

SCREENING-LEVEL HAZARD CHARACTERIZATION

SPONSORED CHEMICAL

Ethylene Glycol Diacetate (CASRN 111-55-7)

SUPPORTING CHEMICAL

Ethylene glycol (CASRN 107-21-1)

The High Production Volume (HPV) Challenge Program¹ was conceived as a voluntary initiative aimed at developing and making publicly available screening-level health and environmental effects information on chemicals manufactured in or imported into the United States in quantities greater than one million pounds per year. In the Challenge Program, producers and importers of HPV chemicals voluntarily sponsored chemicals; sponsorship entailed the identification and initial assessment of the adequacy of existing toxicity data/information, conducting new testing if adequate data did not exist, and making both new and existing data and information available to the public. Each complete data submission contains data on 18 internationally agreed to “SIDS” (Screening Information Data Set^{1,2}) endpoints that are screening-level indicators of potential hazards (toxicity) for humans or the environment.

The Environmental Protection Agency’s Office of Pollution Prevention and Toxics (OPPT) is evaluating the data submitted in the HPV Challenge Program on approximately 1400 sponsored chemicals by developing hazard characterizations (HCs). These HCs consist of an evaluation of the quality and completeness of the data set provided in the Challenge Program submissions. They are not intended to be definitive statements regarding the possibility of unreasonable risk of injury to health or the environment.

The evaluation is performed according to established EPA guidance^{2,3} and is based primarily on hazard data provided by sponsors; however, in preparing the hazard characterization, EPA considered its own comments and public comments on the original submission as well as the sponsor’s responses to comments and revisions made to the submission. In order to determine whether any new hazard information was developed since the time of the HPV submission, a search of the following databases was made from one year prior to the date of the HPV Challenge submission to the present: (ChemID to locate available data sources including Medline/PubMed, Toxline, HSDB, IRIS, NTP, ATSDR, IARC, EXTOXNET, EPA SRS, etc.), STN/CAS online databases (Registry file for locators, ChemAbs for toxicology data, RTECS, Merck, etc.) and Science Direct. OPPT’s focus on these specific sources is based on their being of high quality, highly relevant to hazard characterization, and publicly available.

OPPT does not develop HCs for those HPV chemicals which have already been assessed internationally through the HPV program of the Organization for Economic Cooperation and Development (OECD) and for which Screening Initial Data Set (SIDS) Initial Assessment

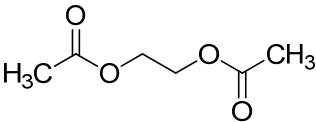
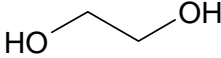
¹ U.S. EPA. High Production Volume (HPV) Challenge Program; <http://www.epa.gov/chemrtk/index.htm>.

² U.S. EPA. HPV Challenge Program – Information Sources; <http://www.epa.gov/chemrtk/pubs/general/guidocs.htm>.

³ U.S. EPA. Risk Assessment Guidelines; <http://cfpub.epa.gov/ncea/raf/rafguid.cfm>.

Reports (SIAR) and SIDS Initial Assessment Profiles (SIAP) are available. These documents are presented in an international forum that involves review and endorsement by governmental authorities around the world. OPPT is an active participant in these meetings and accepts these documents as reliable screening-level hazard assessments.

These hazard characterizations are technical documents intended to inform subsequent decisions and actions by OPPT. Accordingly, the documents are not written with the goal of informing the general public. However, they do provide a vehicle for public access to a concise assessment of the raw technical data on HPV chemicals and provide information previously not readily available to the public.

<p>Chemical Abstract Service Registry Number (CASRN)</p>	<p><u>Sponsored Chemical</u> CASRN 111-55-7</p> <p><u>Supporting Chemical</u> CASRN 107-21-1</p>
<p>Chemical Abstract Index Name</p>	<p><u>Sponsored Chemical</u> 1,2-Ethanediol, 1,2-diacetate</p> <p><u>Supporting Chemical</u> Ethylene glycol</p>
<p>Structural Formula</p>	<p><u>Sponsored Chemical</u></p>  <p><u>Supporting Chemical</u></p> 
<p style="text-align: center;">Summary</p> <p>CASRN 111-55-7 is a colorless liquid with high water solubility and moderate vapor pressure. It is expected to have high mobility in soil. Volatilization of CASRN 111-55-7 is considered low based on its Henry's Law constant. The rate of hydrolysis is expected to be negligible at neutral or acidic pH, but moderate under alkaline (pH 9) conditions. The rate of atmospheric photooxidation is considered slow. CASRN 111-55-7 is expected to have low persistence (P1) and low bioaccumulation potential (B1).</p> <p>The acute oral toxicity of CASRN 111-55-7 is low in rats. Repeated-dose, reproductive and developmental toxicity endpoints are addressed using data for the supporting chemical, ethylene glycol, CASRN 107-21-1. Repeated oral exposure of CASRN 107-21-1 to rats and/or mice for periods of 13 weeks to two years primarily showed renal effects. Following a 16-week dietary exposure, the NOAEL for systemic toxicity in rats is 71 mg/kg-day with a LOAEL of 180 mg/kg-day. The NOAEL for systemic toxicity in rats after 24-month dietary exposure is 200 mg/kg-day with a LOAEL of 1000 mg/kg-day (highest dose tested). For mice, following a 13-week dietary exposure, the lowest NOAEL for systemic toxicity is 600 to 1000 mg/kg-day with a LOAEL of 1200 to 2000 mg/kg-day. The NOAEL for systemic toxicity in mice after 24-month dietary exposure is 1500 mg/kg-day with a LOAEL of 3000 mg/kg-day. In a two-generation reproductive toxicity drinking water study in mice with CASRN 107-21-1, a decrease in the number of litters and decreased pup weights were seen at 1640 mg/kg-day; the NOAEL for reproductive toxicity is 840 mg/kg-day. Developmental effects were observed following oral or dermal exposures to pregnant mice and rats to the supporting chemical, CASRN 107-21-1. For mice, decreased body weights were seen in the dams at 1500 mg/kg-day following oral (gavage) exposure; the NOAEL for maternal toxicity is 750 mg/kg-day. Treatment-related signs of developmental toxicity (skeletal malformations) were seen in this study at the lowest dose tested,</p>	

