

SCREENING-LEVEL HAZARD CHARACTERIZATION

Carbamic acid, 1H-benzimidazol-2-yl, methyl ester (CASRN 10605-21-7)

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.

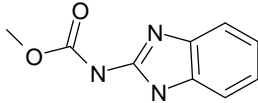
OPPT does not develop HCs for those HPV chemicals which have already been assessed internationally through the HPV program of the Organization for Economic Cooperation and Development (OECD) and for which Screening Initial Data Set (SIDS) Initial Assessment Reports (SIAR) and SIDS Initial Assessment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

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>.

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>10605-21-7</p>
<p>Chemical Abstract Index Name</p>	<p>Carbamic acid, 1H-benzimidazol-2-yl-, methyl ester -</p>
<p>Structural Formula</p>	 <p>The image shows the chemical structure of methyl 1H-benzimidazol-2-ylcarbamate. It consists of a benzimidazole ring system (a benzene ring fused to an imidazole ring) attached at the 2-position to a carbonyl group (-C(=O)-). This carbonyl group is further bonded to a methoxy group (-OCH₃).</p>
<p style="text-align: center;">Summary</p> <p>CASRN 10605-21-7 is an off-white powder possessing low vapor pressure and moderate water solubility. It is expected to possess moderate mobility in soil. Volatilization is considered low based on its Henry's Law constant. The rate of hydrolysis is negligible. The rate of atmospheric photooxidation is considered rapid. CASRN 10605-21-7 is expected to have moderate persistence (P2) and low bioaccumulation potential (B1).</p> <p>The acute oral and inhalation toxicity of CASRN 10605-21-7 in rats is low and the acute dermal toxicity in rabbits is low. In a 2-year chronic toxicity study, the NOAEL and LOAEL with CASRN 10605-21-7 via the diet in rats could not be established due to deaths in the control animals. Repeated-dose toxicity studies show that the liver and thyroid are the primary target organs of CASRN 10605-21-7 with effects in dogs being observed after dietary exposure at 12.5 mg/kg/day; the NOAEL for systemic toxicity is 2.5 mg/kg/day. The testes is a known target organ of CASRN 10605-21-7. In a three-generation reproductive toxicity study with CASRN 10605-21-7 a decrease in litter weights at weaning in all generations were observed at 5000 mg/kg/day; the NOAEL for reproductive toxicity is 500 mg/kg/day. A prenatal oral developmental toxicity study with CASRN 10605-21-7 in rats showed a decrease in maternal body weight gain, effects on liver weight and an increased incidence of resorptions at 90 mg/kg/day; the NOAEL for maternal toxicity is 20 mg/kg/day. In the same study, a significant reduction in fetal body weight was observed at 20 mg/kg/day; the NOAEL for developmental toxicity is 10 mg/kg/day. CASRN 10605-21-7 induced gene mutations in bacteria <i>in vitro</i> and induced chromosomal aberrations in mammalian cells <i>in vitro</i>. CASRN 10605-21-7 induced mouse micronuclei <i>in vivo</i>. CASRN 10605-21-7 did not increase the incidence of tumors in rats but did in female mice. CASRN 10605-21-7 is irritating to rabbit skin and eye, and is not a skin sensitizer in guinea pigs.</p> <p>The 96-h LC₅₀ value for acute toxicity to fish for CASRN 10605-21-7 ranges from 0.007 to 5.5 mg/L. The 48-h EC₅₀ value for acute toxicity to aquatic invertebrates for CASRN 10605-21-7 is 0.16 mg/L and the 72-h EC₅₀ value for toxicity to aquatic plants ranges from 1.3 to 4.5 mg/L for biomass.</p> <p>No data gaps were identified under the HPV Challenge Program.</p>	

The sponsor, Troy Chemical Company, submitted a Test Plan and Robust Summaries to EPA for Carbamic acid, 1H-benzimidazol-2-yl, methyl ester (CAS No. 10605-21-7; 9th CI name: carbamic acid, 1H-benzimidazol-2-yl, methyl ester) on January 11, 2005. EPA posted the submission on the ChemRTK HPV Challenge website on February 23, 2005 (<http://www.epa.gov/chemrtk/pubs/summaries/carbam1h/c15800tc.htm>). EPA comments on the original submission were posted to the website on April 25, 2006. Public comments were also received and posted to the website.

