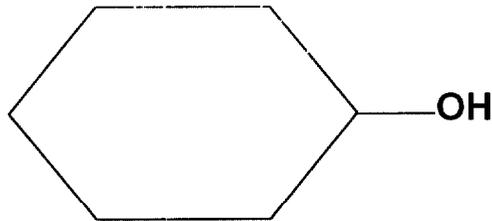


AR201-13221A



CYCLOHEXANOL

CAS Number 108-93-0

USEPA HPV CHALLENGE PROGRAM SUBMISSION

September 26, 2001

Submitted by:

IHF Committee on HPV Challenge for Cyclohexanol

Members.:

BASF Corporation
DuPont Company
DSM Chemicals North America, inc.
Honeywell International: Inc.
Solutia, Inc.

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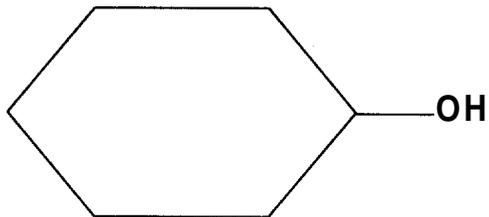
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TESTING PLAN

Table of Contents

Executive Overview.....	2
Testing Plan and Rationale	5
Testing Plan in Tabular Format	6
Introduction	7
Physical-Chemical Data	8
Environmental Fate and Pathways	9
Ecotoxicity	10
Mammalian Toxicity	11
A. Acute Toxicity	11
B. Repeated Dose Toxicity..	12
C. Genotoxicity	12
D. Reproductive Toxicity	14
E. Developmental Toxicity	15
F. Toxicokinetics	15
Conclusions	16
References..	18

EXECUTIVE OVERVIEW

Cyclohexanol is a basic industrial chemical and solvent. It is primarily captively consumed, either isolated or as a mixture, in the production of nylon intermediates (adipic acid and caprolactam). Less than 2% is consumed in other markets such as in the production of cyclohexylamine, and intermediates for plasticizers, rubber chemicals, and selected agricultural chemicals. Total cyclohexanol production in 1998 was estimated at approximately 1240 million pounds. Exposure in the preceding applications is limited by process controls and protective equipment. Environmental releases are primarily limited to vapor released to air at manufacturing sites.

Valid data for cyclohexanol are available for melting and boiling points, vapor pressure, aqueous solubility, octanol-water partitioning, and specific gravity. The data indicate that cyclohexanol will be a solid below about 24° C and liquid at higher ambient temperatures. Based on its vapor pressure, aqueous solubility, and Log P_{ow} value, it will tend to remain in water and only slowly volatilize. Partitioning to soil and sediment and bioaccumulation in aquatic organisms will be low. Assuming equal releases of cyclohexanol to air, water, and soil, Mackay Level III distribution modeling predicted that most would be found in water (50.2%) or soil (47.5%), with the rest in air.

Upon entry into water or soil, the results of an OECD 302 biodegradation study suggest that cyclohexanol will be subject to relatively rapid biodegradation in oxygen-containing environments. Primary and ultimate biodegradation half-lives in water and soil were estimated to be days and weeks, respectively. In the air, hydroxyl radical-mediated photo-oxidation will quickly reduce concentrations with a calculated half-life of less than 15 hours.

Valid acute ecotoxicity data for the freshwater fathead minnow *Pimephales promelas* (96-hr LC50 = 704 mg/l), the invertebrate *Daphnia magna* (48-hr EC50 > 500 mg/l), and the green alga *Scenedesmus subspicatus*

(96-hr EC50 = 29 mg/l) indicate that cyclohexanol is practically nontoxic to fish and invertebrates, and slightly toxic to algae.

