

SCREENING-LEVEL HAZARD CHARACTERIZATION OF HIGH PRODUCTION VOLUME CHEMICALS

CHEMICAL CATEGORY NAME N,N-Dimethylalkanamides Category

SPONSORED CHEMICALS

N,N-Dimethyloctanamide	CASRN 1118-92-9
N,N-Dimethyldecanamide	CASRN 14433-76-2

SUPPORTING CHEMICAL

Hallcomid M-8-10[®]	No CASRN
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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

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>.

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 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 Chemicals</u> 1118-92-9 14433-76-2</p> <p><u>Supporting Chemical</u> No CASRN</p>
<p>Chemical Abstract Index Name</p>	<p><u>Sponsored Chemicals</u> Octanamide, N,N-dimethyl- Decanamide, N,N-dimethyl-</p> <p><u>Supporting Chemical</u> Hallcomid M-8-10[®]</p>
<p>Structural Formula</p>	<p>See Table 2</p>
<p style="text-align: center;">Summary</p> <p>The N,N-dimethylalkanamides category consists of CASRN 1118-92-9 and CASRN 14433-76-2. Commercially, CASRN 1118-92-9 is not manufactured in pure form, but as the major component (50–65% weight) of a mixture also containing 37–50% CASRN 14433-76-2, with minor impurities CASRN 5830-30-8 (0–5%) and CASRN 3007-53-2 (0–2%). N,N-Dimethylalkanamides exist as liquids at room temperature with moderate to high water solubility and moderate vapor pressure. N,N-Dimethylalkanamides are expected to possess moderate mobility in soil. No data are available for the ready biodegradation endpoint. Volatilization is expected to be low-moderate based on the Henry's Law constants for the sponsored chemicals. The rate of hydrolysis is expected to be negligible. The rate of atmospheric photooxidation is considered moderate for the sponsored chemicals. N,N-Dimethylalkanamides are expected to possess low persistence (P1) and low (B1) bioaccumulation potential.</p> <p>No data are available for the sponsored substances: all human health and ecotoxicity endpoints are addressed with the supporting chemical, Hallcomid M-8-10[®] (no CASRN). Hallcomid M-8-10[®] is a commercial product comprised of 50 – 65% N,N-dimethyloctanamide (CASRN 1118-92-9), 37 – 50% N,N-dimethyldecanamide (CASRN 14433-76-2), 0 – 5% N,N-dimethylhexanamide (CASRN 5830-30-8) and 0 – 2% N,N-dimethyldodecanamide (CASRN 3007-53-2).</p> <p>Human Health Hazard</p> <p>The acute toxicity of Hallcomid M-8-10[®] to rats is low via the oral route and moderate via the inhalation and dermal routes. Repeated dietary exposure of rats to Hallcomid M-8-10[®] for 91 days resulted in decreased body weight gain, emaciation, increased serum cholesterol, increased</p>	

liver weights, increased protein in the urine and increased incidence of basophilic regenerative tubuli in the renal cortex at 788 mg/kg-bw/day. These effects were not seen in recovery animals. The NOAEL for systemic toxicity is 137 mg/kg-bw/day. No specific reproductive toxicity studies are available; however, in the 91-day repeated-dose toxicity study in rats, no treatment-related effects were observed on the reproductive organs in rats treated with Hallcomid M-8-10[®]. In a prenatal developmental toxicity study, rats treated via oral gavage with Hallcomid M-8-10[®] showed effects on the dams at 450 mg/kg-bw/day: reduced food consumption, reduced body weight gain and clinical signs of toxicity (ruffled fur, ventral recumbancy, dyspnea, apathy, abdominal hair loss and comatose state). At the same dose, developmental effects included increased mean fetal body weight, increased post-implantation loss and skeletal malformations (non-ossified cervical vertebra, incompletely ossified sternebra and non-ossified metatarsala). The NOAEL for maternal and developmental toxicity in rats is 150 mg/kg-bw/day. In a prenatal developmental toxicity study, rabbits treated via oral gavage showed effects on dams at 1000 mg/kg-bw/day: mortality, clinical signs of toxicity (dyspnea and ventral recumbancy) and decreased food consumption and body weight gain during the dosing period. At the same dose, developmental effects included skeletal malformations (incomplete ossification of limbs). The NOAEL for maternal and developmental toxicity in rabbits is 300 mg/kg-bw/day. Hallcomid M-8-10[®] did not induce gene mutations in bacteria and mammalian cells, chromosomal aberrations or unscheduled DNA synthesis in mammalian cells *in vitro*. Hallcomid M-8-10[®] is irritating to rabbit skin and rabbit eyes and is not a dermal sensitizer in guinea pigs.

No data gaps have been identified under the HPV Challenge Program.

Hazard to the Environment

For the N,N-Dimethylalkanamides Category, based on the supporting chemical, Hallcomid M-8-10[®], the 96-h LC₅₀ for acute toxicity to fish is 21.1 mg/L and the 48-h LC₅₀ for acute toxicity to aquatic invertebrates is 7.7 mg/L. The 72-h EC₅₀ for toxicity to aquatic plants is 5.47 mg/L for biomass and 16.06 mg/L for growth rate.