750 mg/kg-day; the NOAEL for developmental toxicity is not established. For rats, signs of maternal and developmental toxicity were observed following oral (gavage) exposures at the lowest dose tested, 1250 mg/kg-day, based on decreases in body weights in the dams and dose related skeletal malformations in offspring; the NOAELs for maternal and developmental toxicity are not established. For rabbits, mortality was observed in the dams at 2000 mg/kg-day following oral (gavage) exposure; the NOAEL for maternal toxicity is 1000 mg/kg-day. No signs of developmental toxicity were observed at any doses; the NOAEL for developmental toxicity is 2000 mg/kg-day (highest dose tested). Following dermal exposure in mice, renal lesions and increased corrected gestational body weight changes were observed in the dams at 3500 mg/kg-day; the NOAEL for maternal toxicity is 1700 mg/kg-day. Delays in skeletal ossification were observed in offspring at 3500 mg/kg-day; the NOAEL for developmental toxicity is 1700 mg/kg-day. CASRN 111-55-7 did not induce gene mutations in bacteria or chromosomal aberrations in mammalian cells *in vitro*.

The 96-h LC₅₀ for fish for CASRN 111-55-7 is 40.5 mg/L. The 48-h EC₅₀ for aquatic invertebrates for CASRN 111-55-7 is >116.3 mg/L and the 72-h EC₅₀ for aquatic plants for CASRN 111-55-7 is >120 mg/L for both biomass and growth rate.

The sponsor, Eastman Chemical Company, submitted a Test Plan and Robust Summaries to EPA for ethylene glycol diacetate (CASRN 111-55-7; CA Index name: 1,2-ethanediol, 1,2-diacetate) on May 1, 2002. EPA posted the submission on the ChemRTK HPV Challenge website on May 31, 2002 (<http://www.epa.gov/oppt/chemrtk/pubs/summaries/etglydat/c13736tc.htm>). EPA comments on the original submission were posted to the website on September 25, 2002. Public comments were also received and posted to the website. The sponsor submitted updated/revised documents on October 3, 2002, which were posted to the ChemRTK website on November 13, 2002.

Justification for Supporting Chemical

The sponsor provided data for ethylene glycol (EG, CASRN 107-21-1) as a supporting chemical. The toxicity of the sponsored chemical, ethylene glycol diacetate (EGD, CASRN 111-57-7), to mammalian species is strongly believed to be a result of the metabolic conversion to EG by cleavage of the ester bonds through the action of various esterase enzymes that are located throughout the body, including the mucosal surfaces of the respiratory tract. Although there are no pharmacokinetic data detailing the actual rates at which EGD metabolizes into ethylene glycol, there are data available on several other similar compounds formed by ester linkages. These data demonstrate that the ester bond between an acetic acid and an alcohol is readily and rapidly cleaved and that the primary driver for systemic toxicity is the parent alcohol/glycol (the formation of the acetate ion often leads to irritation in nasal epithelial tissues under conditions of respiratory exposure). Examples of such molecules include methyl acetate, ethyl acetate and butyl acetate, whose toxicity following exposure is well recognized as being due to the metabolic formation of the respective alcohol. Studies found in the literature have also demonstrated the formation of oxalic acid (a known EG metabolite) following exposure to ethylene glycol-monoacetate. Since EGD is structurally similar to these aforementioned molecules, it is scientifically plausible to assume it will also be metabolized to ethylene glycol. In addition, similar renal lesions in rats were observed following repeated exposures to EGD and EG, indicating conversion of EGD to EG. In conclusion, although much of the evidence for the metabolic conversion of EGD to EG is somewhat circumstantial in nature, it is still believed to be of sufficient strength to support a conclusion that data from EG can be used for some mammalian toxicity endpoints in lieu of information on EGD. For this hazard characterization, the data from EG are used to address reproductive and developmental toxicity for EGD. Furthermore, while data from repeated-dose toxicity studies are available on EGD; however, their robustness is limited. Therefore, the repeated-dose toxicity endpoint is also addressed using data for EG.

The sponsor provided ecotoxicity data for all three endpoints on the sponsored chemical, CASRN 111-57-7; therefore data for the supporting chemical are not used for environmental effects endpoints.

An OECD SIDS Initial Assessment Report on the ethylene glycol category (includes CASRN 107-21-1) was prepared for evaluation at SIAM 18 in 2004 and is available at: <http://webnet.oecd.org/hpv/ui/Search.aspx>.

1. Chemical Identity

1.1 Identification and Purity

Purity of CASRN 111-55-7 where indicated in the revised Robust Summaries is > 99%.