Acute toxicity to mammals appears to be low-to-moderate as demonstrated by an oral LD50 in rats of about 1550 mg/kg, a 4-hour LC50 in rats >3.6 mg/l (as an aerosol), and a dermal LD50 in rabbits between 500 and 800 mg/kg. Adequate repeated exposure studies have not been conducted on cyclohexanol. Studies of questionable reliability have suggested aspermatogenesis as an adverse effect and no adequate studies to assess developmental toxicity were found. Relative to genetic toxicity potential, *in vitro* studies in bacteria were negative with and without metabolic activation; and *in vitro* cytogenetic assay results using human leukocytes were "equivocal." In an *in vivo* mouse micronucleus study, cyclohexanol was not clastogenic. Toxicokinetic data in animals suggest that cyclohexanol is readily absorbed, subsequently metabolized, and then the parent **compound/metabolites** are excreted in the urine as glucuronides and sulfates within several days.

With regard to the HPV program, the IHF Committee on Cyclohexanol has determined that no additional testing is needed in the areas of "Physicochemical Properties", and "Ecotoxicity." Relative to "Environmental Fate", an existing biodegradation study and modeling data on photodegradation and transport and distribution in the environment are adequate to meet HPV requirements. However, additional testing for water stability (OECD 111, for example) is needed. Relative to mammalian toxicity, acute toxicity data and genotoxicity data are adequate to meet HPV requirements.

Overall, cyclohexanol does not appear to represent an unacceptable risk to human health or the environment. Under the EPA HPV Challenge Program, cyclohexanol was evaluated and data gaps were identified for water stability, repeated exposure toxicity and reproductive/developmental toxicity. In deciding what animal tests/studies to conduct, the IHF Committee on Cyclohexanol considered the animal usage required and recommends a rat 90-day inhalation toxicity study. If reproductive organ effects are seen in that 90-day study, an inhalation one-generation reproduction study will be conducted. If no reproductive

organ effects are seen in the 90-day study, then an inhalation developmental toxicity will be performed. By keeping the number of tests and the number of animals in those tests to a minimum, the Committee feels that animal welfare concerns have been appropriately addressed. Appropriate studies to meet the HPV requirements will reference OECD Guidelines and will be conducted starting in the first quarter of 2002 and take about two years to complete.

Cyclo hexanol

HPV Test Plan

TESTING PLAN AND RATIONALE

TESTING PLAN IN TABULAR FORMAT

Cyclohexanol CAS No. 108-93-o	Information Available?	OECD Study?	GLP Study?	Other Study?	Estimation Method?	Acceptable?	Testing Recommended?	Comments
HPV Endpoint								
Physical/Chemical Properties								
Melting Point	Y	N	N	N	N	Y	N	
Boiling Point	Y	N	N	N	N	Y	N	
Vapor Pressure	Y	N	N	Y	N	Y	N	
Partition Coefficient	Y	Y	N	N	N	Y	N	
Water Solubility	Y	N	N	N	N	Y	N	
Environmental Fate								
Photodegradation	Y	N	N	N	Y	Y	N	
Water Stability	Y	N	N	N	N	N	Y	
Transport	Y	N	N	N	Y	Y	N	
Biodegradation	Y	Y	N	N	N	Y	N	
Ecotoxicity								
96-Hour Fish	Y	N	N	N	N	Y	N	
48-Hour Invertebrate	Y	Y	N	N	N	Y	N	
72-Hour Algae	Y	Y	N	N	N	Y	N	
Mammalian Toxicity								
Acute Toxicity	Y	N	N	N	N	Y	N	
Repeated Dose	Y	N	N	Y	N	N	Y	
Genotoxicity (Point Mutation)	Y	N	N	Y	N	Y	N	
Genotoxicity (Chromosome Aberration)	Y	Y	Y	N	N	Y	N	
Reproductive Toxicity	Y	N	N	Y	N	N	Y/N	Depends on 90-Day Results
Developmental Toxicity	N	N	N	N	N	N	Y/N	Depends on 90-Day Results

INTRODUCTION

Cyclohexanol, CAS No. 108-93-0, is an alcohol used primarily in the production of nylon intermediates (adipic acid and caprolactam); less than 2% is consumed in markets other than nylon.