The ready biodegradation endpoint was identified as a data gap under the HPV Challenge Program.

The sponsor, the C.P. Hall Company, submitted a Test Plan and Robust Summaries to EPA for the N,N-dimethylalkanamides category on December 20, 2002. EPA posted the submission on the ChemRTK HPV Challenge website on January 17, 2003

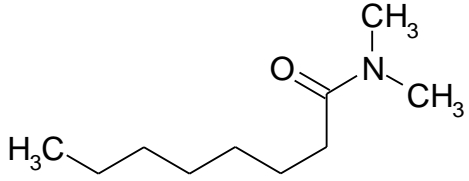
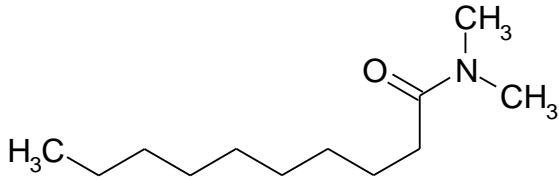
(<http://www.epa.gov/chemrtk/pubs/summaries/dimetoc/c14154tc.htm>). EPA comments on the original submission were posted to the website on May 16, 2003. Public comments were also received and posted to the website. The sponsor submitted updated/revised documents on August 14, 2003, which were posted to the ChemRTK website on October 20, 2003.

Category/Supporting Chemical Justification

The category consists of two substances (see Table 1) that are homologs with the same functionality and differ only in that N, N-dimethyldecanamide has two more carbons in its alkyl chain than N,N-dimethyloctanamide. Dimethyldecanamide is available commercially as Hallcomid M-10[®]. Dimethyloctanamide is not manufactured in pure form, but is commercially available as a major component in Hallcomid M-8-10[®]. Hallcomid M-8-10[®] contains 50 – 65% N,N-dimethyloctanamide (CASRN 1118-92-9), 37 – 50% N,N-dimethyldecanamide (CASRN 14433-76-2), 0 – 5% N,N-dimethylhexanamide (CASRN 5830-30-8) and 0 – 2% N,N-dimethyldodecanamide (CASRN 3007-53-2). The values obtained from the testing of the Hallcomid M-8-10[®] substance are expected to be in good agreement with the toxicities of the individual compounds.

The members of the N,N-dimethylalkanamides category are listed in Table 1 and their structures are in Table 2.

Table 1. Members of the N,N-dimethylalkanamides category	
Name	CASRN
<i>Sponsored Chemical</i>	
Octanamide, N,N-dimethyl-	1118-92-9
Decanamide, N,N-dimethyl-	14433-76-2
<i>Supporting Chemical</i>	
Hallcomid M-8-10 [®]	No CASRN

Table 2. Structure of N,N-Dimethylalkanamides Category Members		
CASRN	CA Index Name	Chemical Structure
SPONSORED CHEMICALS		
1118-92-9	Octanamide, N,N-dimethyl-	 <chem>CCCCCCCC(N(C)C)=O</chem>
14433-76-2	Decanamide, N,N-dimethyl-	 <chem>CCCCCCCCC(N(C)C)=O</chem>
SUPPORTING CHEMICAL		
No CASRN	Hallcomid M-8-10 [®]	Mixture containing 50 – 65% N,N-dimethyloctanamide (CASRN 1118-92-9), 37 – 50% N,N-dimethyldecanamide (CASRN 14433-76-2), 0 – 5% N,N-dimethylhexanamide and 0 – 2% N,N-dimethyldodecanamide.

The N,N-dimethylalkanamides category consists of octanamide, N,N-dimethyl- and decanamide, N,N-dimethyl-. These substances are homologs with the same functionality, and differ only in that decanamide, N,N-dimethyl- has two more carbons in its alkyl chain than octanamide, N,N-dimethyl-. Octanamide, N,N-dimethyl- is not manufactured in pure form, but as the major component (50–65% weight) of a mixture also containing 37–50% decanamide, N,N-dimethyl-, with minor impurities N,N-dimethylhexanamide (0–5%) and N,N-dimethyldodecanamide (0–2%).

1. Chemical Identity

1.1 Identification and Purity

N,N-Dimethylalkanamides exist as liquids at room temperature with moderate to high water solubility and moderate vapor pressure. The N,N-dimethylalkanamides category consists of octanamide, N,N-dimethyl- and decanamide, N,N-dimethyl-. Octanamide, N,N-dimethyl- is not manufactured in pure form, but as the major component (50–65% weigh) of a mixture also containing 37–50% decanamide, N,N-dimethyl-, with minor impurities N,N-dimethylhexanamide (0–5%) and N,N-dimethyldodecanamide (0–2%).

1.2 Physical-Chemical Properties

The physical-chemical properties of the N,N-dimethylalkanamides category are summarized in Table 3.