1. Chemical Identity

1.1 Identification and Purity

Carbamic acid, N-1H-benzimidazol-2-yl-, methyl ester (> 98% pure) is an off-white powder possessing low vapor pressure and moderate water solubility.

1.2 Physical-Chemical Properties

The physical-chemical properties of carbamic acid, N-1H-benzimidazol-2-yl-, methyl ester are summarized in Table 1.

Property	Value
CASRN	10605-21-7
Molecular Weight	191.19
Physical State	Off-white powder
Melting Point	Begins to decompose at approximately 275°C prior to melting (measured)
Boiling Point	Not applicable (Decomposes prior to boiling)
Vapor Pressure	2.2×10^{-7} mm Hg at 25°C (measured)
Water Solubility	12.9 mg/L at 20°C (measured)
Dissociation Constant (pK _a)	4.49 (measured)
Henry's Law Constant	$<1 \times 10^{-10}$ atm-m ³ /mol (estimated) ²
Log K _{ow}	1.60 at 23 °C (measured)

¹Troy Chemical Company. January 11, 2005. Robust Summary for Carbamic acid, N-1H-benzimidazol-2-yl-, methyl ester. Available online from: <http://www.epa.gov/chemrtk/pubs/summaries/carbam1h/c15800tc.htm> as of November 1, 2010.

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

2. General Information on Exposure

2.1 Production Volume and Use Pattern

CASRN 10605-21-7 was not reported in the 2006 IUR.

2.2 Environmental Exposure and Fate

The environmental fate data are provided in Table 2. CASRN 10605-21-7 is expected to possess moderate mobility in soil. CASRN 10605-21-7 achieved 0% of its theoretical biochemical oxygen demand (BOD) in 28 days using the modified MITI (OECD 301C) test and was classified as not readily biodegradable. It was also not readily biodegradable using a closed bottle (OECD 301D) tests, but achieved 22-41% of its theoretical BOD after a 21 day incubation period. Under environmental conditions, the time for 50% dissipation (DT₅₀) was reported as 6-12 months on bare soil, 3-6 months on turf, and 2 months in water under aerobic conditions. The rate of volatilization is considered low based on its Henry's Law constant. The rate of hydrolysis is negligible. CASRN 10605-21-7 is expected to have moderate persistence (P2) and low bioaccumulation potential (B1).

Conclusion: Carbamic acid, N-1H-benzimidazol-2-yl-, methyl ester is an off-white powder possessing low vapor pressure and moderate water solubility. It is expected to possess moderate mobility in soil. Volatilization is considered low based on its Henry's Law constant. The rate of hydrolysis is negligible. The rate of atmospheric photooxidation is considered rapid. Carbamic acid, N-1H-benzimidazol-2-yl-, methyl ester is expected to have moderate persistence (P2) and low bioaccumulation potential (B1).

Table 2. Environmental Fate Characteristics of Carbamic acid, N-1H-benzimidazol-2-yl-, methyl ester¹	
Property	Value
Photodegradation Half-life	0.6 hours (estimated) ²
Hydrolysis Half-life	Stable at pH 5 and 7 and 25 °C. Half-life = 65 days at pH 9 and 25 °C
Biodegradation	22-41% after 21 days (not readily biodegradable); 0% after 28 days (not readily biodegradable) ³ ; Half-life 6-12 months on bare soil, 3-6 months on turf, and 2 months in water under aerobic conditions ⁴
Bioaccumulation Factor	BCF = 0.6-1.1 (measured in carp at 0.020 mg/L) ³ ; BCF = 1.5-3.5 (measured in carp at 0.0020 mg/L) ³ BAF = 2.7 (estimated) ²
Log K _{oc}	2.6 (estimated) ²
Fugacity (Level III Model) ²	
Air (%)	<0.1
Water (%)	13.0
Soil (%)	86.8
Sediment (%)	0.3
Persistence ⁵	P2 (moderate)
Bioaccumulation ⁵	B1 (low)

