersensitivity pneumonitis. Investigators considered symptoms to be ADA related if they were temporally related to work and occurred at times when ADA was handled or in areas where dry ADA was present.

Results of ADA monitoring indicated that direct, measured exposure values ranged from 0.15−12 mg/m^3 (n = 8 samples) with a mean exposure level of 3.6 mg/m^3 (Ahrenholz et al., 1985). Indirect exposure values ranged from nondetectable to 0.1 mg/m^3 (n = 25 samples) with a mean of 0.01 mg/m^3 (Ahrenholz et al., 1985). Control exposure levels ranged between nondetectable and "trace" with 9 out of 12 samples falling below the detection limit. The mean control exposure level was 0.001 mg/m^3 (Ahrenholz et al., 1985). After adjusting for continuous exposure (from 5 working days to the full week) and minute volume, direct exposure values were 0.054−4.3 mg/m^3 with a mean of 1.3 mg/m^3. Indirect adjusted exposures values were nondetectable to 0.036 mg/m^3 with a mean of 0.0036 mg/m^3. See Table B.4 for individual exposure measurements.

Lower respiratory tract symptoms were reported by 18/30 ever-exposed workers and 1/16 unexposed workers. The study authors reported that these symptoms, including coughing, wheezing, or shortness of breath, were significantly increased in ever-exposed workers (direct and indirect exposures combined) versus unexposed workers. The risk of lower respiratory tract symptoms was significantly increased in ever-exposed workers (risk ratio [RR] = 10, $p < 0.0004$). The risk of upper respiratory tract and eye symptoms, including nasal stuffiness, itchy or irritated eyes, and runny nose, was also statistically significantly increased (RR = 2.8, $p < 0.0001$) in ever-exposed workers compared with unexposed workers (symptoms reported by 26/30 ever-exposed workers and 5/16 unexposed workers). See Table B.5 for symptom prevalence and risk values. No statistically or biologically significant differences in lung function were observed, as measured by FEV_1 and FVC tests, between ever-exposed and unexposed workers (15/30 ever-exposed workers and 11/16 unexposed workers). The study authors noted that the increased duration of smoking in the unexposed group (mean duration of smoking: 24 years in unexposed and 16 years in ever-exposed; mean pack-years: 27 years in unexposed and 18 years in ever-exposed) may have contributed to the lack of decreased pulmonary function in ever-exposed compared with unexposed workers. Serum samples did not show positive ADA-specific IgE determinations, and IgG results were not positive in the usual dilution of greater than 1:50. The study authors concluded that it is unclear whether the potential sensitization produced by ADA would be mediated through an immune mechanism. The results suggested that workplace inhalation exposure to ADA may lead to a variety of upper and lower respiratory tract symptoms. Based on significantly increased symptoms in ever-exposed workers

(18/30 and 26/30 for lower and upper respiratory tract symptoms, respectively) compared with unexposed workers (1/16 and 5/16 for lower and upper respiratory tract symptoms, respectively), a mean exposure concentration from the ever-exposed workers could be identified as a LOAEL. However, the study authors combined the indirectly and directly exposed workers in a pooled analysis of symptoms in 18 ever-exposed workers compared with 16 unexposed workers, which resulted in a range of exposure concentrations between indirect and direct exposures (0.0036−1.3 mg/m^3). As a result, there is uncertainty in identifying the true exposure level in the ever-exposed group. Thus, a LOAEL presented as a range of 0.0036−1.3 mg/m^3 is established based on significantly increased respiratory tract symptoms; the data preclude establishing a NOAEL.

Chronic-duration Studies

No chronic-duration inhalation studies were identified.

ANIMAL STUDIES

Oral Exposures

The effects of oral exposure of animals to ADA have been evaluated in three subchronic-duration studies (IRDC, 1982a, b; Gafford et al., 1971), four chronic-duration studies which includes initial 2-year and follow-up 1-year studies in both rats and dogs (Oser et al., 1965a, b, c, d), and one reproductive toxicity study (Oser et al., 1965e).

Subchronic-duration Studies

IRDC (1982a, b)

The original report of IRDC (1982a, b) was unpublished and unavailable for review. Based on the information obtained from secondary sources by Cary et al. (1999), groups of 10 male mice (strain not reported) received 1, 78, 156, 312, 625, or 1,250 mg/kg-day (0.7, 56, 111, 223, 446, or 893 mg/kg-day, adjusted; it is not clear whether the male treatment lacked a control group because no control dose is shown and the original study was not available), and groups of 10 female mice (strain not reported) received 0, 156, 312, 625, 1,250, or 2,500 mg/kg-day (0, 111, 223, 446, 893, or 1,786 mg/kg-day, adjusted) by gavage, 5 days/week for 13 weeks. No mortalities and no histopathological abnormalities were observed. Based on no significant effects in this study, a NOAEL of 893 mg/kg-day was established. In another study by IRDC (1982b), groups of 10 male rats (strain not reported) received 1, 100, 500, or 2,500 mg/kg-day (0.7, 71, 357, or 1,786 mg/kg-day, adjusted; it is not clear whether the male treatment lacked a control group because no control dose is shown and the original study was not available) and groups of 10 female rats (strain not reported) received 0, 200, 1,000, or 5,000 mg/kg-day (0, 143, 714, or 3,571 mg/kg-day, adjusted) by gavage, 5 days/week for 13 weeks. Mortality was observed at 1,786 mg/kg-day in males and at 3,571 mg/kg-day in females. A histopathological study found pyelonephritis and crystalline deposits in renal tubules in males at 1,786 mg/kg-day and in females at 3,571 mg/kg-day. Based on the observation of mortality in males, a frank effect level (FEL) of 1,786 mg/kg-day was identified, with a NOAEL of 357 mg/kg-day.

Gafford et al. (1971)

In a published and peer-reviewed study by(Gafford et al., 1971), groups of male Sprague-Dawley rats were administered a low iodine diet (Remington, General Biochemicals Inc., Chagrin Falls, OH) with ADA (Aldrich Chemical Company, Inc., Cedar Knolls, NJ; purity not reported) thoroughly blended in to produce diets of 0, 1, 5, or 10% ADA, or 5 or 10% HADA

(the product when ADA is reduced). Another positive control group received a low iodine diet containing 0.1% methimazole (MMI, a hyperthyroidism drug). The treatment duration varied by experiment but was either 1 week (0, 1, or 10% ADA; 0.1% MMI positive control; 0 or 10% HADA), 10 days (0 or 5% ADA; 0 or 5% HADA), or 4 weeks (0 or 10% ADA). Only the duration of the 4-week treatment qualifies as a candidate study for the derivation of a subchronic reference dose; thus, only the results of this experiment are presented here. The 4-week study included 11 male rats administered a 10% ADA diet and 12 male rats administered a control diet (containing no ADA or MMI). The calculated adjusted daily doses are 0 and 8,600 mg/kg-day based on a subchronic Sprague-Dawley male rat food intake factor of 0.086 kg/kg-day (U.S. EPA, 1988). Animals were administered 0.1 microcurie (μCi) of ^{125}I intraperitoneally 1 day prior to the end of the experiment. At the end of the experiment, animals were sacrificed, and thyroids were removed. Mean thyroidal ^{125}I uptake, thyroid weight relative to 100 g body weight, and total body weight were determined. The study authors measured 24-hour thyroidal radioiodine uptake (it is assumed that the unit is percent) by counting thyroids and standards in an automatic well counter. No histopathology evaluations were conducted. No details were provided on the husbandry of the animals or the study's compliance with good laboratory practice (GLP).

Table B.6 presents the results of 4-week dietary exposure to ADA as reported by Gafford et al. (1971). Thyroidal ^{125}I uptake was significantly decreased in animals receiving 10% ADA in the diet (31.59 ± 8.37% compared with 42.42 ± 3.86% in controls; $p < 0.001$). Although this effect was statistically significant, the study authors considered it a weak inhibitory effect that was much smaller and less consistent than the inhibitory effect seen in positive controls given MMI for 1 week. No statistically significant differences in relative thyroid weight (per 100 g body weight) and mean body weight were observed compared to the control group. Because only a single dose was examined in the subchronic-duration experiments, a NOAEL cannot be identified. A LOAEL of 8,600 mg/kg-day is identified based on decreased 24-hour ^{125}I uptake. Although the magnitude of this effect was small in the present study, results suggest that thyroid iodine uptake may be depressed at higher doses of ADA.