1.2 Physical-Chemical Properties

The physical-chemical properties of CASRN 111-55-7 are summarized in Table 1.

CASRN 111-55-7 is a colorless liquid with high water solubility and moderate vapor pressure.

Property	Value
CASRN	111-55-7
Molecular Weight	146.14
Physical State	Liquid, colorless
Melting Point	-31°C (measured)
Boiling Point	190–191 °C at 760 mmHg (measured)
Vapor Pressure	0.0774 mm Hg at 25°C (measured)
Water Solubility	178,000 mg/L at 25°C (measured)
Dissociation Constant (pK _a)	Not applicable
Henry's Law Constant	8.4×10 ⁻⁸ atm·m ³ /mole (estimated) ²
Log K _{ow}	0.10–0.38 (measured)

¹ Eastman Chemical Company. 2002. Revised Robust Summary and Test Plan for Ethylene Glycol Diacetate. Available online at <http://www.epa.gov/chemrtk/pubs/summaries/etglydat/c13736tc.htm> as of June 9, 2010.

² U.S. EPA. 2010. Estimation Programs Interface Suite™ for Microsoft® Windows, v4.00. U.S. Environmental Protection Agency, Washington, DC, USA. Available online at <http://www.epa.gov/opptintr/exposure/pubs/episuitedl.htm> as of June 9, 2010.

2. General Information on Exposure

2.1 Production Volume and Exposure

CASRN 111-55-7 had an aggregated production and/or import volume in the United States between 1 and 10 million pounds during calendar year 2005.

Non-confidential information in the IUR indicated that the industrial processing and uses of the chemical include other basic organic chemical manufacturing as functional fluids; solvents which become part of product formulation or mixture; and solvents for chemical manufacture and processing and are not part of product at greater than 1% by weight. Non-confidential commercial and consumer uses of this chemical include paints and coatings; and “other.”

2.2 Environmental Exposure and Fate

The environmental fate properties of CASRN 111-55-7 are summarized in Table 2.

1,2-Ethanediol, 1,2-diacetate is expected to have high mobility in soil. 1,2-Ethanediol, 1,2-diacetate was reported as readily biodegradable in sewage inoculum using a Hach respirometric and OECD screening die-away test assumed to be referring to OECD 301F and 301A, respectively. There was no further experimental details given to support these tests with respect to OECD guidelines; however, the ester functional groups present on 1,2-ethanediol, 1,2-diacetate is likely to undergo microbial-mediated ester hydrolysis leaving readily biodegradable ethylene glycol as the hydrolysis product. The weight of evidence from these data suggest that substantial biodegradation of 1,2-ethanediol, 1,2-diacetate is likely to occur. The rate of abiotic hydrolysis is expected to be negligible at neutral or acidic pH, but moderate under alkaline (pH 9) conditions. The rate of volatilization is considered low based on its Henry's Law constant. 1,2-Ethanediol, 1,2-diacetate is expected to have low persistence (P1) and low bioaccumulation potential (B1).

Property	Value
Photodegradation Half-life	34.1 hours at 25°C (estimated) ²
Hydrolysis Half-life	Half-life = 3,310 hours at pH 4 and 25°C Half life = 549 hours at pH 7 and 25°C >50% hydrolysis in 2.5 hours at pH 9 and 25°C
Biodegradation	Readily biodegradable ³
Bioaccumulation Factor	BAF = 0.9 (estimated) ²
Log K _{oc}	1.0 (estimated) ²
Fugacity (Level III Model) ²	
Air (%)	1.3
Water (%)	33.0
Soil (%)	65.6
Sediment (%)	<0.1
Persistence ⁴	P1 (low)
Bioaccumulation ⁴	B1 (low)

¹Eastman Chemical Company. 2002. Revised Robust Summary and Test Plan for Ethylene Glycol Diacetate. Available online from at <http://www.epa.gov/chemrtk/pubs/summaries/etglydat/c13736tc.htm> as of June 9, 2010.

²U.S. EPA. 2010. Estimation Programs Interface Suite™ for Microsoft® Windows, v4.00. U.S. Environmental Protection Agency, Washington, DC, USA. Available online at <http://www.epa.gov/opptintr/exposure/pubs/episuitedl.htm> as of June 9, 2010.

³Cain, R.B. 1981. Microbiol Degradation of Surfactants and "Builder" Components. FEMS Symp. (Microb Degrad Xenobiotics Recalcitrant Compds) 12:325–70.

⁴Federal Register. 1999. Category for Persistent, Bioaccumulative, and Toxic New Chemical Substances. *Federal Register* 64, Number 213 (November 4, 1999) pp. 60194–60204.

Conclusion: 1,2-Ethanediol, 1,2-diacetate is a colorless liquid with high water solubility and moderate vapor pressure. It is expected to have high mobility in soil. Volatilization of

1,2-ethanediol, 1,2-diacetate is considered low based on its Henry's Law constant. The rate of hydrolysis is expected to be negligible at neutral or acidic pH, but moderate under alkaline (pH 9) conditions. The rate of atmospheric photooxidation is considered slow. 1,2-Ethanediol, 1,2-diacetate is expected to have low persistence (P1) and low bioaccumulation potential (B1).

3. Human Health Hazard

A summary of health effects data submitted for SIDS endpoints are provided in Table 3. The table also indicates where data for the supporting chemical are read-across (RA) to the sponsored chemical.