¹ Troy Chemical Company. January 11, 2005. Robust Summary for Carbamic acid, N-1H-benzimidazol-2-yl-, methyl ester. Available online from: <http://www.epa.gov/chemrtk/pubs/summaries/carbam1h/c15800tc.htm> as of November 1, 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 from: <http://www.epa.gov/opptintr/exposure/pubs/episuitedi.htm> as of November 2, 2010.

³ National Institute of Technology and Evaluation. 2002. Biodegradation and Bioaccumulation of the Existing Chemical Substances under the Chemical Substances Control Law. Available online from: http://www.safe.nite.go.jp/english/kizon/KIZON_start_hazkizon.html as of November 2, 2010.

⁴ Tomlin TDS. 2003. The e-Pesticide Manual 13th edition version 3.0.

⁵ Federal Register. 1999. Category for Persistent, Bioaccumulative, and Toxic New Chemical Substances. *Federal Register* 64, Number 213 (November 4, 1999) pp. 60194–60204.

3. Human Health Hazard

EPA has evaluated the toxicity of CASRN 10605-21-7 as part of its Registration Eligibility Decision (RED) on thiophenate-M (CASRN 23564-05-8). The document can be viewed at the following link: http://www.epa.gov/oppsrrd1/REDs/tm_red.pdf

Acute Oral Toxicity

Fasted Harlan Sprague-Dawley rats (5/sex) were administered a single dose of the test material (LX1132-01) via oral gavage at 5050 mg/kg. The animals were fasted for at least 16 hours prior

to treatment. The animals were observed at least three times a day on initial treatment day and at least once daily thereafter for 14 days. No mortality was observed during the study.

LD₅₀ > 5050 mg/kg

Acute Inhalation Toxicity

See EPA RED document at: http://www.epa.gov/oppsrrd1/REDS/tm_red.pdf

LC₅₀ Rat > 5 mg/L

Acute Dermal Toxicity

See EPA RED document at: http://www.epa.gov/oppsrrd1/REDS/tm_red.pdf

LD₅₀ Rabbit > 2000 mg/kg

Repeated-Dose Toxicity

(1) In a 2-year combined chronic/carcinogenicity toxicity study, wistar rats (60/sex/dose) were administered carbendazim (99% purity) in the diet daily at 0, 150, 300 or 2000 mg/kg-bw/day (approximately 0, 7.5, 15 or 100 mg/kg-bw/day) for 2 years. The 2000 mg/kg-bw/day dose was increased to 5000 mg/kg/day after 1 week, then to 10,000 mg/kg-bw/day (approximately 500 mg/kg-bw/day) after 2 weeks for the remainder of the study. Animals were examined daily for clinical signs of toxicity. Body weight and food consumption were measured regularly throughout the study. Hematological, blood chemistry, and urinalysis were measured periodically during the study. All animals were subjected to complete gross necropsy and selected organs were weighed. Tissues were examined microscopically in 20 males and 20 female rats in the control and high dose groups. There was 50% mortality in control and low-dose females at week 88 and in mid and high dose females at 92-96 weeks. There were no differences between test groups and control animals concerning clinical signs of toxicity or food consumption. Increased liver weight was noted in high-dose females (significance not determined). Body weights were significantly (level of significance not reported) reduced in low dose males from week 88 to term and in high-dose females from week 12 to term. Urinalyses were comparable among all groups. Of the hematological parameters examined, hemoglobin was reduced in high-dose females at weeks 26, 52 and 103 and hematocrit was reduced in high-dose females at week 103. An increased incidence of diffuse proliferation of parafollicular cells of the thyroid, increased liver weight, increased serum glutamic pyruvic transaminase activity and decreased total serum protein were observed in high-dose females.