Chronic-duration Studies

Oser et al. (1965)

Oser et al. (1965) reports four experiments investigating the chronic oral toxicity of ADA or HADA in both rats and dogs for 1- and 2-year durations. No effects were observed in the initial testing conducted in rats and dogs for up to 2 years. In order to elicit toxicity and determine potential target organs, higher doses were administrated in rats and dogs for 1 year in a follow-up study. In this document, the Oser et al. (1965) study is divided into five separate summaries including four chronic-duration studies (Oser et al., 1965a, b, c, d) and one reproductive toxicity study(Oser et al., 1965e; discussed in the Reproductive Studies section below). These studies are peer-reviewed, but the study authors did not report whether the studies were performed in compliance with GLP.

Oser et al. (1965a)

Oser et al. (1965a) conducted a 2-year study in albino rats (FDRL strain; source not reported). This chronic-duration study is within a three-generation reproductive study in which the F0 rats (25/sex/group) were dosed for up to 2 years. No effects were observed in these F0 rats at ADA doses up to 533.1 (males) and 604.7 (females) mg/kg-day. Based on the lack of observed effects in any of the dose groups in this study, a NOAEL of 533.1 mg/kg-day is

identified in males. To keep the study integrity and avoid redundancy, the study details are presented in the Reproductive Studies section in Oser et al. (1965e).

Oser et al. (1965b)

In the follow-up study, Oser et al. (1965b) administered doses of 0, 5%, or 10% HADA (purity and source not reported) to groups of 10/sex/group (controls) or 25/sex/group (treated) weanling FDRL rats (source not reported) via diet made from flour for 1 year. At study initiation, rats weighed 50−70 g. HADA was supplemented in a basal diet of Purina Laboratory Chow; controls received an unmodified basal diet. All animals received extra vitamin supplements in their food. Because body weight was only reported for 3 separate weeks (Weeks 0, 12, and 52), study-specific data could not be used for dosimetry conversion. Using U.S. EPA (1988) body weights and food consumption values, the adjusted ADA daily doses (converted from HADA to ADA) are 0, 3,554, and 7,108 mg/kg-day in males and 0, 4,035, and 8,063 mg/kg-day in females.

Rats were examined daily, and body weights were recorded weekly; however, data were not reported for each week. The efficiency of food utilization was calculated using food intake data. At 12, 26, 44, and 52 weeks, blood was analyzed to determine hemoglobin, hematocrit, total and differential leukocyte counts, glucose, and nonprotein nitrogen levels. Urine was tested for albumin, sugar, and pH. Sediment in the urine was examined microscopically. Rats were necropsied after death or terminal sacrifice at the end of the 1-year study period. At necropsy, animals were examined for gross abnormalities and the liver, kidneys, spleen, heart, and adrenal glands were weighed. Histopathological examinations were conducted for all visible abnormalities as well as salivary, thyroid, and pituitary glands, liver, kidneys, spleen, pancreas, adrenals, lungs, heart, gonads, stomach, large and small intestines, bladder, and lymph nodes. The study authors reported no adverse behavioral effects or clinical signs in treated rats. All animals survived the year with the exception of one male administered 7,108 mg/kg-day. No treatment-related changes in body weight, organ weight, hematology, or histopathology were observed. Based on the lack of observed effects in any of the dose groups in this study, a NOAEL of 7,108 mg/kg-day is identified.

Oser et al. (1965c)

Oser et al. (1965c) also conducted a study where mongrel dogs (2/sex/dose group) received diets of bread supplemented with 0, 750, 2,370, or 7,500 ppm of HADA for 2 years. The adjusted ADA daily doses (converted from HADA to ADA) are 0, 15.33, 48.44, and 153.3 mg/kg-day in males and 0, 13.65, 43.14, and 136.5 mg/kg-day in females. Food intake was recorded weekly for 12 weeks. Body weights were recorded weekly for 12 weeks and monthly thereafter. At 3, 6, 12, 18, and 24 weeks, blood was analyzed for hemoglobin, hematocrit, methemoglobin, total and differential leukocyte counts, glucose, and nonprotein nitrogen. At the end of 2 years, each animal was sacrificed for necropsy. Organ weights were recorded, and histopathological examinations were conducted on multiple organs including salivary, thyroid, and pituitary glands, liver, kidneys, spleen, pancreas, adrenals, lungs, heart, gonads, stomach, large and small intestines, bladder, and lymph nodes. Although this 2-year study in mongrel dogs was limited by a small sample size, no observed effects were reported by the study authors. Based on the absence of observed effects in treated dogs, a NOAEL of 136.5 mg/kg-day is identified.

Oser et al. (1965d)

In the follow-up study, Oser et al. (1965d) administered doses of 5% or 10% HADA to groups of mongrel dogs (2/sex/group) via diet for 1 year. Using U.S. EPA (1988) body weights and food consumption values, the adjusted ADA daily doses (converted from HADA to ADA) are 1,022 and 2,044 mg/kg-day in males and 910 and 1,820 mg/kg-day in females. No control groups were reported. Food intake and body weights were recorded weekly for 12 weeks and monthly thereafter. The food intake data were only reported up to the first 12-week period, and body-weight data were only reported for 0, 12, and 24 weeks and at the terminal stage. At 12, 37, and 40 weeks, blood samples were analyzed to determine hemoglobin, hematocrit, methemoglobin, total and differential leukocyte counts, glucose, and nonprotein nitrogen. All dogs that died or became moribund and were sacrificed were examined grossly and histopathologically. Organ weights were recorded and histopathological examinations were conducted as in the 2-year dog study. Renal and bladder calculi recovered from the dogs at autopsy were analyzed chemically for biurea. Initially, the dogs were reluctant to eat the diet, but eventually, the food intake for the first 12-week period in the 5% HADA groups (average of 17.5 kg per dog) was comparable to the intake of the control dogs in the 2-year study (Oser et al., 1965c). In most of the dogs, the body weight was fairly constant for the first half year; then body weight in some dogs precipitously declined or the dogs died. The hemoglobin and hematocrit values were normal. The total leukocyte counts were within normal limits, but the counts from dogs that died before terminal sacrifice was not included. In the dogs receiving 5 or 10% HADA, the polymorphonuclear:lymphocyte ratio increased in the latter part of their lives. Blood sugar levels were normal, but blood nonprotein nitrogen levels increased terminally in most of the dogs. Weights of the liver, kidneys, spleen, heart, and adrenals were normal within 20−44 weeks. After 44 weeks, the study authors did not provide organ weight information. The most significant gross finding in both the 5 and 10% HADA treatment groups was the presence of massive, multiple, renal calculi which, in about half the cases, were accompanied by bladder calculi. Analyses of calculi specimens indicated the principal constituent (comprising approximately 80−100%) was HADA. The principal microscopic findings were secondary to the local irritation of the stones (i.e., chronic pyelonephritis). Of organs and tissues that were examined, no significant pathological changes were observed in the liver, adrenals, spleen, bladder, pituitary, brain, and lung (pathology evaluations for other organs were not reported). The authors concluded that the presence of chronic pyelonephritis and chronic pyelitis seen in most of the dogs is a consequence of the deposition of the massive urinary and bladder calculi in the dogs. Because this 1-year study lacked a control group and resulted in frank effects (mortality) at high ADA doses (up to 2,044 mg/kg-day), the data preclude establishing a NOAEL or a LOAEL.

Developmental Studies

No oral developmental toxicity studies were identified.

Reproductive Studies

Oser et al. (1965e)

A reproductive toxicity study by Oser et al. (1965e) was selected as the principal study for the derivation of the subchronic and chronic p-RfDs. In a published, peer-reviewed, three-generation study, Oser et al. (1965e) examined the reproductive and developmental effects of ADA (purity and source not reported) or HADA (purity and source not reported) fed to rats in their diet. Twenty-five female and 25 male weanling albino rats (FDRL strain; source not reported) weighing 50−70 g received a diet made using flour containing 0- or

100-ppm ADA, ad libitum. Using body weights and food consumption from U.S. EPA (1988), the adjusted daily doses for the groups dosed with the parent compound (ADA) are 0 and 7 mg/kg-day for males and 0 and 8.20 mg/kg-day for females.