Property	SUPPORTING CHEMICAL Mixture of 1118-92-9 and 14433-76-2²	SPONSORED CHEMICAL Octanamide, N,N- dimethyl-	SPONSORED CHEMICAL Decanamide, N,N- dimethyl-
CASRN		1118-92-9	14433-76-2
Molecular Weight		171.28	199.34
Physical State	Liquid	Liquid	Liquid
Melting Point	-27 to -22 °C (measured)	<25 °C (Liquid)	-11 to -7 °C (measured)
Boiling Point	240–265.5 °C (measured)	257 °C (estimated) ³	290 °C (estimated) ³
Vapor Pressure	Not applicable	0.019 mm Hg at 25 °C (estimated) ^{3,4}	8.6×10 ⁻⁴ mm Hg at 25 °C (measured)
Dissociation Constant (pK _a)	Not applicable	Not applicable	Not applicable
Henry's Law Constant	Not applicable	2.95×10 ⁻⁷ atm-m ³ /mole at 25 °C (estimated) ^{3,4}	6.59×10 ⁻⁷ atm- m ³ /mole at 25 °C (estimated) ³
Water Solubility	4.3×10 ³ mg/L at 20 °C (measured)	1061 mg/L (estimated) ³	340 mg/L at 20 °C (measured)
Log K _{ow}	2.59 at 23 °C (measured)	2.46 (estimated) ³	3.92 (measured)

¹The C.P. Hall Company, Inc. Revised Test Plan and Robust Summary for N,N-Dimethylalkanamides. Available online from: <http://www.epa.gov/chemrtk/pubs/summaries/dimetoc/c14154tc.htm> as of May 31, 2011.

²The measured value is for the commercial product called Hallcomid M-8-10[®], which is a mixture containing 50–60% octanamide, N,N-dimethyl- and 35–45% decanamide, N,N-dimethyl-.

³U.S. EPA. 2011. Estimation Programs Interface Suite™ for Microsoft® Windows, v4.10. U.S. Environmental Protection Agency, Washington, DC, USA. Available online from: <http://www.epa.gov/opptintr/exposure/pubs/episuitedi.htm> as of May 31, 2011.

⁴ Estimation based on the structure of pure octanamide, N,N-dimethyl- (CASRN 1118-92-9), not the commercial mixture

2. General Information on Exposure

2.1 Production Volume and Use Pattern

The N,N-Dimethylalkanamides category chemicals had an aggregated production and/or import volume in the United States between 1 million pounds and 10.5 million pounds during calendar year 2005.

- CASRN 1118-92-9 < 500,000 pounds;
- CASRN 14433-76-2 1 million to <10 million pounds;

CASRN 1118-92-9:

Industrial processing and uses, and commercial and consumer uses for the chemical were claimed confidential. No commercial and consumer uses were reported for this chemical.

CASRN 14433-76-2:

Non-confidential information in the IUR indicated that the industrial processing and uses for the chemical include other basic organic chemical manufacturing as intermediates. Non-confidential commercial and consumer uses of these chemicals include "other."

2.2 Environmental Exposure and Fate

The environmental fate properties are provided in Table 4.

N,N-Dimethylalkanamides are expected to possess moderate mobility in soil. Biodegradation data exists for one sponsored chemical in this category. Decanamide, N,N-dimethyl- (CASRN 14433-76-2) degraded >70% after 4 days in three soil types in an inherent biodegradation in soil test (similar to OECD 304A) and is considered inherently biodegradable. In another inherent biodegradation test, decanamide, N,N-dimethyl- degraded 50% in 2.2 hours and 83.3% in 154 days in soil. Based on these data, N,N-dimethylalkanamides may be readily biodegradable. Volatilization is expected to be low to moderate based on the Henry's Law constants for the sponsored chemicals. The rate of hydrolysis is expected to be negligible. The rate of atmospheric photooxidation is considered moderate for the sponsored chemicals. N,N-Dimethylalkanamides are expected to possess low persistence (P1) and low (B1) bioaccumulation potential.

Property	SPONSORED CHEMICAL Octanamide, N,N-dimethyl-	SPONSORED CHEMICAL Decanamide, N,N-dimethyl-
CASRN	1118-92-9	14433-76-2
Photodegradation Half-life	4.8 hours (estimated) ²	4.3 hours (estimated) ² ; 33 days (direct photolysis)
Hydrolysis Half-life	Stable	Stable; <6% hydrolysis after 30 days at pH 5, 7, and 9 at 25 °C
Biodegradation	No Data >70% after 4 days (inherently biodegradable in soil); 50% after 2.2 hours, 83.3% after 154 days (inherently biodegradable in soil) (RA)	>70% after 4 days (inherently biodegradable in soil); 50% after 2.2 hours, 83.3% after 154 days (inherently biodegradable in soil)
Bioaccumulation Factor	BAF = 18 (estimated) ²	BAF = 75 (estimated) ²
Log K _{oc}	2.1 (estimated) ²	2.6 (estimated) ²

Property	SPONSORED CHEMICAL Octanamide, N,N-dimethyl-	SPONSORED CHEMICAL Decanamide, N,N-dimethyl-
Fugacity (Level III Model) ²		
Air (%)	0.8	0.8
Water (%)	26.2	24.9
Soil (%)	72.9	74.0
Sediment (%)	0.2	0.4
Persistence ³	P1 (low)	P1 (low)
Bioaccumulation ³	B1 (low)	B1 (low)

¹ The C.P. Hall Company, Inc. Revised Test Plan and Robust Summary for N,N-Dimethylalkanamides. Available online at: <http://www.epa.gov/chemrtk/pubs/summaries/dimetoc/c14154tc.htm> as of May 31, 2011.