NOAEL/LOAEL = Not determined

(2) In a two-year dietary dog study, effects were observed in the liver at 12.5 mg/kg/day. See data evaluation in EPA RED document: http://www.epa.gov/oppsrrd1/REDS/tm_red.pdf

LOAEL = 12.5 mg/kg/day (based on histopathological lesions of the liver characterized as swollen, vacuolated hepatic cells, hepatic cirrhosis and chronic hepatitis in both sexes)

NOAEL = 2.5 mg/kg/day

(3) Repeated-dose studies in several species are summarized in the WHO monograph (1993): <http://www.inchem.org/documents/ehc/ehc/ehc149.htm#SectionNumber:7.4>

Reproductive Toxicity

(1) The testes is a target organ of CASRN 10605-21-7.

See EPA RED document at: http://www.epa.gov/oppsrrd1/REDS/tm_red.pdf

(2) In a three-generation reproductive toxicity study, Chr-CD rats (3 male and 16 – 20 female/dose) were administered carbendazim (purity not stated) daily in the diet at 0, 100, 500, 5000 or 10,000 mg/kg-bw/day (approximately 0, 5, 25, 250 or 500 mg/kg-bw/day). The parental animals were fed the treated diet at 21 days of age and mated to produce the F1_a litter at 100 days of age. The number of matings, pregnancies and number of pups in each litter at birth was recorded. The litters were culled to 10 pups/litter on day 4. The number of live pups was recorded on days 4, 12 and 21 as well as pup weight at weaning. The parental animals were mated again to produce the F1_b litters. The F1_b litters were maintained on respective diets (not clearly stated) for 110 days and then mated to produce the F2_a and F2_b litters. The F3_a and F3_b litters were produced in the same manner as the previous generation. Gross and histopathological examinations of selected tissues and organs were performed on two males and two females in each of the five F3_b litters from the control, 500 and 5000 mg/kg-bw/day dose groups. There were no treatment related effects on fertility, gestation, viability or lactation. The average litter weights at weaning were reduced in all generations at 250 and 500 mg/kg-bw/day (significance not reported). Examination of F3_b weanlings showed no significant treatment-related effects.

LOAEL (reproductive toxicity) = 5000 mg/kg-bw/day (based on decreased litter weight at weaning)

NOAEL (reproductive toxicity) = 500 mg/kg-bw/day

Developmental Toxicity

(1) In a prenatal developmental toxicity study, pregnant CrI: CDBR rats (25 /dose) were administered carbendazim (purity not stated) daily via oral gavage at 0, 5, 10, 20 or 90 mg/kg/day during days 7 – 16 of gestation. Decreased body weight gain and increased relative and absolute liver weight were observed at the high-dose level. Decreased pregnancy rate was observed at the high-dose level. An increase in the incidence of early resorptions per dam, decreased litter size and the total resorptions of three litters occurred at the highest dose, only the reductions in females per litter was significant. Significant reductions in mean fetal body weight were observed at 20 and 90 mg/kg/day. A significant increase in the incidence of fetal malformations was also seen at the high dose. Malformations consisted of hydrocephaly, microphthalmia (unnatural smallness of the eye resulting from disease or imperfect development), anophthalmi (sightlessness especially because of a structural defect in or the absence of an eye), malformed scapulae and axial skeletal malformations. Statistical significance of treatment-related effects was not reported for the previous endpoints.

LOAEL (maternal toxicity) = 90 mg/kg/day (based on decreased body weight gain, liver effects and increased incidence in resorptions)

NOAEL (maternal toxicity) = 20 mg/kg/day

LOAEL (developmental toxicity) = 20 mg/kg/day (based on reduced fetal weight)

NOAEL (developmental toxicity) = 10 mg/kg/day

(2) In the three generation study described above, administration of the test substance via the diet up to 10,000 mg/kg-bw/day showed decreased litter weight at weaning at 5000 and 10000 mg/kg-bw/day. Effects on parental animals were not reported.