Acute Oral Toxicity

Male Wistar rats (10/dose) were administered CASRN 111-55-7 via gavage at unspecified dose levels. No other details were provided.

LD₅₀ = 6860 mg/kg-bw

Repeated-Dose Toxicity (CASRN 107-21-1, supporting chemical)

(1) Fischer 344 and Wistar rats (10/sex/concentration) were administered CASRN 107-21-1 via diet at 0, 150, 500, or 1000 mg/kg-day continuously for 16 weeks. In Wistar rats, at 500 and 1000 mg/kg-day, the following treatment-related effects were seen: mortality (at 1000 mg/kg-day); lower mean body weights and mean body weight changes; lower mean food consumption; higher mean water consumption; lower mean specific gravity and higher mean total urine volume; macroscopic findings of pale kidneys, presence of calculi, rough surface and dilated pelvis; higher mean absolute and relative kidney weights; and renal macroscopic findings of crystal nephropathy (with more severity than in the F344 strain). At 150 mg/kg-day, no treatment-related effects were seen. In Fischer 344 rats, at 1000 mg/kg/day, higher mean water consumption; lower mean specific gravity and higher mean total urine volume; macroscopic findings of pale kidneys, presence of calculi, rough surface and dilated pelvis; higher mean absolute and relative kidney weights; and renal macroscopic findings of crystal nephropathy. At 500 mg/kg/day, renal macroscopic findings of crystal nephropathy were seen. At 150 mg/kg-day, no treatment-related effects were seen. (SIDS Dossier, SIAM 18, 2004)

NOAEL = 150 mg/kg-day

LOAEL = 500 mg/kg-day (based on effects on kidneys)

(2) Concise International Chemical Assessment Document 45 mentioned the unpublished study (Gaunt et al. 1974) in which Wistar rats (25/sex/dose) were administered CASRN 107-21-1 in the diet for up to 16 weeks at doses of 35, 71, 180, or 715 mg/kg-day for males and 38, 85, 185, or 1128 mg/kg-day for females. Statistically significant microscopic changes in the kidney (dilation, degeneration, protein casts, deposition of calcium oxalate crystals in nephrons) were observed at the highest doses for both males (715 mg/kg-day) and females (1128 mg/kg-day). In males, severe tubular damage and heavy accumulation oxalate crystals were also seen at 180 mg/kg-day. In females, although an increased incidence of kidney damage (similar to male rats) was seen at 1128 mg/kg-day, it was not statistically significant.

NOAEL_{Males} = 71 mg/kg-day

LOAEL_{Males} = 180 mg/kg-day (based on kidney effects)

NOAEL_{Females} = 185 mg/kg-day

LOAEL_{Females} = 1128 mg/kg-day (based on kidney effects)

(3) Sprague-Dawley rats (10/sex/dose) were administered CASRN 107-21-1 in drinking water for 90-days at concentrations of 0, 0.25, 0.5, 1.0, or 2.0% for males and 0, 0.5, 1, 2, or 4.0% for females (corresponding to approximately 0, 205, 407, 947 or 3134 mg/kg-day for males and 0, 597, 1145, 3087 or 5744 mg/kg-day for females). In males, a statistically significant decrease in body weight was seen at 2% and a statistically significant increase in the relative kidney weights at 1.0 and 2.0%. In addition, a statistically significant decrease in absolute heart, liver and lung weights and a statistically significant increase in relative kidneys, brain and gonads weights were seen in males at 2%. These changes were not seen in females. There was a statistically significant decrease in leukocyte counts in females at 0.5, 2 and 4%. (No data are provided for 1%) Other observed changes in clinical pathology parameters, although statistically significant, either did not show a dose response or were not biologically significant. Statistically significant increases in both the incidence and severity of histological lesions were seen in the kidneys of males (at 1 and 2%) and females (at 2 and 4%). Significant lesions included tubular dilation, tubular degeneration, acute inflammation, and birefringent crystals in the tubules and the pelvis epithelium. (Robinson, et al., 1990)

NOAEL_{Male} = 407 mg/kg-day

LOAEL_{Male} = 947 mg/kg-day (based on signs of kidney toxicity)

NOAEL_{Female} = not established

LOAEL_{Female} = 597 mg/kg-day (decreased leukocyte count)

(4) Fischer 344 rats and B6C3F1 mice (10/sex/concentration) were administered CASRN 107-21-1 via the diet continuously for 13 weeks at 0 (control), 0.32, 0.63, 1.25, 2.5 and 5.0% (approximate conversion—0, 160, 315, 625, 1250, 2500 mg/kg-day). Effects in rats at 2.5 and 5.0% included increases in relative kidney weights in males and females, and increases in serum urea nitrogen and serum creatinine levels in males. Toxic nephrosis and oxalate crystal deposits in renal tubules were observed in male rats at 2.5 and 5.0%. Crystals were also observed in brains of male rats in the 5.0% dose group. Nephrosis was the only lesion observed in female rats at 5.0%. Effects in mice included mild, compound-related lesions in the kidneys (nephrosis) and livers (centrilobular degeneration) of male mice in the 2.5 and 5.0% dose groups. Relative kidney weights were decreased in females. There were no other adverse effects

observed in female mice. (Melnick, 1984) The SIDS document presented only the approximate NOAEL and LOAEL values as they are listed below.