Additional groups of 25 female and 25 male weanling albino rats were fed diets of untreated bread supplemented with 0, 750, 2,370, or 7,500 ppm of HADA. Body weight and food consumption data available in the study report were limited and insufficient to use for dosimetry calculations. However, using food intake and body weights for a chronic exposure duration from U.S. EPA (1988)and adjusting for the difference in molecular weight between ADA and HADA, doses are calculated as 0, 53.3, 168.5, and 533.1 mg/kg-day for males and 0, 60.5, 191.1, and 604.7 mg/kg-day for females.

All animals were housed individually, but environmental parameters (e.g., temperature, humidity, and lighting) were not described. Mating procedures were not described; therefore, it is unclear if sibling matings were avoided. F0 rats from both ADA and HADA treatment groups received their respective diets for 2 years, during which time they delivered two litters, designated F1a and F1b. Male and female rats (10/sex) from the second F1b litters were mated to produce two litters of F2offspring (F2a and F2b). Male and female rats of the F2b generation (10/sex) were also mated to produce F3 offspring (F3a and F3b) although the specific number of animals mated was not reported. Rats were examined daily, and body weights were recorded weekly; however, body-weight data were only reported for Weeks 0, 12, 52, and 104. For each generation of rats, the efficiency of food utilization was calculated using food intake data recorded during the first 12 weeks of the study. At 6 and 12 weeks (for rats from all generations) and at 6 months (for rats from the F0, F1, and F2 generations), blood was analyzed to determine hemoglobin, hematocrit, total and differential leukocyte counts, glucose, and nonprotein nitrogen levels. Urine was tested for albumin, sugar, and pH. Sediment in the urine was examined microscopically. All rats were necropsied after death or terminal sacrifice at the end of the 2-year study period. At this time, F0 rats had completed 2 years on the test diets, whereas F1 and F2 rats had completed 28 or more weeks, and F3 rats had completed 14 weeks.

At necropsy, all rats from each generation were examined for gross abnormalities, and the liver, kidneys, spleen, heart, and adrenal glands were weighed. Histopathological examinations were conducted in all rats for all visible abnormalities as well as the salivary, thyroid, pituitary glands, the liver, kidneys, spleen, pancreas, adrenals, lungs, heart, gonads, stomach, large and small intestines, bladder, and lymph nodes. Reproduction and lactational parameters examined in F0, F1, and F2 rats included the average number of pups per litter at birth and weaning, the average weight of pups at 21 days, the fertility index, the gestation index, the viability index, and the lactation index. Although the study authors included statements regarding statistical difference in their conclusions, the statistical tests used to analyze the data were not reported.

Compared with controls, no differences in survival, growth, food consumption, hematology, or pathology (in F0, F1, F2, and F3 rats) and reproduction and lactation (in F0, F1, and F2 rats) were observed in animals administered either the ADA or HADA diets. See Table B.7 for a summary of reproduction and lactation outcomes. Although there appear to be no consistent dose-related trends or generational trends, it should be noted that a number of the indices may have been affected in a biologically significant manner (e.g., fertility index [pregnancies ÷ matings × 100] in the F0 generation at the highest dose, which was only 70%,

one-third lower than the index for the control dams). A number of the control groups had low indices, including fertility in the F0 generation (57% in controls) and viability in several groups (68% in F0 controls, 62% in F1 controls, and 60% in F2 controls). The study authors stated that the low fertility indices in F0 rats (control and treatment groups) were possibly due to an environmental factor (i.e., moving of the laboratory). This study is also limited because it did not examine all reproductive end points required in the Organisation for Economic Co-Operation and Development (OECD) Guideline 416 or OPPTS 870.3800. Parental animals were weanlings at dose initiation rather than the suggested 5 to 9 weeks old. Body weights were not reported for gestation and lactation Days 0, 7, 14, and 20 or 21. The average weight of pups was only reported at 21 days. Individual data were not available for pups or adult animals. The study authors did not monitor female estrous cycles or male sperm parameters (sperm motility and sperm morphology; total number of homogenization-resistant testicular spermatids and cauda epididymal sperm). The study authors reported that the "gonads" (strictly defined as the ovaries and testes) were weighed and examined; it is unclear whether the study authors also included the uterus, epididymides (total and cauda), prostate, and seminal vesicles with coagulating glands and their fluids. The number of resorptions and stillbirths were not reported. The study authors provided no information on gross anomalies, age of vaginal opening and preputial separation, or anogenital distance in pups, but stated that "all other parameters of reproduction and lactation, including the number of pups born and weaned, as well as their growth and development, were comparable among test and control groups". Despite the missing data, this reproductive study is still considered acceptable. The study involved the treatment of a sufficient number of animals (25/sex/group, yielding 50 matings in the F0 and 20 in the F1 and F2 generations) for up to 2 years. Based on the reproductive and lactation data provided, it appears that doses of up to 604.7 mg/kg-day ADA did not affect reproduction in FDRL rats. While male gonad weight was unaffected, no other male parameters were directly measured by the study authors. Because the female parameters are more comprehensive and closely related to pups, they are used for identification of the reproductive NOAEL. In females, gonad weight, fertility index (pregnancies/matings), gestation index, and lactation index were evaluated and unaffected by treatment. Therefore, a reproductive NOAEL of 604.7 mg/kg-day is identified based on the lack of effects in females at this dose (the highest tested). In addition, this dose of ADA did not cause significant changes in hematology, histopathology, and organ/body weights in treated animals. Based on the absence of effects in treated rats of either sex, a NOAEL of 533.1 mg/kg-day is identified for systemic effects.

Inhalation Exposures

The effects of inhalation exposure of animals to ADA have been evaluated in three subchronic-duration experiments within two studies (Medinsky et al., 1990; Gerlach et al., 1989).

Medinsky et al. (1990)

In a published, peer-reviewed subchronic-duration study, Medinsky et al. (1990) examined the toxic effects of ADA aerosol (98% purity) on F344 rats. Four-week-old F344 rats were exposed by inhalation, 6 hours/day, 5 days per week for a total 13 weeks. In the basic study group, 10 female and 10 male per concentration group were exposed to 0, 50, 100, or 204 mg/m^3 ADA aerosol with corresponding mass median aerodynamic diameters (MMADs) of 0, 2.33, 2.45, and 2.37 µm, respectively. Concentrations were adjusted for continuous exposure and converted to a human equivalent concentration (HEC) using a regional deposited dose ratio (RDDR) for particles; the HECs are 0, 29.7, 60.6, or 121 mg/m^3 in males and 0, 30.6, 62.7, or

125 mg/m^3 in females (based on the extrarespiratory RDDR). Mortality/morbidity was observed twice daily. Histopathology, hematology, body weight, organ weight, sperm morphology, and vaginal cytology were also evaluated. No mortality or clinical signs related to ADA exposure were observed. Lung weights of male and female rats were increased (111% of control) only at the 50-mg/m^3 exposure level. In addition, males and females exposed to 50 mg/m^3 ADA had enlarged bronchial and mediastinal lymph nodes at gross necropsy. Histopathological examination of these nodes suggested moderate-to-severe lymphoid hyperplasia. Both male and female rats in the 50-mg/m^3 exposure group showed lung lesions that consisted of perivascular cuffing with lymphocytes and a multifocal type II cell hyperplasia that was associated with a moderate number of mixed inflammatory cells. The study authors suggested a possible immune reaction to an antigen in the lung. However, no exposure-related lesions were observed microscopically in rats exposed to 100 or 204 mg/m^3 ADA; therefore, the pulmonary effects observed at 50 mg/m^3 may not be related to exposure. The study authors reported no exposure-related alterations in blood parameters and no significant changes in the amounts of examined urinary enzymes. Further, neither effects in right caudal weight, right epididymal weight, right testicular weight, sperm motility, sperm account per gram caudal tissue, or incidence of abnormal sperm nor apparent effects on estrual cyclicity or on estrous cycle length were observed.

In second study group, 10 female and 10 male F344 rats were exposed to the same levels of ADA as the basic study group mentioned above. Acetylcholinesterase activity in whole blood and T3 and T4 levels in serum were determined at the end of this 13-week study. While no significant difference in acetylcholinesterase activities was observed compared to controls, T3 and T4 levels were significantly increased approximately 50% and 40%, respectively, relative to controls at the highest exposure level in male rats. Therefore, a NOAEL of 100 mg/m^3 (HEC = 60.6 mg/m^3) and a LOAEL of 204 mg/m^3 (HEC = 121 mg/m^3) were identified from the Medinsky et al. (1990) study based on significantly increased T3 and T4 levels in the highest male exposure group.