NOAEL (maternal toxicity) = Effects on parental animals not reported

LOAEL (developmental toxicity) = 5000 mg/kg-bw/day (based on decreased litter weight at weaning)

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

Genetic Toxicity – Gene Mutation

In vitro

(1) Two assays were performed with *Salmonella typhimurium* strains TA 98, TA 100, TA 1535, TA 1537, , and *Escherichia coli* strain WP2 *uvrA* in the presence and absence of S9 metabolic activation to carbendazim (98% purity) at concentrations of 0, 62, 185, 566, 1667, and 5000 µg/plate in the first assay and 0, 313, 625, 1250, 2500, and 5000 µg/plate in the second assay. Positive and negative controls were conducted concurrently and responses were appropriate. Three replicates were conducted per concentration. Precipitate was noted in the agar at and above 556 µg/plate. No cytotoxicity was observed in any strain at any dose level. The test substance produced a two-fold increase in mean number of revertants in two strains of *S. typhimurium* (TA 1537 and TA 98) with metabolic activation at 5000 ug/plate, with a tentative dose-response relationship. No treatment-related affects were seen in any other strains.

Carbamic acid, 1H-benzimidazol-2-yl-, methyl ester was mutagenic in these assays.

(2) Carbamic acid, 1H-benzimidazol-2-yl-, methyl ester was also tested by the National Toxicology Program (NTP) in a bacterial reverse mutation assay, in strains TA 98, 100, 1535 and 1537 up to 10mg/plate with and without metabolic activation. Precipitate was observed at 1 mg/plate and above. The test substance was negative without metabolic activation and positive with activation in strains TA 98, 100 and 1537. The test substance was negative with and without metabolic activation in strain TA 1535.

Carbamic acid, 1H-benzimidazol-2-yl-, methyl ester was mutagenic in this assay.

Genetic Toxicity – Chromosomal Aberrations

In vitro

(1) Chinese Hamster Ovary (CHO) cells were treated with carbendazim (98% purity) with and without S9 metabolic activation at concentrations of 0, 0.05, 0.1, 0.2, 0.4, 0.78, 1.56, 3.13, 6.25,

12.5, 25, 80, 100 or 200 µg/mL and again at concentrations of 0, 1, 2.5, 5, 10, 30, 50, 75, 100, 150 or 200 µg/mL. The dosing/harvest times were 1/8 hours (pulse treatment) in the first experiment and 18/18 and 32/32 hours without activation (both continuous treatment) and 4/18 and 4/32 hours with activation (both pulse treatment). Negative and positive controls were used and produce the appropriate response. In the first experiment, the test substance did not induce a significant (level of significance not reported) increase in the number of cells with chromosomal aberrations at any of the dose levels analyzed when compared with the negative control values. In the second test, in the absence of S9 (in both groups) and the presence of S9 (in the 4/18 hour group), the test substance induced a significant (level of significance not reported) increase in the number of cells with chromosomal aberrations. Clear evidence of polyploidy was observed at all time-points and concentrations analyzed in the second experiment.

Carbamic acid, 1H-benzimidazol-2-yl-, methyl ester induced chromosomal aberrations in this assay.

(2) Carbamic acid, 1H-benzimidazol-2-yl-, methyl ester was also tested by the National Toxicology Program (NTP) and was found to be negative for induction of chromosomal aberrations and sister chromatid exchange in mammalian (CHO) cells. In the NTP chromosomal aberrations study (study ID # 053570) mammalian (CHO) cells were treated with 50, 100, and 160 micrograms per milliliter of Carbamic acid, 1H-benzimidazol-2-yl-, methyl ester and with Mitomycin, the positive control, at 0.0625 and 0.25 micrograms per milliliter with activation. Additionally the mammalian (CHO) cells were also treated with 50, 100, and 160 micrograms per milliliter of Carbamic acid, 1H-benzimidazol-2-yl-, methyl ester and Cyclophosphamide, a positive control, at 2.5 and 7.5 micrograms per milliliter with activation (http://ntp-apps.niehs.nih.gov/ntp_tox/index.cfm?fuseaction=invitroca.cadata&study_no=053570&cas_no=10605%2D21%2D7&endpointlist=CAB).