NOAEL_{Rat} ~ 600-1000 mg/kg-day

LOAEL_{Rat} ~ 1200-2000 mg/kg-day (based on kidney toxicity)

NOAEL_{Mice} ~ 600-1000 mg/kg-day

LOAEL_{Mice} ~ 1200-2000 mg/kg-day (based on mild lesions in the kidney and liver)

(5) In a National Toxicology Program (NTP) study, B6C3F1 mice (10 /sex/concentration) were administered CASRN 107-21-1 in the diet at 0, 3200, 6300, 12,500, 25,000 or 50,000 ppm (approximately 0, 750, 1500, 3000, 6000 or 12,000 mg/kg-day) for 13 weeks. All mice survived to the end of the study. Final mean body weights of treated male and female mice and food consumption of treated males were similar to those of the controls. Feed consumption of treated females was significantly greater at the two high doses than that of controls. Absolute and relative organ weights of mice administered CASRN 107-21-1 were generally similar to those of controls throughout the study. Treatment-related histopathological lesions were noted only in the kidneys and livers of male mice that received 25,000 or 50,000 ppm. Liver lesions included hyaline degeneration in the in the centri-lobular hepatocytes consisting of cytoplasmic accumulations of nonbirefringent eosinophilic (hyaline), globular, or crystalline material. Nephropathy was characterized by tubule dilatation, cytoplasmic vacuolation, or regenerative hyperplasia of tubule epithelial cells. These changes were of minimal to mild severity. In females, no treatment-related lesions were seen in any organ. (NTP, 1993)

NOAEL ~ 3000 mg/kg-day

LOAEL ~ 6000 mg/kg-day (based on kidney and liver lesions)

(6) Fischer 344 rats (130/sex/concentration) were administered CASRN 107-21-1 via the diet at 0, 40, 200 or 1000 mg/kg-day for 24 months. At 1000 mg/kg-day, males showed increases in neutrophils, blood urea nitrogen, serum creatinine, urine volume, urine calcium oxalate crystals, water consumption rates, kidney weight (absolute and relative), mortality, mineralization of the heart, lungs, stomach, vas deferens; and urinary system pathological changes (tubular cell hyperplasia, tubular dilation, peritubular nephritis); and decreases red blood cells, hematocrit, hemoglobin, serum glutamic pyruvic transaminase, mean corpuscular volume, urine specific gravity, urine pH, liver weight (absolute and relative), body weight gain, and life span. At 1000 mg/kg-day, females showed increases in mean corpuscular volume, urine specific gravity, urine calcium oxalate crystals, urine uric acid crystals, and kidney weight (absolute and relative); and decreases in mean corpuscular hemoglobin concentration, urine pH, and urine volume. No other treatment-related effects were seen. (Union Carbide, 1982)

NOAEL = 200 mg/kg-day

LOAEL = 1000 mg/kg-day (based on possible signs of blood and kidney toxicity mainly on the effects on urinary system)

(7) In an NTP study, B6C3F1 mice (60 /sex/concentration) were administered CASRN 107-21-1 in the diet for 103 weeks at concentrations of 0, 6250, 12,500, 25,000 ppm for males (approximately 0, 1500, 3000 or 6000 mg/kg-day) and 0, 12,500, 25,000 or 50,000 ppm for females (approximately 0, 3000, 6000 or 12,000 mg/kg-day). At the end of the study, survival rates of male and female mice exposed to CASRN 107-21-1 were similar to those of controls. Mean body weights and food consumption of exposed male and female groups were also similar to those of controls. No clinical findings associated with the administration of CASRN 107-21-1 were observed. Hepatocellular hyaline degeneration was seen in male mice at the mid- and high-

concentrations, and in female mice at the high-concentration. Pulmonary arterial medial hyperplasia was observed at an increased incidence in exposed females at mid and high concentrations, but not in exposed males. Nephropathy was not observed in males or females in any treatment group. Small numbers of oxalate-like crystals, calculi, or both, were noted in renal tubules, urethrae, and/or urinary bladders in a few male mice at the highest concentration. (NTP, 1993)

NOAEL_{Males} = 1500 mg/kg-day

LOAEL_{Males} = 3000 mg/kg-day (based on liver lesions and kidney toxicity in males)

LOAEL_{Females} = 3000 mg/kg-day

LOAEL_{Females} = 6000 mg/kg-day (based on arterial hyperplasia)

Reproductive Toxicity (CASRN 107-21-1, supporting chemical)

In a continuous breeding study, CD-1 mice (20/sex/concentration, control—40/sex) were administered CASRN 107-21-1 via the drinking water at 0, 0.25, 0.5 or 1% (approximately, 0, 410, 840 or 1640 mg/kg-day) continuously for two-generations. Treatment at 1% or less did not result in significant effects on clinical signs of toxicity or survival of the P (parental) generation. Two deaths occurred at 0.5% that, according to the study authors may be related to oxalate crystal deposition in the kidney. Small, but statistically significant effects on the numbers of litters per fertile pair, the number of live pups per litter, and live pup weight were observed at 1%. No significant effects were reported at 0.25 or 0.5% concentrations. The number of live pups per litter in both the F1 and F2 generations was lower in the treated groups, but the differences were not dose-related or statistically significant. Unusual facial features (i.e., shorter snout and wide-set eye) and skeletal defects (shortened frontal, nasal, and parietal bones; fused ribs abnormally shaped or missing sternebrae, abnormally shaped vertebrae; and twisting of the spine) were noted in some of the offspring of the treated mice at the high dose, but not in the controls. The offspring at 0.25 or 0.5% were not significantly affected. No information on dose-response is provided. (SIDS Dossier, SIAM 18, 2004)