Since cyclohexanol is a liquid of low volatility with a vapor pressure of 1 mmHg @ 20° C, little vapor exposure occurs. In the industrial setting, exposures are well controlled and air concentrations are kept at least an order of magnitude below the current OSHA PEL and ACGIH TLV® of 50 ppm (8-hour TWA) under normal operating conditions. Since cyclohexanol can be absorbed through the skin in toxicologically significant amounts, the current ACGIH TLV® also carries a "SKIN Notation." As a result, dermal exposure to cyclohexanol is kept to a minimum in the workplace. Since there are few sites of manufacture, the number of potentially-exposed workers is also small.

Various studies have been conducted on the fate and toxicity of cyclohexanol. These studies are reviewed with comments describing whether or not they meet the requirements of the USEPA High Production Volume (HPV) program. Robust summaries, using a SIDS format, have been prepared for key and some supporting studies and are included in a separate document; other supporting studies are referenced in this document.

PHYSICAL-CHEMICAL DATA

Physical/chemical properties for cyclohexanol are available from the literature and manufacturing company sources.

Melting Point	24° C (1)
Boiling Point	161° C (2)
Vapor Pressure	1.0 mm Hg @ 20° C (1)
Partition Coefficient	$\text{Log}_{10} P_{ow} = 1.25 @ 25^{\circ}\text{C} (3)$
Water Solubility	3.6 wt% @ 20° C (2)

Cyclohexanol is a 6-carbon ring with an OH group on C1. It is characterized as colorless needles at temperatures below its melting point (1) of 24°C or as a viscous hygroscopic liquid with a camphor-like odor above its melting point. Its boiling point is 161° C (2) and its specific gravity is 0.945, nearly that of water. Data for cyclohexanol are available for vapor pressure, aqueous solubility, and octanol-water partitioning. Based on a measured vapor pressure of 0.8 mm Hg (25°C), and aqueous solubility of about 36,000 mg/L (2), calculated from a measured log Kow 1.23, it will tend to remain in water and only slowly volatilize. A Henry's Law constant of 2.5 E-6 atm-m³/mol was calculated from vapor pressure and water solubility. Using these data, volatilization from a model stream and lake were calculated to have half-lives of 5.6 and 64 days, respectively. Partitioning to soil and sediment and bioaccumulation in aquatic organisms will be low, as indicated by a calculated Koc value of 8 L/kg and bioconcentration factor of 2 L/kg (both based on a log Kow of 1.23). Assuming equal releases of cyclohexanol to air, water, and soil, Mackay Level III

distribution modeling predicted that most would be found in water (50.2%) or soil (47.5%), with most of the rest in air (2.25%).

Recommendation: No additional studies are needed to fulfill the HPV required endpoints for physical/chemical properties.

ENVIRONMENTAL FATE AND PATHWAYS

Atmospheric photo-oxidation is an important removal process for cyclohexanol. Using the EPA-developed model AOPWIN (part of EPIWIN), a secondary rate constant for hydroxyl radical mediated atmospheric photo-oxidation was calculated to be $17.48 \text{ E-12 cm}^3/\text{molecule-set}$ for cyclohexanol. Using the standard assumptions of 1.5 E+6 hydroxyl radicals per cubic centimeter, and 12 hr/day of daylight, a pseudo first-order half-life of 0.61 days (14.7 hours) was calculated. No data for hydrolysis is available and EPIWIN models cannot estimate hydrolysis rates for compounds with a structure like cyclohexanol.