Medinsky et al. (1990) also conducted a 13-week inhalation study in B6C3F$_1$ mice. The experimental design (including number of animals, study duration, target concentrations, and endpoints [including T3 and T4 measurements] examined) was the same as the 13-week F344 rat study describe above. The mean terminal body weights in male mice were statistically significantly depressed by 7% and 9% relative to controls at the 100-mg/m^3 (HEC = 99.4 mg/m^3) and 204-mg/m^3 (HEC = 202 mg/m^3) exposure levels, respectively. For female mice, the terminal body weights were statistically significantly decreased by 6% at the highest concentration (204 mg/m^3; HEC = 196 mg/m^3). However, all these changes were less than 10% compared to the control; therefore, the decreased body weight is not considered a biologically significant effect. No additional effects were observed. Therefore, a NOAEL of 204 mg/m^3 (HEC = 196 mg/m^3; highest concentration tested) is identified (based on the extrarespiratory RDDR). The data preclude establishing a LOAEL.

Gerlach et al. (1989)

In a peer-reviewed study by Gerlach et al. (1989), groups of male Hartley strain guinea pigs were exposed by inhalation to aerosolized ADA at 0, 51, or 200 mg/m^3, 6 hours/day, 5 days/week for 4 consecutive weeks. The HECs are 0, 14.4, and 52.8 mg/m^3 (based on the extrarespiratory RDDR). One group (10 animals per concentration) was tested for specific airway sensitization to ADA before and 3 days after the 4-week ADA exposure. The other group

was tested for nonspecific airway sensitization by inhalation challenge with aerosolized histamine before and after the 4-week ADA exposure. Body, lung, liver, kidney, and thymus weights were recorded after sacrifice. A skin test for immunological response was also conducted. Histopathological examination was performed in the nasal cavity, larynx, trachea, lungs, tracheobronchial and popliteal lymph nodes, and skin test site. No significant effects were reported. Due to a lack of effects at concentrations up to 200 mg/m^3 (HEC = 52.8 mg/m^3), a NOAEL of 200 mg/m^3 (HEC = 52.8 mg/m^3) was identified (based on the extrarespiratory RDDR) for this study.

OTHER DATA

Several studies examining the mutagenic and genotoxic potential of ADA were identified. Data on the mutagenicity of ADA are mixed. In vitro studies have found that ADA is mutagenic with and without metabolic activation in bacteria (Mortelmans et al., 1986; Pharmakon Research International, 1984a). However, in vitro assays in mammalian cell systems, including gene mutation assays in Chinese hamster ovary cells and mouse lymphoma cells, were negative (Pharmakon Research International, 1984b). In addition, a sex-linked recessive lethal assay (Yoon et al., 1985) was negative for mutagenicity. Pharmakon Research International (1984c) and (Hachiya, 1987) also completed intraperitoneal (i.p.) in vivo bone marrow micronucleus assays in mice (0 or 150 mg/kg-day) which were negative for genotoxicity. Another in vitro liver unscheduled DNA synthesis assay indicated that ADA is not genotoxic (Pharmakon Research International, 1984d).

Carcinogenicity

No carcinogenicity studies were identified.

DERIVATION OF PROVISIONAL VALUES

Tables 4 and 5 present summaries of noncancer and cancer reference values, respectively. IRIS information are indicated in the tables, if available.

Table 4. Summary of Noncancer Reference Values for ADA (CASRN 123-77-3)

Toxicity Type (units)	Species/Sex	Critical Effect	p-Reference Value	POD Method	$POD_{HED/HEC}$	UF_C	Principal Study
Subchronic p-RfD (mg/kg-d)	Rat/M+F	No observed reproductive effects	1×10^{0}	NOAEL	147.5	100	Oser et al. (1965e) reproductive study
Chronic p-RfD (mg/kg-d)	Rat/M+F	No observed reproductive effects	1×10^{0}	NOAEL	147.5	100	Oser et al. (1965e) reproductive study
Subchronic p-RfC (mg/m^3)	Human/not provided	Respiratory effects, supported by decrements in lung function (FEV_1 and FVC)	7×10^{-6}	LOAEL	0.00689	1,000	Whitehead et al. (1987)
Chronic p-RfC (mg/m^3)	Human/not provided	Respiratory effects, supported by decrements in lung function (FEV_1 and FVC)	7×10^{-6}	LOAEL	0.00689	1,000	Whitehead et al. (1987)

Table 5. Summary of Cancer Values for ADA (CASRN 123-77-3)

Toxicity Type	Species/Sex	Tumor Type	Cancer Value	Principal Study
p-OSF	NDr			
p-IUR	NDr			

DU = data unsuitable; DUB = data unamenable to BMDS; NA = not applicable; NV = not available; ND = no data; NDr = not determined; NI = not identified; NP = not provided; NR = not reported; NR/Dr = not reported but determined from data; NS = not selected.

DERIVATION OF ORAL REFERENCE DOSES

Derivation of Subchronic Provisional RfD (Subchronic p-RfD)

The principal study selected for derivation of the chronic p-RfD is the reproductive study by Oser et al. (1965e). The database for ADA oral toxicity includes three subchronic–duration toxicity studies (IRDC, 1982a, b; Gafford et al., 1971), four chronic-duration toxicity studies (Oser et al., 1965a, b, c, d), and one reproductive toxicity study (Oser et al., 1965e). Among the subchronic-duration studies, the IRDC study (1982a) in mice identified a NOAEL of 893 mg/kg-day based on no observed effects. The IRDC study (1982b) in rats reported an FEL and renal effects at the highest dose of 1,786 mg/kg-day. The two IRDC studies (1982a, b), however, were not considered principal study candidates because the original report was unpublished and unavailable for review, and information could only be obtained from secondary sources. The subchronic-duration rat study by Gafford et al. (1971) had a LOAEL of 8,600 mg/kg-day based on decreased thyroid ^{125}I uptake. The 2-year dog chronic-duration study had a NOAEL of 136.5 mg/kg-day based on no observed effects (Oser et al., 1965c). However, the 1-year and 2-year dog chronic-duration studies (Oser et al., 1965c, d) are limited because both studies were conducted with a very small sample size (2/sex/group) and the 1-year study lacked a control group (Oser et al., 1965d). Although the subchronic-duration study by Gafford et al. (1971) showed potential thyroid effects as suggested by the decreased iodine uptake in rat thyroid at a dose of 8,600 mg/kg-day, and the IRDC (1982b) study showed an FEL and kidney effects in rats at the highest dose of 1,786 mg/kg-day, these observations were limited due to limited endpoints examined (no histopathology evaluation in Gafford et al., 1971) or lack of toxicity information (original study was not available for review for IRDC, 1982b). Compared to the subchronic-duration studies, the 1- and 2-year rat chronic-duration studies (Oser et al., 1965a, b) had large sample sizes, longer treatment durations, and evaluated a comprehensive set of endpoints. These studies are therefore considered more reliable. The 1- and 2-year rat chronic-duration studies had NOAELs of 7,108 mg/kg-day (Oser et al., 1965b) and 533.1 mg/kg-day (Oser et al., 1965a), respectively, based on no observed effects at the highest dose tested, suggesting that the NOAEL of 7,108 mg/kg-day is protective for systemic toxicity. A NOAEL of 604.7 mg/kg-day was established based on no observed effects in the rat reproductive study by Oser et al. (1965e). This study included the examination of parental animals and three generations of offspring. While the NOAEL of 7,108 mg/kg-day from the 1-year rat study (Oser et al., 1965b) is protective for systemic toxicity, the lower reproductive NOAEL of 604.7 mg/kg-day from the rat reproductive toxicity study (Oser et al., 1965e) is selected for derivation of both subchronic and chronic p-RfDs because (1) there are no data indicating whether reproductive toxicity would be observed at doses between the reproductive NOAEL of 604.7 mg/kg-day and the systemic NOAEL of 7,108 mg/kg-day, and (2) the reproductive NOAEL is more sensitive than the systemic NOAEL, thus, it is protective for all potential reproductive and systemic toxicity.