NOAEL (systemic toxicity) = 1640 mg/kg-day (based on no effects at the highest dose tested)

NOAEL (reproductive toxicity) = 840 mg/kg-day

LOAEL (reproductive toxicity) = 1640 mg/kg-day (based on decreases in the numbers of litters, number of live pups, and pup weight)

NOAEL (offspring toxicity) = 840 mg/kg-day

LOAEL (offspring toxicity) = 1640 mg/kg-day (based on skeletal malformations)

Developmental Toxicity (CASRN 107-21-1, supporting chemical)

(1) Pregnant CD-1 mice (30/dose) were administered CASRN 107-21-1 via gavage at 0, 50, 150, 500 or 1500 mg/kg-day during gestation days 6-15. There was no apparent treatment-related maternal toxicity. Developmental effects observed at 1500 mg/kg-day included reduced body weights, fused ribs and arches, poor ossification in thoracic and lumbar centra, and statistically significantly ($p < 0.01$) increased occurrence of an extra 14th rib. At 500 mg/kg-day, slight reductions in fetal body weight and increased incidences of extra ribs were observed. The authors describe a NOEL as 500 mg/kg-day. IPCS (2001) agrees that the effects at 500 mg/kg-day are not adverse, and accepts 500 mg/kg-day as the NOAEL. (SIDS Dossier, SIAM 18, 2004)

NOAEL (maternal toxicity) = 1500 mg/kg-day (based on no effects at the highest dose tested)

NOAEL (developmental toxicity) = 500 mg/kg-day

LOAEL (developmental toxicity) = 1500 mg/kg-day (based on decreased body weight and skeletal malformations)

(2) Pregnant CD-1 mice (28-29/dose) were administered CASRN 107-21-1 via gavage at 0, 750, 1500, or 3000 mg/kg-day during days 6–15 of gestation. A significant decrease in maternal body weight gain (32%, $P < 0.01$) and absolute liver weight (9%, $P < 0.01$) were reported at 1500 mg/kg-day and above. Dose-related and statistically significant ($p < 0.01$) reductions in mean fetal body weights per litter (9–27%) were observed at all doses. Statistically significant ($p < 0.01$) and dose-related increases in the incidence of malformed (visceral and skeletal) live fetuses per litter (0.25% in the controls and 10–57%) were observed at all doses. Dose-related increases in skeletal malformations of the ribs, arches, centra, and sternbrae (4% in controls and 63–96% in treated groups) were observed at all dose levels. No effects were reported for the number of implantations, resorption sites, or live and dead fetuses. (Price et al., 1985)

NOAEL (maternal toxicity) = 750 mg/kg-day

LOAEL (maternal toxicity) = 1500 mg/kg-day (based on decrease in body weight)

NOAEL (developmental toxicity) = not established

LOAEL (developmental toxicity) = 750 mg/kg-day (based on decreases in pup body weight and increases in malformations)

(3) Pregnant CD-1 mice (30/dose) were administered CASRN 107-21-1 via gavage at 0, 50, 150, 500, or 1500 mg/kg-day during days 6–15 of gestation. There was no significant effect on maternal body weight or body weight gain. There was no other treatment-related toxicity noted in dams. Exposure to the highest dose produced a statistically significant increase in the incidence of 25 of the 27 skeletal malformations/variations examined. At 1500 mg/kg-day, an increased incidence of skeletal malformations and variations and a reduction in fetal body weight per litter were observed. The 500 mg/kg-day dose produced a statistically significant increase in the incidence of the occurrence of an extra 14th rib. Exposure produced no effects on the number of corpora lutea or viable implantation sites, pre-implantation loss or sex ratio, or maternal toxicity. (Neeper-Bradley, et al., 1995)

NOAEL (maternal toxicity) = 1500 mg/kg-day (based on no effects at the highest dose tested)

NOAEL (developmental toxicity) = 150 mg/kg-day

LOAEL (developmental toxicity) = 500 mg/kg-day (based on increased incidence of extra rib)

(4) Pregnant CD-1 mice (30/dose) were exposed (by occluded cutaneous application) to aqueous solutions of 0, 12.5, 50, or 100% CASRN 107-21-1 (estimated doses of 0, 400, 1700, or 3500 mg/kg-day) during days 6–15 of gestation. Signs of maternal toxicity consisted of minimal-grade renal lesions and increased corrected gestational body weight change. Signs of developmental toxicity consisted of significant increases in the incidence of poorly ossified skull bone and unossified intermediate phalanges of the hindlimb at 3500 mg/kg-day. No effects were reported for the number of corpora lutea, implantation and resorption sites, or live and dead fetuses. (Tyl et al., 1995c)

NOAEL (maternal toxicity) = 1700 mg/kg-day

LOAEL (maternal toxicity) = 3500 mg/kg-day (based on renal lesions and increased body weight changes)

NOAEL (developmental toxicity) = 1700 mg/kg-day

LOAEL (developmental toxicity) = 3500 mg/kg-day (based on delays in skeletal ossification)