Biodegradation is an important removal process for cyclohexanol. The biodegradation of cyclohexanol was determined by measuring consumption of dissolved organic carbon (DOC). The study (4) employed OECD method 302, Zahn-Wellens test. The 6-day study was initiated using non-adapted activated sludge as microbial seed. DOC was measured at 3 hours, 1 day, 4 days, and 6 days. At 3 hours, 11% DOC removal was reported. On days 1, 4, and 6 of the test, 45%, 98% and 98% DOC removal were achieved. Cyclohexanol is considered inherently biodegradable and the data suggest that it will be subject to relatively rapid biodegradation in oxygen-containing environments. The biodegradability of cyclohexanol is supported by results obtained using BIOWIN v4.00 (of the EPIWIN models), which estimated primary and ultimate biodegradation half-lives in water and soil of days and weeks, respectively.

Recommendation: The preceding biodegradation study (OECD 302B) and the modeling data for photodegradation (AOPWIN) and transport and distribution (Mackay Level III) are adequate to meet SIDS/HPV requirements. Cyclohexanol is readily biodegradable; thus, this information supports not measuring stability in water (hydrolysis). The EPIWIN model cannot estimate hydrolysis rates for a chemical with a structure like cyclohexanol. Therefore, we propose to conduct a study (OECD 111, for example) to measure the stability (hydrolysis) of cyclohexanol in water.

ECOTOXICITY

Acute aquatic toxicity data are available for cyclohexanol in fish, invertebrates and algae. An EPA sponsored study (5,6) was performed with the freshwater fathead minnow *Pimephales promelas*. The study followed EPA-developed flo-through guidelines on ecotoxicity testing and was deemed valid. The fathead minnow 96-hr LC50 based on survival was 704 mg/L. A study (7) with the pelagic aquatic invertebrate *Daphnia magna* was performed using OECD method 202. No effects were observed at the highest concentration tested, 500 mg/L, so the 48-hr EC50 was >500 mg/L. A static study (8) with the green alga *Scenedesmus subspicatus* was also performed according to OECD method 201, which measures the inhibitory effect on cell multiplication, a measure of growth rate. Both the 72-h EC50 and the 96-hr EC50 values were 29 mg/L.

Recommendation: No additional testing is recommended based on available data. The preceding ecotoxicity studies do not suggest that cyclohexanol represents a major concern for aquatic environmental species,

MAMMALIAN TOXICITY

A. Acute Toxicity

The acute oral toxicity of cyclohexanol was determined in male SD rats using a method consistent with OECD Test Guideline 401. Doses of 1000, 1260, 1580, 2000, 2510 and 3160 mg/kg were used. No mortality occurred at 1000 or 1260 mg/kg. The LD50 was reported to be 1550 mg/kg (1390-l 710 mg/kg CL) (9). This low order of toxicity is supported by an older acute oral toxicity study in Car-worth-Wistar rats with a reported LD50 of 2060 mg/kg for cyclohexanol (10).

An adequate inhalation toxicity study using one exposure level in SD rats also suggests a low order of toxicity. Ten male and 10 female rats were exposed to a cyclohexanol aerosol for 4 hours at an analytical concentration of 3.63 mg/l and were observed up to 14 days post-exposure. No rats died and clinical observations, body weight changes and gross autopsy results were unremarkable (11).

In a dermal absorption toxicity study, using a method consistent with OECD Test Guideline 402, cyclohexanol was applied undiluted to the skin of rabbits for 24 hours at 7 doses ranging from 316 to 5010 mg/kg. The dermal LD50 was reported as >501 <794 mg/kg, values reflecting a slightly greater toxicity by the dermal route compared to the oral route. These data also suggest that cyclohexanol can be absorbed through the skin in toxicologically significant amounts (12). As a result, the current ACGIH TLV® of 50 ppm (8-hr TWA) for cyclohexanol also has a 'SKIN' notation.

Recommendation: The oral toxicity studies, as well as supporting studies by inhalation and dermal routes, suggest that cyclohexanol has a relatively low

order of acute toxicity. These studies adequately fulfill the HPV acute toxicity requirement and no additional testing is recommended.