An example calculation of the adjusted dosimetry for ADA from Oser et al. (1965) is as follows:

$$\text{Dose}_{\text{ADJ}} = \text{Dose} \times \text{Food Consumption per Day} \times (1 \div \text{Body Weight Animal}) \times (\text{Days Dosed} \div \text{Total Days})$$

Where:

Food Consumption = 0.0262 kg/day
Body Weight Animal = 0.3194 kg

$Dose_{ADJ}$ = 7,500 ppm (HADA) × 0.0262 kg/day × (1 ÷ 0.3194 kg) × (730 ÷ 730)
= 196.5 × 3.1309 kg^{-1} × 1
= 615.2 mg/kg-day (HADA)

Note: Food consumption and body weight are default values from average of five strains of female rats (Fischer, Long-Evans, Osborne-Mendel, Sprague-Dawley, and Wistar; data from Tables 3-5 and Tables 1-6 (U.S. EPA, 1988).

Conversion from HADA to ADA

Where:
Molecular wt. ADA = 116.08 g/mol
Molecular wt. HADA = 118.09 g/mol

$Dose_{ADJ}$ = 615.2 × 116.08 ÷ 118.09
= 604.7 mg/kg-day (ADA)

In *Recommended Use of Body Weight$^{3/4}$ as the Default Method in Derivation of the Oral Reference Dose* (U.S. EPA, 2011b), the Agency endorses a hierarchy of approaches to derive human equivalent oral exposures from data from laboratory animal species, with the preferred approach being physiologically based toxicokinetic modeling. Other approaches may include using some chemical-specific information, without a complete physiologically based toxicokinetic model. In lieu of chemical-specific models or data to inform the derivation of human equivalent oral exposures, EPA endorses body-weight scaling to the 3/4 power (i.e., $BW^{3/4}$) as a default to extrapolate toxicologically equivalent doses of orally administered agents from all laboratory animals to humans for the purpose of deriving an RfD under certain exposure conditions. More specifically, the use of $BW^{3/4}$ scaling for deriving an RfD is recommended when the observed effects are associated with the parent compound or a stable metabolite, but not for portal-of-entry effects or developmental end points.

A validated human PBPK model for ADA is not available for use in extrapolating doses from animals to humans. The selected NOAEL from the rat reproductive study was associated with the parent compound or a stable metabolite. Furthermore, the NOAEL is not based on portal-of-entry or developmental effects. Therefore, scaling by $BW^{3/4}$ is relevant for deriving human equivalent doses (HEDs) for these effects.

Following U.S. EPA (2011b) guidance, the POD for the rat reproductive study is converted to an HED through an application of a dosimetric adjustment factor (DAF^1) derived as follows:

$$DAF = (BW_a^{1/4} \div BW_h^{1/4})$$

[1]As described in detail in *Recommended Use of Body Weight$^{3/4}$ as the Default Method in Derivation of the Oral Reference Dose* (U.S. EPA, 2011b), rate-related processes scale across species in a manner related to both the direct ($BW^{1/1}$) and allometric scaling ($BW^{3/4}$) aspects such that $BW^{3/4} \div BW^{1/1} = BW^{-1/4}$, converted to a $DAF = BW_a^{1/4} \div BW_h^{1/4}$.

Where:
DAF = dosimetric adjustment factor
BW_a = animal body weight
BW_h = human body weight

Using a BW_a of 0.25 kg for rats and a BW_h of 70 kg for humans (U.S. EPA, 1988), the resulting DAF is 0.244. Applying this DAF to the NOAEL identified in the rat reproductive study yields a POD_{HED} as follows:

$$\begin{aligned} POD_{HED} &= NOAEL_{ADJ}\ (mg/kg\text{-}day) \times DAF \\ &= NOAEL_{ADJ}\ (mg/kg\text{-}day) \times 0.244 \\ &= 604.7\ (mg/kg\text{-}day) \times 0.244 \\ &= 147.5\ mg/kg\text{-}day \end{aligned}$$

$$\begin{aligned} \textbf{Subchronic p-RfD} &= POD_{HED} \div UF_C \\ &= 147.5\ mg/kg\text{-}day \div 100 \\ &= \mathbf{1 \times 10^0\ mg/kg\text{-}day} \end{aligned}$$

Table 6 summarizes the uncertainty factors (UFs) for the subchronic p-RfD for ADA.

Table 6. UFs for the Subchronic p-RfD for ADA

UF	Value	Justification
UF_A	3	A UF_A of 3 ($10^{0.5}$) has been applied to account for uncertainty in characterizing the toxicodynamic differences between rats and humans following oral ADA exposure. The toxicokinetic uncertainty has been accounted for by calculation of a HED through application of a DAF as outlined in the EPA's *Recommended Use of Body Weight$^{3/4}$ as the Default Method in Derivation of the Oral Reference Dose* U.S. EPA (2011b).
UF_D	3	A UF_D of 3 has been applied because there is one acceptable multi-generation reproductive toxicity study in rats (Oser et al., 1965e) in addition to subchronic- and chronic-duration studies. However, there is no acceptable developmental toxicity study via the oral route.
UF_H	10	A UF_H of 10 has been applied for inter-individual variability to account for human-to-human variability in susceptibility in the absence of quantitative information to assess the toxicokinetics and toxicodynamics of ADA in humans.
UF_L	1	A UF_L of 1 has been applied for LOAEL-to-NOAEL extrapolation because the POD is a NOAEL.
UF_S	1	A UF_S of 1 has been applied because lack of reproductive toxicity was used as the POD/critical effect and is more sensitive than effects observed in the available subchronic- and chronic-duration studies.
UF_C	100	$UF_C = UF_A \times UF_D \times UF_H \times UF_L \times UF_S$

The confidence in the subchronic p-RfD for ADA is medium as explained in Table 7 below.

Table 7. Confidence Descriptors for Subchronic p-RfD for ADA

Confidence Categories	Designation[a]	Discussion
Confidence in study	M	The study does not meet OECD Guideline 416 and OPPTS 870.3800 guidelines. For example, average weight of pups was only reported at 21 days, and the study authors did not monitor female estrous cycles or male sperm parameters (sperm motility and sperm morphology; total number of homogenization-resistant testicular spermatids and cauda epididymal sperm); however, it is a three-generation study with a suitable number of test animals and a variety of systemic parameters evaluated.
Confidence in database	M	The database lacks a developmental toxicity study.
Confidence in subchronic p-RfD[b]	M	The overall confidence in the subchronic p-RfD is medium.

[a]L = low; M = medium; H = high.
[b]The overall confidence cannot be greater than the lowest entry in the table.

Derivation of Chronic Provisional RfD (Chronic p-RfD)

The principal study selected for derivation of the chronic p-RfD is the reproductive study by Oser et al. (1965e). The database includes four chronic-duration studies in rats and dogs (Oser et al., 1965a, b, c, d). Two of the studies in rats are comprehensive studies and have NOAELs based on no observed effects at doses up to 533.1 mg/kg-day (Oser et al., 1965a) and 7,108 mg/kg-day (Oser et al., 1965b). The 1- and 2-year dog chronic-duration studies by Oser et al. (1965c, d) are limited due to small sample size (2/sex/group) and lack of a control group in the 1-year study. While the NOAEL of 7,108 is protective for systemic effects after chronic exposure, the NOAEL of 604.7 mg/kg-day based on no observed reproductive effects from the reproductive toxicity study (Oser et al., 1965e) is selected because it is more sensitive and is protective for any potential chronic and reproductive toxicity. Therefore, the same POD of 147.5 mg/kg-day (a NOAEL) used for deriving the subchronic p-RfD is used to derive the chronic p-RfD.

$$\textbf{Chronic p-RfD} = POD_{HED} \div UF_C$$
$$= 147.5 \text{ mg/kg-day} \div 100$$
$$= \mathbf{1 \times 10^0 \text{ mg/kg-day}}$$

Table 8 summarizes the UFs for the chronic p-RfD for ADA.