(5) Pregnant CD rats (28-29/dose) were administered CASRN 107-21-1 via gavage at 0, 1250, 2500 or 5000 mg/kg-day during gestation days 6-15. Signs of maternal toxicity consisted of statistically significant ($p < 0.01$) and dose-related decreases in maternal weight gain were reported beginning at all doses. Gravid uterine weight was reduced at the mid- and high-doses. Corrected maternal gestational weight gain also showed a significant decreasing trend beginning at 2500 mg/kg-day. Statistically significant ($p < 0.05$) increases in post-implantation loss per litter were observed at 5000 mg/kg-day. Signs of developmental toxicity consisted of reductions in fetal body weight on a per litter basis in the mid- and high dose groups. Statistically significant ($p < 0.01$ to $p < 0.001$) and dose-related increases in the percentages of malformed live fetuses per litter and/or the litters with malformed fetuses were observed at all doses, with >95% of litters affected at the highest dose. A wide variety of malformations were observed, the most common being craniofacial and neural tube closure defects, and axial skeletal dysplasia. (Price et al., 1985)

NOAEL (maternal toxicity) = not established

LOAEL (maternal toxicity) = 1250 mg/kg-day (based on decreases in body weight gain)

NOAEL (developmental toxicity) = not established

LOAEL (developmental toxicity) = 1250 mg/kg-day (based on fetal skeletal malformations)

(6) Pregnant New Zealand white rabbits (23-25/dose) were administered CASRN 107-21-1 via gavage at 0, 100, 500, 1000 or 2000 mg/kg-day. Maternal toxicity consisted of mortality (42% mortality, three early deliveries and one spontaneous abortion) at 2000 mg/kg-day possibly associated with renal pathology (involving cortical renal tubules and included intraluminal oxalate crystals, epithelial necrosis and tubular dilation and degeneration). No dose-related maternal toxicity was seen at 100-1000 mg/kg-day. There was no indication of developmental toxicity at any dose tested, including no effects on pre- or post-implantation loss, number of fetuses, fetal body weight or sex ratio per litter. (Tyl, et al., 1993)

NOAEL (maternal toxicity) = 1000 mg/kg-day

LOAEL (maternal toxicity) = 2000 mg/kg-day (based on mortality and renal effects)

NOAEL (developmental toxicity) = 2000 mg/kg-day (based on no effects at the highest dose tested)

Genetic Toxicity - Gene mutation

In vitro

Salmonella typhimurium strains TA98, TA100, TA1535 and TA1537 and *Escherichia coli* WP2uvrA pKM101 were exposed to CASRN 111-55-7 at concentrations up to 5000 $\mu\text{g}/\text{plate}$ in the presence and absence of metabolic activation. No evidence of cytotoxicity was observed at any dose level in any strain. Positive controls were tested concurrently, but the results were not reported.

Ethylene glycol diacetate was not mutagenic in this assay.

Genetic Toxicity – Chromosomal Aberrations

In vitro

Chinese hamster ovary cells were exposed to CASRN 111-55-7 at concentrations of 10.2 – 1500 µg/ml in the presence and absence of metabolic activation. No signs of cytotoxicity were observed at any dose level. Positive controls were tested concurrently, but the responses were not reported.

Ethylene glycol diacetate did not induce chromosomal aberrations in this assay.

Conclusion: The acute oral toxicity of CASRN 111-55-7 is low in rats. Repeated-dose, reproductive and developmental toxicity endpoints are addressed using data for the supporting chemical, ethylene glycol, CASRN 107-21-1. Repeated oral exposure of CASRN 107-21-1 to rats and/or mice for periods of 13 weeks to two years primarily showed renal effects. Following a 16-week dietary exposure, the NOAEL for systemic toxicity in rats is 71 mg/kg-day with a LOAEL of 180 mg/kg-day. The NOAEL for systemic toxicity in rats after 24-month dietary exposure is 200 mg/kg-day with a LOAEL of 1000 mg/kg-day (highest dose tested). For mice, following a 13-week dietary exposure, the lowest NOAEL for systemic toxicity is 600 to 1000 mg/kg-day with a LOAEL of 1200 to 2000 mg/kg-day. The NOAEL for systemic toxicity in mice after 24-month dietary exposure is 1500 mg/kg-day with a LOAEL of 3000 mg/kg-day. In a two-generation reproductive toxicity drinking water study in mice with CASRN 107-21-1, a decrease in the number of litters and decreased pup weights were seen at 1640 mg/kg-day; the NOAEL for reproductive toxicity is 840 mg/kg-day. Developmental effects were observed following oral or dermal exposures to pregnant mice and rats to the supporting chemical, CASRN 107-21-1. For mice, decreased body weights were seen in the dams at 1500 mg/kg-day following oral (gavage) exposure; the NOAEL for maternal toxicity is 750 mg/kg-day. Treatment-related signs of developmental toxicity (skeletal malformations) were seen in this study at the lowest dose tested, 750 mg/kg-day; the NOAEL for developmental toxicity is not established. For rats, signs of maternal and developmental toxicity were observed following oral (gavage) exposures at the lowest dose tested, 1250 mg/kg-day, based on decreases in body weights in the dams and dose related skeletal malformations in offspring; the NOAELs for maternal and developmental toxicity are not established. For rabbits, mortality was observed in the dams at 2000 mg/kg-day following oral (gavage) exposure; the NOAEL for maternal toxicity is 1000 mg/kg-day. No signs of developmental toxicity were observed at any doses; the NOAEL for developmental toxicity is 2000 mg/kg-day (highest dose tested). Following dermal exposure in mice, renal lesions and increased corrected gestational body weight changes were observed in the dams at 3500 mg/kg-day; the NOAEL for maternal toxicity is 1700 mg/kg-day. Delays in skeletal ossification were observed in offspring at 3500 mg/kg-day; the NOAEL for developmental toxicity is 1700 mg/kg-day. CASRN 111-55-7 did not induce gene mutations in bacteria or chromosomal aberrations in mammalian cells *in vitro*.