Carbamic acid, 1H-benzimidazol-2-yl-, methyl ester did not induce chromosomal aberrations or sister chromatid exchange in these assays.

In vivo

An *in vivo* bone marrow micronucleus assay was performed with the test substance in CD-1 mice (10/sex/dose). Following a fasting period of 2 hours, mice were treated once via oral gavage with 2000 gm/kg/day of test substance. The negative control group was treated in a similar way with corn-oil (the vehicle). A positive control group, consisting of 5 male and 5 female mice, was given a single intraperitoneal injection with the mutagen mitomycin C (0.75 mg/kg/bw). At 24 hours after treatment, 10 animals of the negative control (5/sex) of the test group (5/sex) and 10 animals(5/sex) of the positive control group were sacrificed. At 48 hours after treatment, 10 animals of the negative control group (5/sex) and 10 animals of the test group (5/sex) were sacrificed. At both sacrifice times of 24 hours and 48 hours post treatment, for both male and female mice treated with the test substance a clearly significant difference in the number of polychromatic erythrocyte (PE) was observed, when compared with the negative control. This indicated that treatment with the test substance resulted in cytotoxicity to bone marrow cells of both male and female mice.

Carbamic acid, 1H-benzimidazol-2-yl-, methyl ester induced mouse micronuclei in this assay.

Additional Information

Skin Irritation

Rabbits were exposed to the test substance via the dermal route. Slight irritation was observed at 24 hours; skin was deemed normal by 72 hours.

See EPA RED document at: http://www.epa.gov/oppsrrd1/REDs/tm_red.pdf

Carbamic acid, 1H-benzimidazol-2-yl-, methyl ester was slightly irritating to rabbit skin.

Eye Irritation

Rabbit eye was exposed to the test substance. Minimal to no irritation was observed.

See EPA RED document at: http://www.epa.gov/oppsrrd1/REDs/tm_red.pdf

Carbamic acid, 1H-benzimidazol-2-yl-, methyl ester was minimally irritating to rabbit eye.

Sensitization

Guinea pigs were tested for dermal sensitization.

See EPA RED document at: http://www.epa.gov/oppsrrd1/REDs/tm_red.pdf

Carbamic acid, 1H-benzimidazol-2-yl-, methyl ester was not a skin sensitizer when tested in guinea pigs.

Carcinogenicity

(1) In a repeated-dose 2-year combined chronic/carcinogenicity toxicity study described above, wistar rats (60/sex/dose) were administered carbendazim (99% purity) in the diet daily at 0, 150, 300 or 2000 mg/kg-bw/day (approximately 0, 7.5, 15 or 100 mg/kg-bw/day) for 2 years. The 2000 mg/kg-bw/day dose was increased to 5000 mg/kg/day after 1 week, then to 10,000 mg/kg-bw/day (approximately 500 mg/kg-bw/day) after 2 weeks for the remainder of the study. All animals were subjected to complete gross necropsy and selected organs were weighed. Tissues were examined microscopically in 20 male and 20 female rats in the control and high dose groups. All tumors and gross abnormalities were also examined histologically. There were no test substance related effects on mortality, (50% mortality at week 76 in control males and at week 92 in treated males). There was 50% mortality in control and low dose females at week 92 in treated males).

Carbamic acid, 1H-benzimidazol-2-yl-, methyl ester did not increase the incidence of tumors in rats.

(2) Mouse studies are summarized in the WHO (1993) document:

<http://www.inchem.org/documents/ehc/ehc/ehc149.htm#SectionNumber:7.4>

Carbamic acid, 1H-benzimidazol-2-yl-, methyl ester increased the incidence of tumors in mice.