Table 8. UFs for the Chronic p-RfD for ADA

UF	Value	Justification
UF_A	3	A UF_A of 3 ($10^{0.5}$) has been applied to account for uncertainty in characterizing the toxicodynamic differences between rats and humans following oral ADA exposure. The toxicokinetic uncertainty has been accounted for by calculation of a HED through application of a DAF as outlined in the EPA's *Recommended Use of Body Weight$^{3/4}$ as the Default Method in Derivation of the Oral Reference Dose* U.S. EPA (2011b).
UF_D	3	A UF_D of 3 has been applied because there is one acceptable multi-generation reproductive toxicity study in rats (Oser et al., 1965e) in addition to two comprehensive chronic-duration studies. However, there is no acceptable developmental toxicity study via the oral route.
UF_H	10	A UF_H of 10 has been applied for inter-individual variability to account for human-to-human variability in susceptibility in the absence of quantitative information to assess the toxicokinetics and toxicodynamics of ADA in humans.
UF_L	1	A UF_L of 1 has been applied for LOAEL-to-NOAEL extrapolation because the POD is a NOAEL.
UF_S	1	A UF_S of 1 has been applied because lack of reproductive toxicity was used as the POD/critical effect and is more sensitive than effects observed in the available subchronic- and chronic-duration studies.
UF_C	100	$UF_C = UF_A \times UF_D \times UF_H \times UF_L \times UF_S$

The confidence in the chronic p-RfD for ADA is medium as explained in Table 9 below.

Table 9. Confidence Descriptors for Chronic p-RfD for ADA

Confidence Categories	Designation[a]	Discussion
Confidence in study	M	The study does not meet OECD Guideline 416 and OPPTS 870.3800 guidelines. For example, average weight of pups was only reported at 21 days, and the study authors did not monitor female estrous cycles or male sperm parameters (sperm motility and sperm morphology; total number of homogenization-resistant testicular spermatids and cauda epididymal sperm); however, it is a three-generation study with a suitable number of test animals and a variety of systemic parameters evaluated.
Confidence in database	M	The database lacks a developmental toxicity study.
Confidence in chronic p-RfD[b]	M	The overall confidence in the chronic p-RfD is medium.

[a]L = low; M = medium; H = high.
[b]The overall confidence cannot be greater than the lowest entry in the table.

DERIVATION OF INHALATION REFERENCE CONCENTRATIONS

Derivation of Subchronic Provisional RfC (Subchronic p-RfC)

Whitehead et al. (1987) is chosen as the principal study for the derivation of the subchronic p-RfC. The effects of inhalation exposure of humans to ADA were evaluated in seven long-term-duration studies and case reports (Kim et al., 2004; Normand et al., 1989; Whitehead et al., 1987; Ahrenholz et al., 1985; Malo et al., 1985; Slovak, 1981; Ferris et al., 1977). Kim et al. (2004), Normand et al. (1989), and Malo et al. (1985) are case studies (1−4 cases). The case study reports are of limited use because the subjects were self-reported, and the reports had no control (unexposed subjects) and dosimetry data. While Ferris et al. (1977) and Slovak (1981) provided dosimetry data, the subjects were exposed to much a higher concentration of ADA (0.25−0.75 mg/m^3 and 0.7−1.8 mg/m^3, respectively) than the Whitehead et al. (1987) study (0.00689 mg/m^3). The Ahrenholz et al. (1985) study design is problematic. For instance, in this study, the exposed subjects were actually from two different groups: one group with direct exposure (handling ADA directly), and the other group with indirect exposure (working in the same room but not handling ADA). As a result, the ADA exposure concentrations collected from indirectly exposed workers actually are much lower than the direct exposure (0.0036 mg/m^3 vs. 1.3 mg/m^3). The study authors combined indirectly and directly exposed workers in a pooled analysis of symptoms compared with unexposed workers, which resulted in uncertainty in identifying a true exposure level in the exposed worker group.

In the Whitehead et al. (1987) study, a LOAEL was identified as 0.00689 mg/m^3 (adjusted) based on respiratory effects including irritation, cough, wheezing (associated with shortness of breath), and chronic bronchitis, supported by decrements in FEV_1 and FVC in ADA-exposed injection molding workers. In the group of 17 workers given pre- and postshift pulmonary function tests, statistically significant, but modest decrements in mean FEV_1 and FVC values were reported although no consistent dose-response trend was present among exposure levels or years worked in injection molding.

Although the LOAEL of 0.00689 mg/m^3 from the Whitehead et al. (1987) study is not the lowest and most sensitive value in the human database, of all the available human studies, it is the only study considered as a candidate principal study because the study design was the most rigorous with (1) a relatively large sample size (total of 227 subjects), (2) comparison of exposed groups to unexposed controls, (3) complete exposure and health effect data, (4) reporting and measurement of other chemical exposures in the workplace, and (5) consideration and adjustment for possible confounders.

Limited subchronic-duration animal inhalation data (Medinsky et al., 1990; Gerlach et al., 1989) were available for ADA, but these studies were not selected as the principal study for derivation of the subchronic p-RfC because their identified NOAEL values (52.8 [guinea pig], 60.6 [rat], and 196 mg/m^3 [mouse]) were well above the LOAEL identified in the Whitehead et al. (1987) human study (0.00689 mg/m^3). Furthermore, adequate human data are considered the most relevant for determining the health effects of a substance to humans and should be used to establish reference values when available. Thus, the LOAEL of 0.00689 mg/m^3 from the Whitehead et al. (1987) study is identified as the POD for derivation of the subchronic p-RfC.

An example calculation of the adjusted concentration for ADA is as follows:

$$Conc_{ADJ} = Conc \times (VEho \div VEh) \times (\text{work days per week} \div 7 \text{ days})$$

Where (U.S. EPA, 1994b):

VEho (human occupational default minute volume) = 10 m^3/8 hour
VEh (human ambient minute volume) = 20 m^3/24 hour

$Conc_{ADJ}$ = 0.0193 mg/m^3 × (10 ÷ 20) × (5 ÷ 7)
= 0.00689 mg/m^3. Based on the LOAEL of 0.00689 mg/m^3 from the Whitehead et al. (1987) study as the POD, the subchronic p-RfC is derived as follows:

Subchronic p-RfC = POD ÷ UFc
= 0.00689 mg/m^3 ÷ 1,000
= **7×10^{-6} mg/m^3**

Table 10 summarizes the UFs for the subchronic p-RfC for ADA.

Table 10. UFs for the Subchronic p-RfC for ADA

UF	Value	Justification
UF_A	1	A UF_A of 1 has been applied because a human study is selected as the principal study.
UF_D	10	A UF_D of 10 has been applied because there are no acceptable two-generation reproductive toxicity or developmental toxicity studies via the inhalation route.
UF_H	10	A UF_H of 10 has been applied for inter-individual variability to account for human-to-human variability in susceptibility in the absence of quantitative information to assess the toxicokinetics and toxicodynamics of ADA in humans.
UF_L	10	A UF_L of 10 has been applied for LOAEL-to-NOAEL extrapolation because the POD is a LOAEL.
UF_S	1	A UF_S of 1 has been applied because a subchronic-duration study was selected as the principal study.
UF_C	1,000	$UF_C = UF_A \times UF_D \times UF_H \times UF_L \times UF_S$

The confidence in the subchronic p-RfC for ADA is medium as explained in Table 11 below.

Table 11. Confidence Descriptors for the Subchronic p-RfC for ADA

Confidence Categories	Designation[a]	Discussion
Confidence in study	M	Confidence in the principal study is medium. Whitehead et al. (1987) is a peer-reviewed, occupational study with individual exposure data. The critical respiratory effects were also reported in several other peer-reviewed studies (Kim et al., 2004; Normand et al., 1989; Ahrenholz et al., 1985; Slovak, 1981). However, it is unclear if respiratory effects occurred in workers exposed below the mean personal sampling value of 0.00689 mg/m^3 (adjusted), which was identified as the LOAEL and used as the POD.
Confidence in database	M	The database contains three long-term human occupational studies that suffer from some methodological weaknesses but provide convincing data in support of the critical respiratory effects; four other human case studies provide supporting evidence. However, no developmental and reproductive toxicity studies are available.
Confidence in subchronic p-RfC[b]	M	The overall confidence in the subchronic p-RfC is medium.

[a]L = low; M = medium; H = high.
[b]The overall confidence cannot be greater than the lowest entry in the table.