² U.S. EPA. 2011. Estimation Programs Interface Suite™ for Microsoft® Windows, v4.10. U.S. Environmental Protection Agency, Washington, DC, USA. Available online from: <http://www.epa.gov/opptintr/exposure/pubs/episuitedi.htm> as of May 31, 2011.

³ Federal Register. 1999. Category for Persistent, Bioaccumulative, and Toxic New Chemical Substances. *Federal Register* 64, Number 213 (November 4, 1999) pp. 60194–60204.

Conclusion: The N,N-dimethylalkanamides category consists of octanamide, N,N-dimethyl- and decanamide, N,N-dimethyl-. Commercially, octanamide, N,N-dimethyl- is not manufactured in pure form, but as the major component (50–65% weight) of a mixture also containing 37–50% decanamide, N,N-dimethyl-, with minor impurities N,N-dimethylhexanamide (0–5%) and N,N-dimethyldodecanamide (0–2%). N,N-Dimethylalkanamides exist as liquids at room temperature with moderate to high water solubility and moderate vapor pressure. N,N-Dimethylalkanamides are expected to possess moderate mobility in soil. No data are available for the ready biodegradation endpoint. Volatilization is expected to be low to moderate based on the Henry's Law constants for the sponsored chemicals. The rate of hydrolysis is expected to be negligible. The rate of atmospheric photooxidation is considered moderate for the sponsored chemicals. N,N-Dimethylalkanamides are expected to possess low persistence (P1) and low (B1) bioaccumulation potential.

3. Human Health Hazard

A summary of health effects data submitted for SIDS endpoints is provided in Table 5. The table also indicates where data for the tested supporting chemical (Hallcomid M-8-10[®]) are read-across (RA) to untested members of the N,N-dimethylalkanamides category.

The commercial mixture Hallcomid M-8-10[®], containing 50 – 65% N,N-dimethyloctanamide (CASRN 1118-92-9), 37-50% N,N-dimethyldecanamide (CASRN 14433-76-2), 0 – 5% N,N-dimethylhexanamide (CASRN 5830-30-8) and 0 – 2% N,N-dimethyldodecanamide (CASRN 3007-53-2) was used for testing for the human health endpoints.

Acute Oral Toxicity

Hallcomid M-8-10[®] (no CASRN, supporting chemical)

Sprague-Dawley rats (2/sex/dose; 5/sex at the highest dose) were administered Hallcomid M-8-10[®], via gavage at 625, 1250, 2500 or 5000 mg/kg and observed for up to 14 days. Mortalities were noted at dose levels \geq 1250 mg/kg: 1/2 females at 1250 mg/kg, 2/2 females and 1/2 males at 2500 mg/kg, all animals at 5000 mg/kg.

LD₅₀ = 1250 mg/kg

Acute Inhalation Toxicity

Hallcomid M-8-10[®] (no CASRN, supporting chemical)

Wistar rats (5/sex/concentration) were exposed head-/nose-only to Hallcomid M-8-10[®], aerosols at nominal concentrations of 1000, 5000, 20,000 or 50,000 mg/m³ for 4 hours and observed for up to 14 days. Average analytical concentrations were 118.5, 586.4, 2007.6 and 3550.7 mg/m³, respectively (approximately 0.1, 0.6, 2 and 3.6 mg/L). The average MMAD of the aerosols at each concentration ranged from 1.14 to 1.37 μ m; essentially all of the particles were in the respirable range ($<$ 3 μ m). Toxicity data were based on analytical concentrations. One death occurred in the highest exposure group; there were no deaths at lower exposure concentrations.

LC₅₀ > 3.6 mg/L

Acute Dermal Toxicity

Hallcomid M-8-10[®] (no CASRN, supporting chemical)

Wistar rats (5/sex/dose) were administered Hallcomid M-8-10[®], via the dermal route at 50, 200, 2000 or 5000 mg/kg (males) or 50, 200, 400 or 2000 mg/kg (females) in cellulose under occluded conditions for 24 hours and observed for up to 14 days. Mortalities were noted at dose levels \geq 2000 mg/kg: 5/5 females and 2/5 males at 2000 mg/kg and 5/5 males at 5000 mg/kg.