(3) In a two-year mouse study, hepatocellular (adenoma and/or carcinoma) tumors were observed in female CD-1 mice.

See data evaluation in EPA RED document: http://www.epa.gov/oppsrrd1/REDs/tm_red.pdf

Carbamic acid, 1H-benzimidazol-2-yl-, methyl ester increased the incidence of tumors in female mice.

Conclusion: The acute oral and inhalation toxicity of CASRN 10605-21-7 in rats is low and the acute dermal toxicity in rabbits is low. In a 2-year chronic toxicity study, the NOAEL and LOAEL with CASRN 10605-21-7 via the diet in rats could not be established due to deaths in the control animals. Repeated-dose toxicity studies show that the liver and thyroid are the primary target organs of CASRN 10605-21-7 with effects in dogs being observed after dietary exposure at 12.5 mg/kg/day; the NOAEL for systemic toxicity is 2.5 mg/kg/day. The testes is a known target organ of CASRN 10605-21-7. In a three-generation reproductive toxicity study with CASRN 10605-21-7 a decrease in litter weights at weaning in all generations were observed at 5000 mg/kg/day; the NOAEL for reproductive toxicity is 500 mg/kg/day. A prenatal oral developmental toxicity study with CASRN 10605-21-7 in rats showed a decrease in maternal body weight gain, effects on liver weight and an increased incidence of resorptions at 90 mg/kg/day; the NOAEL for maternal toxicity is 20 mg/kg/day. In the same study, a significant reduction in fetal body weight was observed at 20 mg/kg/day; the NOAEL for developmental toxicity is 10 mg/kg/day. CASRN 10605-21-7 induced gene mutations in bacteria *in vitro* and induced chromosomal aberrations in mammalian cells *in vitro*. CASRN10605-21-7 induced mouse micronuclei *in vivo*. CASRN10605-27-7 did not increase the incidence of tumors in rats but did in female mice. CASRN 10605-21-7 is irritating to rabbit skin and eye, and is not a skin sensitizer in guinea pigs.

Table 3. Summary of the Screening Information Data Set as Submitted under the U.S. HPV Challenge Program - Human Health Data	
Endpoint	SPONSORED CHEMICAL Carbamic acid, 1H-benzimidazol-2-yl-, methyl ester - (10605-21-7)
Acute Oral Toxicity LD₅₀ (mg/kg)	> 5050
Acute Inhalation Toxicity LC₅₀ (mg/L)	> 5
Acute Dermal Toxicity LD₅₀ (mg/kg)	> 2000
Repeated-Dose Toxicity NOAEL/LOAEL Diet (mg/kg-bw/day)	NOAEL = 2.5 mg/kg/day LOAEL = 12.5 mg/kg/day
Reproductive Toxicity NOAEL/LOAEL Oral (mg/kg/day)	NOAEL = 500 mg/kg/day LOAEL = 5000 mg/kg/day

Table 3. Summary of the Screening Information Data Set as Submitted under the U.S. HPV Challenge Program - Human Health Data	
Endpoint	SPONSORED CHEMICAL Carbamic acid, 1H-benzimidazol-2-yl-, methyl ester - (10605-21-7)
Developmental Toxicity NOAEL/LOAEL Oral (mg/kg/day) Maternal toxicity Developmental toxicity	 NOAEL = 20 mg/kg/day LOAEL = 90 mg/kg/day NOAEL = 10 mg/kg/day LOAEL = 20 mg/kg/day
Genetic Toxicity – Gene Mutation <i>In vitro</i>	Positive
Genetic Toxicity – Chromosomal Aberrations <i>In vitro</i>	Positive
Genetic Toxicity – Chromosomal Aberrations <i>In vivo</i>	Positive
Additional Information Skin Irritation Eye Irritation Skin Sensitization Carcinogenicity	Positive Positive Negative Negative (rat) Positive(mouse)

4. Hazard to the Environment

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

Acute Toxicity to Fish

(1) Zebra fish (*Brachydanio rerio*) were exposed to the test substance at nominal concentrations of 0 and 10 mg/L under semi-static condition for 96 hours. Measured concentrations were < 0.05 and 5.0 mg/L. Triethylene glycol was used as a solvent. Throughout the test, undissolved material was present on the surface of the medium. No mortality was observed at any concentration level.