B. Repeated Dose Toxicity

The data available to assess the repeated exposure toxicity of cyclohexanol are inadequate to meet the HPV requirements for this endpoint. Limited repeated exposure studies have been conducted by the oral route (13-17), the inhalation route (18-21), and the dermal route (18-22). From these studies, it appears that the major adverse effects of repeated exposure to cyclohexanol are CNS effects, liver and kidney damage, and mucous membrane irritation.

Recommendation: The IHF Committee on Cyclohexanol recommends that a 90-day inhalation toxicity study in rats (OECD Guideline No. 413) be conducted to satisfy this HPV endpoint. This study will include a recovery group and complete histopathological examination of tissues with special emphasis on testes and ovaries. In addition, recovery groups will be included to assess the reversibility of any lesion seen after 90 days of exposure. Such a study will provide sufficient information to adequately assess repeated exposure toxicity potential. In addition, it will provide some guidance in deciding whether to conduct studies to assess the reproductive toxicity (See Section D) and/or the developmental toxicity (See Section E) potential of cyclohexanol.

C. Genotoxicity

In vitro studies conducted on cyclohexanol have shown negative or ambiguous results. In an adequate *Salmonella typhimurium* reverse mutation assay (23), four strains (TA 98, TA1535, TA 1537 and TA 1538) were exposed to cyclohexanol at concentrations up to 15,000 g/p late. Two replicates were used at each concentration and all tests were performed with and without metabolic activation. No evidence of mutagenicity was seen in

this study. Three other *in vitro* point mutation assays using *Salmonella typhimurium* were also conducted on cyclohexanol. In two of these studies (24,25), there was no evidence of mutagenicity but details were limited. In a third study (26), cyclohexanol tested at 3300 and 9100 g/plate, with and without activation, produced less than a two-fold increase in revertants, a result that would be considered negative by today's standards. In one *in vitro*, non-bacterial assay (27) measuring chromosomal aberration, human leukocytes were tested at concentrations as high as 0.01 moles/l without metabolic activation. Cyclohexanol reportedly induced achromatic regions, breaks and deletions in chromosomes. However, this study used a non-validated protocol and technical details were very limited.

One *in vivo* genotoxicity study (28), considered "valid without restrictions", was conducted by BASF on cyclohexanol using a mouse micronucleus assay. Male and female mice were dosed by oral gavage at concentrations of 500,1000 and 1500 mg/kg, sacrificed 16, 24 and 48 hours later, and bone marrow was examined. Cyclohexanol produced no chromosome-damaging (clastogenic) effects and did not impair chromosome distribution in mitosis. In one other limited *in vivo* gene mutation assay (29) in *Drosophila melanogaster*, results were negative.

Recommendation: No additional testing is required. The HPV requirement for genetic testing has been met by the preceding *in vitro* and *in vivo* studies sensitive to both point mutations and chromosome aberrations. From these studies, the overall weight of evidence suggests a lack of genotoxic activity for cyclohexanol.

D. Reproductive Toxicity

A few limited studies, involving evaluation of the testis, have been conducted but are not adequate to meet HPV requirements.

In one study (30), 20 adult male gerbils and 20 male rats were subcutaneously injected with 15 mg cyclohexanol/kg/day for a period of 21 and 37 days, respectively. A significant reduction in the weights of the testes, epididymides, seminal vesicles and ventral prostate was detected. In addition, spermatogenesis in both species was arrested. Recovery was not investigated. In another study, (31), groups of 15 male rabbits received 25 mg cyclohexanol/kg/day by gavage for a period of 40 days. One group was allowed a 70-day recovery period following cessation of cyclohexanol administration. A significant reduction in the weights of the testis and epididymides was observed. Additionally, marked degenerative changes were noted upon microscopic examination of the testes. These changes were consistent with those previously described for the gerbil and the rat. Normal spermatogenesis was seen after 70 days following cessation of cyclohexanol treatment. The organ weights were also comparable to the controls. In a third study (14), male rats were given 455 mg cyclohexanol/kg/day by gastric intubation for 7 days. Cyclohexanol increased liver size and stimulated certain parameters of hepatic xenobiotic metabolism in the rat but had no effect on testis weight. Other studies cited under "Repeated Dose Toxicity" (See Section B) make no mention that gonadal tissue was ever examined histopathologically.