400 <LD₅₀ < 2000 mg/kg

Repeated-Dose Toxicity

Hallcomid M-8-10[®] (no CASRN, supporting chemical)

(1) In a 91-day study, Wistar rats (10/sex/dose) were administered Hallcomid M-8-10[®], in the diet at concentrations of 0, 400, 2000 or 10,000 ppm (0, 27.4, 136.8 and 787.6 mg/kg-bw/day, respectively, for males and 0, 35.2, 178.5 and 894.6 mg/kg-bw/day, respectively, for females) *ad libitum*. Two additional groups (10/sex) were administered 0 or 10,000 ppm (726.7 and 907.7 mg/kg-bw/day for males and females, respectively) for 91 days followed by a control diet during a recovery period of 28 days. There were no treatment-related mortalities. No treatment-related effects were seen regarding clinical signs or gross pathological assessments. Decreased body weight gain and emaciation were noted in high-dose males (5/20 males). Decreased body weight gain was also observed in mid-dose males (6 – 8% less than controls) and high-dose recovery females. Increased cholesterol concentrations observed in high-dose male and female rats were

considered a consequence of hepatic fat metabolism that was reversible on the cessation of treatment. Increased relative liver weights in high-dose male and female rats were regarded as an adaptive effect resulting from impaired fat metabolism. Increased protein in the urine and increased incidences of basophilic regenerated tubuli in the renal cortex were noted in the high-dose group of male rats and were considered to be treatment-related effects. Assessments of low-dose males and females revealed no apparent exposure-related adverse effects. Several findings in clinical chemistry parameters and hematology assessments were reported, but were not considered to have been indicators of treatment-related adverse effects.

LOAEL ~ 787.6 mg/kg-bw/day (based on decreased body weight gain and emaciation in males, liver effects in both sexes and kidney effects in males)

NOAEL ~ 136.8 mg/kg-bw/day

(2) In a 28-day rangefinding study for the 91-day repeated-dose study described above, Wistar rats (10/sex/dose) were administered Hallcomid M-8-10[®], in the diet at concentrations of 0, 1000, 3000 or 10,000 ppm (0, 82.9, 250.6 and 965.0mg/kg-bw/day, respectively, for males and 0, 93.7, 293.2 and 1075.7 mg/kg-bw/day, respectively, for females) *ad libitum*. No differential blood counts, urinalyses or histological examinations were done. A dose of 20000 ppm was inadvertently fed to the animals in the first week; treatment group not specified. Appearance, general behavior and mortality rate were not affected by treatment with the test substance. One animal in the 1000 ppm group died during handling (blood sampling). No clinical signs of toxicity were observed in treated animals; feed and water consumption of controls when compared to treated animals was similar. The study personnel did not assign a NOAEL/LOAEL; however, no significant findings were observed other than a significant dose-dependent increase in relative liver weight at 3000 ppm and 10,000 ppm.

Reproductive Toxicity

No specific reproductive toxicity studies are available for the sponsored chemicals. Evaluation of effects on fertility and male reproductive organs reported in the 91-day repeated-dose oral toxicity study and available developmental toxicity studies of the supporting chemical, Hallcomid M-8-10[®], were used to address the reproductive toxicity endpoint for purposes of the HPV Challenge Program.

Hallcomid M-8-10[®] (no CASRN, supporting chemical)

In the above-described 91-day, repeated-dose oral toxicity study in Wistar rats, effects seen on the male reproductive organs (tubular dilation of the testes, round cell infiltration in the epididymides, sperm granuloma in the prostate or epididymides, tubular atrophy, aspermia of the epididymides and testicular atrophy) in one or two test animals were not considered to be treatment-related. No effects on the female reproductive organs were observed.

Developmental Toxicity

Hallcomid M-8-10[®] (no CASRN, supporting chemical)

(1) Pregnant Wistar rats (25 females/dose) were administered Hallcomid M-8-10[®] via gavage at 50, 150 or 450 mg/kg-bw/day on days 6 – 15 of gestation. Animals were observed until gestation day 21. Maternal effects included reduced food consumption in mid- and high-dose females, reduced body weight gain in high-dose females and clinical signs of toxicity in high-dose females (ruffled fur, ventral recumbancy, dyspnea, apathy, abdominal hair loss and comatose state). Blood was found in the uterus in one control and two low-dose females. The significant developmental effects observed at the high dose included increased mean fetal body weight, increased post-implantation loss and skeletal malformations (non-ossified cervical vertebra, incompletely ossified sternebra and non-ossified metatarsala). No treatment-related developmental effects were noted regarding mean number of corpora lutea, implantations, pup sex ratio, pre-implantation loss, number of fetuses or mean number of live fetuses.