96-h LC₅₀ > 5.0 mg/L

(2) Rainbow trout (*Oncorhynchus mykiss*) were exposed to the test substance at unreported concentrations under static condition for 96 hours. The toxicities reported are based on the nominal concentration.

96-h LC₅₀ = 0.1 – > 1.8 mg/L (Palawski DU & Knowles CO 1986)

(3) Bluegill sunfish (*Lepomis macrochirus*) were exposed to the test substance at unreported concentrations under static condition for 96 hours.

96-h LC₅₀ = > 3.2 – 5.5 mg/L (Palawski DU & Knowles CO 1986)

(4) Channel catfish (*Ictalurus punctatus*) were exposed to the test substance at unreported concentrations under static condition for 96 hours. The toxicities reported are based on the nominal concentration.

96-h LC₅₀ = 0.007 – > 0.56 mg/L (Palawski DU & Knowles CO 1986)

Acute Toxicity to Aquatic Invertebrates

Daphnia magna were exposed to the test substance at nominal concentrations of 0.056, 0.1, 0.18, 0.32, 0.56 or 1.0 mg/L. Measured concentrations ranged from 96 to 110% of nominal at the start of the test and from 87 to 110% at the end of the test. Triethylene glycol was used as a solvent. The toxicity reported is based on the nominal concentration.

48-h EC₅₀ = 0.16 mg/L

Toxicity to Aquatic Plants

(1) Green algae (*Pseudokirchneriella subcapitata*) were exposed to the test substance at nominal concentrations of 0, 0.33, 1.0, 3.3, 10 or 33 mg/L for 72 hours. The corresponding measured concentrations were < 0.05, 0.35, – (not reported), 2.82, – (not reported) or 10.8 mg/L. Triethylene glycol was used as a solvent. The toxicity reported is based on the nominal concentration.

72-h EC₅₀ (biomass) = 4.5 mg/L

(2) Green algae (*Pseudokirchneriella subcapitata*) were exposed to the test substance at unreported concentrations for 72 hours.

72-h EC₅₀ (biomass) = 1.3 mg/L (EHC 149)

Conclusion: The 96-h LC₅₀ value for acute toxicity to fish for CASRN 10605-21-7 ranges from 0.007 to 5.5 mg/L. The 48-h EC₅₀ value for acute toxicity to aquatic invertebrates for CASRN 10605-21-7 is 0.16 mg/L and the 72-h EC₅₀ value for toxicity to aquatic plants ranges from 1.3 to 4.5 mg/L for biomass.

Table 4. Summary of the Screening Information Data Set as Submitted under the U.S. HPV Challenge Program – Aquatic Toxicity Data	
Endpoint	SPONSORED CHEMICAL Carbamic acid 1H-benzimidazol-2-yl, methyl ester (10605-21-7)
Fish 96-h LC₅₀ (mg/L)	0.007 – 5.5
Aquatic Invertebrates 48-h EC₅₀ (mg/L)	0.16
Aquatic Plants 72-h EC₅₀ (mg/L) (biomass) (growth rate)	1.3 – 4.5 -

bold = experimental data (i.e., derived from testing); – indicates that endpoint was not addressed for this chemical.

5. References

Environmental health criteria; 149 Carbendazim, 1993
<http://www.inchem.org/documents/ehc/ehc/ehc149.htm>

Palawski DU & Knowles CO (1986) Toxicological studies of benomyl and carbendazim in rainbow trout, channel catfish and bluegills. Environ Toxicol Chem, 5: 1039-1046.