Table 3. Summary Table of the Screening Information Data Set as Submitted under the U.S. HPV Challenge Program – Human Health Data		
Endpoints	SPONSORED CHEMICAL Ethylene glycol diacetate (111-55-7)	SUPPORTING CHEMICAL Ethylene glycol (107-21-1)
Acute Oral Toxicity LD₅₀ (mg/kg-bw)	6860	–
Repeated-Dose Toxicity NOAEL/LOAEL Oral (mg/kg-day)	No data NOAEL = 71 LOAEL = 180 (RA)	NOAEL = 71 LOAEL = 180
Reproductive Toxicity Oral (mg/kg-day)	No data	
Systemic Toxicity	NOAEL = 1640	NOAEL = 1640 (highest dose tested)
Reproductive Toxicity	NOAEL = 840 LOAEL = 1640 (RA)	NOAEL = 840 LOAEL = 1640
Developmental Toxicity Oral (mg/kg-day)	No data	
Maternal Toxicity	(Mice) NOAEL = 750 LOAEL = 1500	(Mice) NOAEL = 750 LOAEL = 1500
Developmental Toxicity	NOAEL = Not Established LOAEL = 750 (RA)	NOAEL = Not Established LOAEL = 750
Maternal Toxicity	(Rat) NOAEL = Not Established LOAEL = 1250	(Rat) NOAEL = Not Established LOAEL = 1250
Developmental Toxicity	NOAEL = Not Established LOAEL = 1250 (RA)	NOAEL = Not Established LOAEL = 1250
Maternal Toxicity	(Rabbit) NOAEL = 1000 LOAEL = 2000	(Rabbit) NOAEL = 1000 LOAEL = 2000
Developmental Toxicity	NOAEL = 2000 (RA)	NOAEL = 2000 (highest dose tested)

Table 3. Summary Table of the Screening Information Data Set as Submitted under the U.S. HPV Challenge Program – Human Health Data		
Endpoints	SPONSORED CHEMICAL Ethylene glycol diacetate (111-55-7)	SUPPORTING CHEMICAL Ethylene glycol (107-21-1)
Developmental Toxicity Dermal (mg/kg-day) Maternal and Developmental Toxicity	No data (Mice) NOAEL = 1700 LOAEL = 3500 (RA)	(Mice) NOAEL = 1700 LOAEL = 3500
Genetic Toxicity – Gene Mutation <i>In vitro</i>	Negative	–
Genetic Toxicity – Chromosomal Aberrations <i>In vitro</i>	Negative	–

Measured data in bold text; RA = Read Across; – indicates that endpoint was not addressed for this chemical

4. Hazard to the Environment

A summary of aquatic toxicity data submitted for SIDS endpoints is provided in Table 4.

Acute Toxicity to Fish

Fathead minnow (*Pimephales promelas*) were exposed to CASRN 111-55-7 at nominal concentrations of 7.5, 15, 30, 60 or 120 mg/L under static-renewal conditions for 96 hours. The corresponding measured concentrations were 6.1, 13.6, 28.5, 57.4 or 115.0 mg/L. Mortality was observed at concentrations of 57.4 (100% at 48 hours) and 115.0 mg/L (100% at 24 hours).

96-h LC₅₀ = 40.5 mg/L

Acute Toxicity to Aquatic Invertebrates

Daphnia magna were exposed to CASRN 111-55-7 at a nominal concentration of 120 mg/L under static conditions for 48 hours. The measured concentration was 116.3 mg/L. Mortality rates (not reported) were similar in the CASRN 111-55-7 and control groups. Daphnids in the control and CASRN 111-55-7 exposure solutions exhibited normal behavior and appearance throughout the test.

48-h EC₅₀ > 116.3 mg/L

Toxicity to Aquatic Plants

Green algae (*Pseudokirchneriella subcapitata*) were exposed to CASRN 111-55-7 at a nominal concentration of 125 mg/L under static conditions for 72 hours. The measured concentration was 119.86 mg/L. Endpoints evaluated were biomass and growth. No treatment-related effects were observed.

72-h EC₅₀ (biomass) > 120 mg/L

72-h EC₅₀ (growth rate) > 120 mg/L

Conclusion: The 96-h LC₅₀ for fish for CASRN 111-55-7 is 40.5 mg/L. The 48-h EC₅₀ for aquatic invertebrates for CASRN 111-55-7 is >116.3 mg/L and the 72-h EC₅₀ for aquatic plants for CASRN 111-55-7 is >120 mg/L for both biomass and growth rate.

Table 4. Summary of the Screening Information Data Set as Submitted under the U.S. HPV Challenge Program – Aquatic Toxicity Data	
Endpoint	SPONSORED CHEMICAL Ethylene Glycol Diacetate (111-55-7)
Fish 96-h LC₅₀ (mg/L)	40.5
Aquatic Invertebrates 48-h EC₅₀ (mg/L)	>116.3
Aquatic Plants 72-h EC₅₀ (mg/L) (biomass)	> 120
(growth rate)	> 120

bold = measured data (i.e., derived from testing)

5. References

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