LOAEL (maternal toxicity) = 450 mg/kg-bw/day (based on adverse clinical signs in dams and effects on mean body weight and post-implantation loss)

NOAEL (maternal toxicity) = 150 mg/kg-bw/day

LOAEL (developmental toxicity) = 450 mg/kg-bw/day (based on post-implantation loss and skeletal malformations in fetuses)

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

(2) Pregnant Chinchilla rabbits (16 females/dose) were administered Hallcomid M-8-10[®] via gavage at 100, 300 or 1000 mg/kg-bw/day on gestation days 6 – 18. Animals were observed until gestation day 28. Mortality was observed in the low- (3 animals), mid- (1 animal) and high-(1 animal) dose groups. The cause of death in two low-dose animals was attributed to intubation error, but the cause of death in all others was undetermined. Clinical signs of toxicity noted in the high-dose female that died included slight dyspnea and ventral recumbency; dyspnea was also observed in a surviving female. No abnormal clinical signs were noted in controls or animals treated with 100 or 300 mg/kg-bw/day. High-dose animals experienced decreased food consumption (21% lower than controls) and decreased body weight gain (> 50% less than controls) during the dosing period and increased food consumption and weight gain during the recovery period. Two mid-dose animals experienced total resorptions, but this effect was considered incidental by the study authors due to a lack of post-implantation loss at the higher dose. Isolated histopathological findings included discolored foci and nodules or crateriform retractions in the mucosa of the fundus, forestomach or stomach. These findings were considered incidental because they are common findings in rabbits of similar strain and age. Excepting two runts in the control and 300 mg/kg-bw/day groups, external examination showed no abnormal findings in the 100 or 1000 mg/kg-bw/day groups. No treatment-related effects for corpora lutea, pre-implantation loss, post-implantation loss, number of fetuses, mean numbers of live fetuses, mean fetal body weight, external pup examination or pup sex ratios were observed. Skeletal malformations (incomplete ossification) were sporadic at the low and mid-doses, but were consistently significant at the high dose.

LOAEL (maternal toxicity) = 1000 mg/kg-bw/day (based on mortality, reduced food consumption and body weight gain and clinical signs of toxicity)

NOAEL (maternal toxicity) = 300 mg/kg-bw/day

LOAEL (developmental toxicity) = 1000 mg/kg-bw/day (based on incomplete ossification of limbs)

NOAEL (developmental toxicity) = 300 mg/kg-bw/day

Genetic Toxicity – Gene Mutation

In vitro

Hallcomid M-8-10[®] (no CASRN, supporting chemical)

(1) In a reverse mutation assay, *Salmonella typhimurium* strains TA98, TA100, TA1535 and TA1537 were exposed to Hallcomid M-8-10[®] at 8, 40, 200, 1000 or 5000 µg/plate during test 1 and 0, 25, 50, 100, 200, 400 or 800 µg/plate during test 2, both in the presence and absence of metabolic activation. The cytotoxic concentration was 200 µg/plate (TA1535 and TA1537), 400 µg/plate (TA98) and 800 µg/plate (TA100). Positive and negative controls produced appropriate responses.

Hallcomid M-8-10[®] was not mutagenic in this assay.

(2) V79 Chinese hamster lung cells were exposed to Hallcomid M-8-10[®] at 25, 50, 100, 125, 150, 200 or 250 µg/mL in the presence and absence of metabolic activation. The cytotoxic concentration was 200µg/mL in the absence of metabolic activation and 250 µg/mL in the presence of metabolic activation. Positive and negative controls produced appropriate responses.

Hallcomid M-8-10[®] did was not mutagenic in this assay.

Genetic Toxicity – Chromosomal Aberrations

In vitro

Hallcomid M-8-10[®] (no CASRN, supporting chemical)

Chinese hamster ovary cells (CHO) were exposed to Hallcomid M-8-10[®] at 10, 40 or 160 µg/mL in the absence of metabolic activation and 7.2, 36 or 180 µg/mL in the presence of metabolic activation. Positive controls produced an appropriate response.

Hallcomid M-8-10[®] did not induce chromosomal aberrations in this assay.

Genetic Toxicity – Other

In vitro

Hallcomid M-8-10[®] (no CASRN, supporting chemical)

In the unscheduled DNA synthesis assay, rat primary hepatocytes were exposed to Hallcomid M-8-10[®] at 29.8 – 118.6 µg/mL in the absence of metabolic activation. Positive controls produced an appropriate response.

Hallcomid M-8-10[®] did not induce unscheduled DNA synthesis in this assay.

Additional Information

Skin Irritation

Hallcomid M-8-10[®] (no CASRN, supporting chemical)

(1) New Zealand White rabbits (3/sex) were administered 0.5 mL undiluted Hallcomid M-8-10[®] to clipped, intact skin under occlusive conditions for 4 hours and observed for 72 hours. Effects included erythema, eschar formation, blanching, light or dark brown coloration on the site and coriaceousness. The primary irritation index was 4.625.

Hallcomid M-8-10[®] was irritating to rabbit skin.

(2) One male New Zealand White rabbit was administered 0.5 mL undiluted Hallcomid M-8-10[®] to clipped, intact skin under occlusive conditions for 4 hours and observed for 72 hours. Effects included moderate to severe erythema, severe edema, blanching, light and dark brown coloration on the site, coriaceousness, necrosis and slight fissuring. The study was terminated without testing additional animals. The primary irritation index was 7.