Derivation of Chronic Provisional RfC (Chronic p-RfC)

Whitehead et al. (1987) is chosen as the principal study for the derivation of the chronic p-RfC. The human database is discussed in the Derivation of Subchronic Provisional RfC section; please refer to this section for an explanation of principal study selection. The LOAEL (and POD) for the critical effects was identified as 0.00689 mg/m^3 after adjusting for continuous exposure. Although the principal study, Whitehead et al. (1987), does not meet the guideline definition of chronic exposure duration for humans put forth in U.S. EPA guidance (U.S. EPA, 2002), there is no need to extrapolate from subchronic to chronic exposure duration with respect to effects induced by a respiratory sensitizer. Once sensitized, longer exposure-duration does not make any difference compared to a short-duration exposure. This also helps explain why the effect is not dose dependent but still biologically significant. As a result, the chronic p-RfC has a UF_S of 1 (see Table 12). When combined with the other uncertainty factors, the UF_C is 1,000.

Based on the LOAEL of 0.00689 mg/m^3 from the Whitehead et al. (1987) study as the POD, the subchronic p-RfC is derived as follows:

$$\begin{aligned} \textbf{Chronic p-RfC} &= \text{POD} \div UF_C \\ &= 0.00689 \div 1{,}000 \\ &= \mathbf{7 \times 10^{-6}\ mg/m^3} \end{aligned}$$

Table 12 summarizes the UFs for the chronic p-RfC for ADA. The confidence in the subchronic p-RfC for ADA is medium as explained in Table 13 below.

Table 12. UFs for Screening Chronic p-RfC for ADA

UF	Value	Justification
UF_A	1	A UF_A of 1 has been applied because a human study is selected as the principal study.
UF_D	10	A UF_D of 10 has been applied because there are no acceptable two-generation reproductive toxicity or developmental toxicity studies via the inhalation route.
UF_H	10	A UF_H of 10 has been applied for inter-individual variability to account for human-to-human variability in susceptibility in the absence of quantitative information to assess the toxicokinetics and toxicodynamics of ADA in humans.
UF_L	10	A UF_L of 10 has been applied for LOAEL-to-NOAEL extrapolation because the POD is a LOAEL.
UF_S	1	A UF_S of 1 has been applied for using data from a subchronic-duration human study because with respect to respiratory sensitization, there is no need to extrapolate from subchronic- to chronic-duration exposure.
UF_C	1,000	$UF_C = UF_A \times UF_D \times UF_H \times UF_L \times UF_S$

Table 13. Confidence Descriptors for the Chronic p-RfC for ADA

Confidence Categories	Designation[a]	Discussion
Confidence in study	M	Confidence in the key study is medium. Whitehead et al. (1987) is a peer-reviewed, occupational study with individual exposure data. The critical effects of respiratory effects were also reported in several other peer-reviewed studies (Kim et al., 2004; Normand et al., 1989; Ahrenholz et al., 1985; Slovak, 1981). However, it is unclear if respiratory effects occurred in workers exposed below the mean personal sampling value of 0.00689 mg/m^3 (adjusted), which was identified as the LOAEL and used as the POD.
Confidence in database	M	The database contains three long-term human occupational studies that suffer from some methodological weaknesses but provide convincing data in support of the critical effects; four other human case studies provide supporting evidence. However, no developmental and reproductive studies are available.
Confidence in chronic p-RfC[b]	M	The overall confidence in the subchronic p-RfC is medium.

[a]L = low; M = medium; H = high.
[b]The overall confidence cannot be greater than the lowest entry in the table.

CANCER WEIGHT-OF-EVIDENCE (WOE) DESCRIPTOR

A cancer WOE descriptor for ADA cannot be identified (see Table 14).

Table 14. Cancer WOE Descriptor for ADA			
Possible WOE Descriptor	**Designation**	**Route of Entry (Oral, Inhalation, or Both)**	**Comments**
"Carcinogenic to Humans"	NS	NA	No human carcinogenicity data are available.
"Likely to Be Carcinogenic to Humans"	NS	NA	No animal carcinogenicity data are available.
"Suggestive Evidence of Carcinogenic Potential"	NS	NA	No animal carcinogenicity data are available.
"Inadequate Information to Assess Carcinogenic Potential"	**Selected**	**Both**	**This descriptor is selected due to the lack of any information on the carcinogenicity of ADA.**
"Not Likely to Be Carcinogenic to Humans"	NS	NA	There are no data to indicate that ADA is not carcinogenic.

NA = not applicable; NS = not selected.

DERIVATION OF PROVISIONAL CANCER POTENCY VALUES

The lack of data on the carcinogenicity of ADA precludes the derivation of quantitative estimates for either oral (p-OSF) or inhalation (p-IUR) exposure.

APPENDIX A. PROVISIONAL SCREENING VALUES

No screening values are presented.

APPENDIX B. DATA TABLES

Table B.1. Measured ADA Exposure by Occupation in the Leon Plastics Plant in Grand Rapids, Michigan[a]

Sample Description			ADA Concentration (µg/m^3) (personal sampling)
Job Title	Workshift Hours	Duration (min)	
Injection mold operator	11−7	451	Trace
Injection mold operator	11−7	447	14
Injection mold operator	11−7	415	10
Injection mold operator	11−7	428	13
Injection mold operator	11−7	449	10
Injection mold operator	11−7	424	11
Injection mold operator	11−7	420	6
Injection mold operator	11−7	448	8
Injection mold operator	11−7	445	6
Material handler	11−7	468	12
Injection mold operator	7−3	444	26
Injection mold operator	7−3	442	22
Injection mold operator	7−3	442	24
Injection mold operator	7−3	412	34
Injection mold operator	7−3	392	27
Injection mold operator	7−3	422	36
Injection mold operator	7−3	22	48
Injection mold operator	7−3	24	57
Injection mold operator	7−3	34	368[b]
Material handler	7−3	27	752[c]
Injection mold operator	7−3	36	33
Injection mold operator	3−11	48	12
Injection mold operator	3−11	427	27
Injection mold operator	3−11	455	30
Injection mold operator	3−11	85[d]	47
Injection mold operator	3−11	455	45
Injection mold operator	3−11	452	48
Injection mold operator	3−11	434	43
Injection mold operator	3−11	437	9
Injection mold operator	3−11	452	8

Table B.1. Measured ADA Exposure by Occupation in the Leon Plastics Plant in Grand Rapids, Michigan[a]

Sample Description			ADA Concentration (µg/m^3) (personal sampling)
Job Title	**Workshift Hours**	**Duration (min)**	
Injection mold operator	3−11	447	24
Material handler	3−11	436	57

[a]NIOSH (1985).
[b]Work station was located across from the resin mixing area.
[c]Worker mixed ADA with resins.
[d]Sample was terminated early due to the employee's refusal to continue wearing sampling pump.

Table B.2. Symptoms Reported After Occupational Exposure to ADA in Current Departments Versus Former Departments[a]

Symptom	% of Current Other Department Workers Reporting Symptom (*n* = 93)	% of Current Injection Mold Workers Reporting Symptom (*n* = 110)	Odds Ratio (*p*-value) Reported for Current Department	Odds Ratio (*p*-value) Reported for Former Departments[b]
Irritation[c]	34.4	48.2	1.77 (0.04)	5.25 (<0.0001)
Cough	31.2	47.3	1.98 (0.02)	2.83 (0.03)
Wheezing[d]	14.0	30.9	2.75 (0.004)	2.96 (0.06)
Shortness of breath[e]	20.4	20.0	0.97 (0.99)	2.87 (0.03)
Chest tightness[f]	15.1	16.4	1.11 (0.80)	1.45 (0.55)
Headache	35.5	50.0	1.82 (0.04)	2.88 (0.02)
Skin rash	18.3	23.6	1.38 (0.35)	1.34 (0.59)

[a]Whitehead et al. (1987).
[b]Excludes current department.
[c]Question asked "Did you have irritation or burning of the eyes, nose, or throat at least once per month while working in (department name)?"
[d]Questions asked about "wheezing or whistling sound in your chest apart from colds."
[e]Questions asked about "shortness of breath, difficulty catching your breath, or a smothering feeling."
[f]Questions asked about "chest tightness or a sensation of a band around the chest."