Recommendation: If adverse effects on gonads (sperm damage, for example) are observed in the proposed 90-day rat inhalation study (Section B), a one-generation rat inhalation reproduction study (OECD No.415) will be conducted on cyclohexanol to assess functional effects on fertility/reproductive performance.

E. Developmental Toxicity

No adequate studies were found to assess the developmental toxicity potential of cyclohexanol.

Recommendation: If no adverse gonadal effects are seen in our proposed 90-day rat inhalation study (Section B), an inhalation teratology study (OECD No. 414) in rats will be conducted to fulfill the HPV reproductive/developmental toxicity requirement.

F. Toxicokinetics

Limited data exist on specific aspects of toxicokinetics - namely, metabolism and excretion. The major occupational exposure routes for cyclohexanol are inhalation and the skin. Several animal studies dealing with absorption, metabolism and excretion are subsequently discussed.

Little quantitative data on absorption and distribution of cyclohexanol in animals were found. The dermal LD50 in rabbits was reported to be between 501 and 794 mg/kg, suggesting that cyclohexanol can be absorbed through the skin in toxicologically significant amounts (12). Cyclohexanol has also been reported to facilitate the penetration of externally applied drugs through the skin (32), but no recent confirmatory studies were found.

The literature suggests that cyclohexanol is a substrate for alcohol dehydrogenase (ADH), has a stronger affinity for the enzyme than ethanol, and would competitively inhibit the oxidation of ethanol (25, 33-35). Cyclohexanol also interacts with cytochrome P450 (36-37). In one recent study (17), cyclohexanol remarkably enlarged the mitochondria in the hepatocytes of rats, but only after the solvent was given for 30 days.

In studies on dogs, results have been equivocal. One study (18) reported the presence of glucuronides in the urine of one dog after oral administration of

cyclohexanol. However, other investigators (13, 38) could not detect any cyclohexanol, conjugated or free, or metabolites in the urine of a dog after subcutaneous administration for 6 days or after oral administration for 7 days. Data on rabbits appears to be more consistent. Following oral or inhalation administration to rabbits, cyclohexanol was excreted in the urine in conjugation with sulfuric and glucuronic acids. At an oral dose of 1200 mg/kg, 45-50% was conjugated with glucuronic acid, accompanied by an increased percentage of inorganic sulfates. Cyclohexanone as a possible oxidation product of cyclohexanol was not found in the urine (22). In another study (39), rabbits given 250 mg/kg of labeled cyclohexanol excreted 58-60% of the dose in the urine as glucuronides and 12% of the dose as trans-cyclohexane-1,2-diol glucuronide. About 71% of the radioactivity was excreted in the urine in 48 hours

From the preceding animal studies, it is evident that cyclohexanol can be absorbed by all three major routes of administration. Most absorbed cyclohexanol is metabolized and subsequently excreted as glucuronide and sulfate conjugates. One investigator (22) calculated a half-life of about 12 hours for these metabolites.

CONCLUSIONS

Under the EPA HPV Challenge Program, adequate data to meet HPV requirements are available for cyclohexanol relative to Physical/Chemical Properties, Environmental Fate and Pathways, (except for water stability), Ecotoxicity, Acute Toxicity and Genotoxicity. A study on water stability (hydrolysis) will be conducted. A rat 90-day inhalation toxicity study with a recovery phase will also be conducted on cyclohexanol. Depending on results from this study, either a one-generation inhalation reproduction study or an inhalation developmental toxicity study in rats will be conducted. The preceding proposed studies, coupled with toxicity and environmental data already

available, should adequately characterize cyclohexanol relative to HPV requirements.

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