Hallcomid M-8-10[®] was corrosive to rabbit skin.

Eye Irritation

Hallcomid M-8-10[®] (no CASRN, supporting chemical)

One male New Zealand White rabbit was administered 0.1 mL undiluted Hallcomid M-8-10[®] into the eye. The eye was rinsed after 24 hours and observed 96 hours after instillation. Effects included corneal opacity, iritis and conjunctival irritation. Total irritation scored ranged from 26 at 1 hour to 66 at day 4.

Hallcomid M-8-10[®] was highly irritating to rabbit eyes.

Sensitization

Hallcomid M-8-10[®] (no CASRN, supporting chemical)

Dunkin-Hartley guinea pigs (10/sex) were treated with Hallcomid M-8-10[®]. Intradermal induction consisted of 5% test material in 80% ethanol/20% distilled water (0.3 mL) applied once weekly (6-hour exposures) for 3 weeks. After 2 weeks, 2.5% test material in acetone was applied to treated animals. Ten naïve animals (5/sex) were concurrently treated with 2.5% test material in acetone. The mean severity scores of test animals were not different from those of controls.

Hallcomid M-8-10[®] was not a dermal sensitizer in guinea pigs.

Conclusion: The acute toxicity of Hallcomid M-8-10[®] to rats is low via the oral route and moderate via the inhalation and dermal routes. Repeated dietary exposure of rats to Hallcomid M-8-10[®] for 91 days resulted in decreased body weight gain, emaciation, increased serum cholesterol, increased liver weights, increased protein in the urine and increased incidence of basophilic regenerative tubuli in the renal cortex at 787.6 mg/kg-bw/day. These effects were not seen in recovery animals. The NOAEL for systemic toxicity is 136.8 mg/kg-bw/day. No specific reproductive toxicity studies are available; however, in the 91-day repeated-dose toxicity

study in rats, no treatment-related effects were observed on the reproductive organs in rats treated with Hallcomid M-8-10[®]. In a prenatal developmental toxicity study, rats treated via oral gavage with Hallcomid M-8-10[®] showed effects on the dams at 450 mg/kg-bw/day: reduced food consumption, reduced body weight gain and clinical signs of toxicity (ruffled fur, ventral recumbancy, dyspnea, apathy, abdominal hair loss and comatose state). At the same dose, developmental effects included increased mean fetal body weight, increased post-implantation loss and skeletal malformations (non-ossified cervical vertebra, incompletely ossified sternebra and non-ossified metatarsala). The NOAEL for maternal and developmental toxicity in rats is 150 mg/kg-bw/day. In a prenatal developmental toxicity study, rabbits treated via oral gavage showed effects on dams at 1000 mg/kg-bw/day: mortality, clinical signs of toxicity (dyspnea and ventral recumbancy) and decreased food consumption and body weight gain during the dosing period. At the same dose, developmental effects included skeletal malformations (incomplete ossification of limbs). The NOAEL for maternal and developmental toxicity in rabbits is 300 mg/kg-bw/day. Hallcomid M-8-10[®] did not induce gene mutations in bacteria and mammalian cells, chromosomal aberrations or unscheduled DNA synthesis in mammalian cells *in vitro*. Hallcomid M-8-10[®] is irritating to rabbit skin and rabbit eyes and is not a dermal sensitizer in guinea pigs.

Table 5. Summary Table of the Screening Information Data Sets Submitted under the U.S. HPV Challenge Program – Human Health Data			
Endpoint	N,N-Dimethyloctanamide (1118-92-9)	N,N-Dimethyldecanamide (14433-76-2)	Hallcomid M-8-10[®] (no CASRN, supporting chemical)
Acute Oral Toxicity LD₅₀ (mg/kg)	No Data 1250 (RA)	No Data 1250 (RA)	1250
Acute Inhalation Toxicity LC₅₀ (mg/L)	No Data > 3.6 (RA)	No Data > 3.6 (RA)	> 3.6
Acute Dermal Toxicity LD₅₀ (mg/kg)	No Data > 400 and < 2000 (RA)	No Data > 400 and < 2000 (RA)	> 400 and < 2000
Repeated-Dose Toxicity NOAEL/LOAEL Oral (mg/kg-bw/day)	No Data NOAEL = 136.8 LOAEL = 787.6 (RA)	No Data NOAEL = 136.8 LOAEL = 787.6 (RA)	NOAEL = 136.8 LOAEL = 787.6
Reproductive Toxicity NOAEL/LOAEL Oral (mg/kg-bw/day)	No Data No treatment-related histopathological effects were seen in reproductive organs of rats administered Hallcomid M-8-10 [®] for 91 d (RA)	No Data No treatment-related histopathological effects were seen in reproductive organs of rats administered Hallcomid M-8-10 [®] for 91 d (RA)	No treatment-related histopathological effects were seen in reproductive organs of rats administered Hallcomid M-8-10 [®] for 91 d
Developmental Toxicity NOAEL/LOAL Oral (mg/kg-bw/day) Maternal/ Developmental Toxicity Maternal / Developmental Toxicity	No Data (rat) NOAEL = 150 LOAEL = 450 NOAEL = 300 LOAEL = 1000 (RA)	No Data (rat) NOAEL = 150 LOAEL = 450 NOAEL = 300 LOAEL = 1000 (RA)	(rat) NOAEL = 150 LOAEL = 450 (rabbit) NOAEL = 300 LOAEL = 1000
Genetic Toxicity – Gene Mutation <i>In vitro</i>	No Data Negative (RA)	No Data Negative (RA)	Negative
Genetic Toxicity – Chromosomal Aberrations <i>In vitro</i>	No Data Negative (RA)	No Data Negative (RA)	Negative
Genetic Toxicity – Other <i>In vitro</i> Unscheduled DNA Synthesis	No Data Negative (RA)	No Data Negative (RA)	Negative
Additional Information Skin Irritation Eye Irritation Sensitization	– – –	– – –	Irritating Highly irritating Not sensitizing