Table B.3. Symptoms Reported by Presence or Absence of Potentially Significant Exposure to ADA in Injection Molding[a,b]

Symptom	% Reporting, Unexposed (*n* = 34)	% Reporting, Exposed (*n* = 136)	Odds Ratio (*p*-value)
ATS symptoms[c]			
Wheezing associated with:			
Shortness of breath	2.9	19.1	7.80 (0.01)
Wheeze most days	11.8	19.1	1.77 (0.27)
Chronic bronchitis[d]	11.8	31.6	3.47 (0.02)
Grade 2+ dypsnea[e]	5.9	12.5	2.29 (0.27)
Symptoms reported while working in injection molding			
Irritation	38.2	47.8	1.48 (0.21)
Cough	32.4	41.9	1.51 (0.31)
Wheezing	2.9	33.1	16.32 (0.0001)
Shortness of breath	17.6	20.6	1.21 (0.70)
Chest tightness	2.9	16.9	6.72 (0.02)
Headache	35.3	43.4	1.40 (0.25)
Skin rash	17.6	19.9	1.16 (0.49)

[a]Whitehead et al. (1987).
[b]"Potentially significant exposure to ADA" defined as persons who worked in injection molding for 1 day or longer during the period from January 1, 1980, through 4 mo before the interview date.
[c]ATS = American Thoracic Society; standard set of questions.
[d]Cough or phlegm on most days for 3 mo of yr for 2 or more yr.
[e]Answered "yes" to "have to walk slower than other people of your age on level ground because of shortness of breath."

Table B.4. Measured ADA Exposure by Occupation in an Armstrong World Industries Floor Plant in Lancaster, Pennsylvania[a,b]

Sample Description		ADA Concentration (mg/m^3)	
Job Title	**Duration (min)**	**Indirect Exposure[c]**	**Direct Exposure[c]**
Exposed workers (individual measures)			
Leader	346	0.01	ND
Helper	344	0.02	ND
Grinder	32	ND	3.8
	308	0.03	ND
Leader	396	BD	ND
Helper	419	Trace	ND
Grinder	56	ND	12
	354	BD	ND
Grinder	406	Trace	ND
Grinder	305	BD	ND
Helper	311	BD	ND
Leader	304	0.02	ND
Grinder	53	ND	0.15
	257	0.02	ND
Leader	354	0.01	ND
Helper	27	ND	4.8
	391	0.02	ND
Leader	397	0.01	ND
Helper	401	0.04	ND
	31	ND	4.8
	373	0.10	ND
Leader	388	Trace	ND
Helper	385	Trace	ND
	11	ND	0.59
	353	Trace	ND
Leader	418	BD	ND
Helper	415	BD	ND
	7	ND	0.63
	409	Trace	ND
Leader	426	Trace	ND
Helper	414	BD	ND
	21	ND	1.6
	330	0.03	ND

Table B.4. Measured ADA Exposure by Occupation in an Armstrong World Industries Floor Plant in Lancaster, Pennsylvania[a,b]

Sample Description		ADA Concentration (mg/m^3)	
Job Title	**Duration (min)**	**Indirect Exposure[c]**	**Direct Exposure[c]**
Unexposed workers (coating and fusion department; individual measures)			
Coater operator	423	BD	ND
Roll-up operator	430	Trace	ND
Unroll operator	415	Trace	ND
Roll-up operator	421	BD	ND
Line Operator	380	Trace	ND
Laborer	368	BD	ND
Roll-up operator	363	BD	ND
Leader	369	BD	ND
Coater operator	414	BD	ND
Coater operator	403	BD	ND
Unroll operator	401	BD	ND
Roll-up operator	397	BD	ND

[a]Ahrenholz et al. (1985).
[b]Two workers who had combined indirect and direct exposure are not included in this table.
[c]Direct exposure: short-term exposure while handling the compound; indirect exposure: full-shift worker, working in the vicinity where ADA was used.

BD = below detection level; ND = no data.

Table B.5. Symptom Observations and Risk Calculations After Occupational Exposure to ADA[a]

Observations	Exposure Group	
	Ever Exposed[b]	Never Exposed
Number of participants examined	30	16
Number (%) of participants with lower respiratory tract symptoms	18 (60)	1 (6)
Risk ratio for lower respiratory tract symptoms	10*	1
Number (%) of participants with upper respiratory tract/eye symptoms	26 (87)	5 (31)
Risk ratio for upper respiratory tract/eye symptoms	2.8**	1

[a]Ahrenholz et al. (1985).
[b]The ever-exposed group included workers both directly and indirectly exposed to ADA.

*p = 0.0004.
**p = 0.0001.

Table B.6. ^{125}I Uptake, Relative Thyroid Weight, Body Weight, and Protein-Bound Iodine of Male Sprague-Dawley Rats After Dietary Exposure to ADA for 4 Weeks[a]

Parameter[c]	Exposure Group, % Diet (Adjusted Daily Dose, ADD, mg/kg-d)[b]	
	0 (0)	10 (8,600)
Sample size	12	11
^{125}I Uptake[d]	42.42 ± 3.86	31.59 ± 8.37 (74%)***
Relative thyroid weight (g per 100 g body weight)	14.8 ± 2.3	13.6 ± 1.9 (92%)
Mean total body weight on last day of experiment (g)	214 ± 17	200 ± 17 (93%)

[a]Gafford et al. (1971).
[b]Calculated by reviewers using the average body weight provided in the study.
[c]Values expressed as mean ± SD (% of control); % was calculated.
[d]24-hr thyroidal ^{125}I uptake (%) ± SD.

***Statistically significant relative to controls, $p < 0.001$.

Table B.7. Mean Reproduction and Lactation Data for Three-Generation Reproductive Toxicity Study of ADA[a]

Parameter[b]	Dose Group (mg/kg-d, adjusted)					
	0 ppm (0) HADA	750 ppm (60.5) HADA	2,370 ppm (191.1) HADA	7,500 ppm (604.7) HADA	0 ppm (0) ADA	100 ppm (8) ADA
F0 generation						
Average # pups						
At birth	8.3	7.8 (94)	9.2 (111)	9.7 (117)	8.8	8.7 (99)
At weaning	6.5	6.8 (105)	7.8 (120)	7.6 (117)	8.0	7.5 (94)
Average pup weight at 21 d	49.5	47.3 (96)	50.2 (101)	50.8 (103)	44.5	44.3 (100)
Fertility index[c]	57	64 (112)	72 (126)	40 (70)	88	80 (91)
Gestation index[d]	100	100 (100)	100 (100)	100 (100)	96	94 (98)
Viability index[e]	68	70 (103)	67 (99)	84 (124)	84	86 (102)
Lactation index[f]	89	89 (100)	85 (96)	88 (99)	84	85 (101)
F1 generation						
Average # pups						
At birth	9.5	9.9 (105)	9.8 (103)	9.7 (102)	10.0	10.1 (101)
At weaning	7.2	7.9 (110)	8.6 (119)	8.3 (115)	8.2	8.3 (101)
Average pup weight at 21 d	45.0	49.0 (109)	44.0 (98)	46.7 (104)	46.3	47.7 (103)
Fertility index[c]	95	90 (95)	70 (74)	85 (89)	90	65 (72)
Gestation index[d]	95	94 (99)	100 (105)	100 (105)	100	100 (100)
Viability index[e]	62	80 (129)	83 (134)	82 (132)	80	73 (91)
Lactation index[f]	88	95 (108)	96 (109)	92 (105)	91	96 (105)
F2 generation						
Average # pups						
At birth	9.3	8.4 (90)	7.8 (84)	9.1 (98)	9.4	9.5 (101)
At weaning	6.6	6.0 (91)	6.7 (102)	7.9 (120)	8.0	7.9 (99)
Average pup weight at 21 d	47.1	47.4 (101)	46.4 (99)	45.5 (97)	44.2	40.0 (90)
Fertility index[c]	90	80 (89)	95 (106)	90 (100)	95	90 (95)
Gestation index[d]	100	94 (94)	100 (100)	100 (100)	100	95 (95)
Viability index[e]	60	60 (100)	72 (120)	82 (137)	84	85 (101)
Lactation index[f]	93	99 (106)	99 (106)	99 (106)	96	98 (102)

[a]Oser et al. (1965).
[b]Parameters presented as mean (% of controls); based on 50 matings per group in F0 and 20 matings per group in F1 and F2.
[c]Pregnancies ÷ matings × 100 (%).
[d]Litters born ÷ pregnancies × 100 (%).
[e]Pups surviving at 4 d ÷ pups born × 100 (%).
[f]Pups weaned ÷ pups at 4 d × 100 (%).

HADA = biurea, metabolite of ADA parent compound.

APPENDIX C. BMD OUTPUTS

BMDS was not run on any of the studies in the database because data were unsuitable.

APPENDIX D. REFERENCES

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