Measured data in bold; (RA) = Read Across; – indicates that endpoint not addressed for this substance

4. Hazard to the Environment

A summary of aquatic toxicity data submitted for SIDS endpoints is provided in Table 6. The table also indicates where data for the tested supporting chemical (Hallcomid M-8-10[®]) are read-across (RA) to untested members of the N,N-dimethylalkanamides category.

Aquatic toxicity testing was conducted with the commercial mixture Hallcomid M-8-10[®], containing 50 – 65% N,N-dimethyloctanamide (CASRN 1118-92-9), 37 – 50% N,N-dimethyldecanamide (CASRN 14433-76-2), 0 – 5% N,N-dimethylhexanamide (CASRN 5830-30-8) and 0 – 2% N,N-dimethyldodecanamide (CASRN 3007-53-2). This mixture is considered adequate to satisfy the aquatic toxicity endpoints for the N,N-dimethylalkanamides category.

Acute Toxicity to Fish

Hallcomid M-8-10[®] (no CASRN, supporting chemical)

Rainbow trout (*Oncorhynchus mykiss*) were exposed to Hallcomid M-8-10[®] at nominal concentrations of 0 (control), 5.00, 8.89, 15.8, 28.1 or 50.0 mg/L under static conditions for 96 hours. Measured concentrations were not provided. Sublethal and lethal effects were evident at concentrations ≥ 8.89 and ≥ 28.1 mg/L, respectively.

96-h LC₅₀ = 21.1 mg/L

Acute Toxicity to Aquatic Invertebrates

Hallcomid M-8-10[®] (no CASRN, supporting chemical)

Water fleas (*Daphnia magna*) were exposed to Hallcomid M-8-10[®] at nominal concentrations of 0 (solvent and untreated control), 1, 2, 4, 8 or 16 mg/L under static conditions for 48 hours. Measured concentrations were not provided. No effects were seen at concentrations ≤ 4 mg/L.

48-h LC₅₀ = 7.7 mg/L

Toxicity to Aquatic Plants

Hallcomid M-8-10[®] (no CASRN, supporting chemical)

Green algae (*Pseudokirchneriella subcapitata*) were exposed to Hallcomid M-8-10[®] at concentrations of 0, 1.8, 3.2, 5.6, 10, 18, 32 or 56 mg/L under static conditions for 72 hours. Analytical concentrations of test substance were approximately 95% of nominal concentrations.

72-h EC₅₀ (biomass) = 5.47 mg/L

72-h EC₅₀ (growth rate) = 16.06 mg/L

Conclusion: For the N,N-Dimethylalkanamides Category, based on the supporting chemical, Hallcomid M-8-10[®], the 96-h LC₅₀ for acute toxicity to fish is 21.1 mg/L and the 48-h LC₅₀ for acute toxicity to aquatic invertebrates is 7.7 mg/L. The 72-h EC₅₀ for toxicity to aquatic plants is 5.47 mg/L for biomass and 16.06 mg/L for growth rate.

Table 6. Summary of the Screening Information Data Set under the U.S. HPV Challenge Program - Aquatic Toxicity Data			
Endpoints	SPONSORED CHEMICAL N,N-Dimethyloctanamide (1118-92-9)	SPONSORED CHEMICAL N,N-Dimethyldecanamide (14433-76-2)	SUPPORTING CHEMICAL Hallcomid M-8-10[®] (No CASRN)
Fish 96-h LC₅₀ (mg/L)	No Data 21.1 (RA)	No Data 21.1 (RA)	21.1
Aquatic Invertebrates 48-h LC₅₀ (mg/L)	No Data 7.7 (RA)	No Data 7.7 (RA)	7.7
Aquatic Plants 72-h EC₅₀ (biomass) (mg/L)	No Data 5.47	No Data 5.47	5.47
72-h EC₅₀ (growth rate) (mg/L)	16.06 (RA)	16.06 (RA)	16.06

Bold = measured data (i.e., derived from experiment); (RA) = Read Across