201-14154

Nguyet Phan
12/20/2002 12:55 PM

To: NCIC HPV
cc:
Subject: Submission forThe EPA's High Production Volume Chemical Program

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Subject: Submission forThe EPA's High Production Volume Chemical Program

The C.P. Hall Company is pleased to provide the attached dossiers and test plans for N.N-dimethyloctanamide (CAS # 1118-92-9) and N.N-dimethyl-decanamide (CAS # 14433-76-2) as part of its continuing commitment to the U.S. EPA High Production Volume Chemical Program.

These two substances are analogs of very similar chemical structure and properties. We believe that the screening information data needs for this category are fulfilled using the reported data combined with structure activity relationships (SAR) as summarized in the dossiers and presented in the test plan, and that no new testing should be necessary for this program.

Please address any response to this submission to me as the designated technical representative for The C.P. Hall Company.

Gary Wentworth, PhD
Vice President, R&D
The C.P. Hall Company
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(See attached file: Octanamide Test Plan.pdf)(See attached file: Decanamide Test Plan.pdf)(See attached file: Test Plan Summary.pdf)

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TEST PLAN FOR DIMETHYLOCTANAMIDE AND DIMETHYLDECANAMIDE (CHEMICAL ANALOGS)

OVERVIEW

The C.P. Hall Company agrees to sponsor N,N-dimethyloctanamide (CAS No. 1118-92-9) and N,N-dimethyldecanamide (CAS No. 14433-76-2) as two closely related analogs in the Environmental Protection Agency's (EPA) High Production Volume (HPV) Chemical Challenge Program. The company hereby submits a test plan and dossiers for these two substances. It is the intent of the sponsoring company to use existing data combined with structure activity relationships (SAR) to fulfill the Screening Information Set (SIDS) endpoints for environmental fate, ecotoxicity and human health effects.

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Table 1. Test Plan Matrix for N,N-dimethyloctanamide (CAS No. 1118-92-9) and N,N-dimethyldecanamide (CAS No. 14433-76-2)

CAS Nos. 1118-92-9 and 14433-76-2	Information	OECD Study	Other	Estimation	GLP	Acceptable	New Testing Required
ENDPOINT	Y/N	Y/N	Y/N	Y/N	Y/N	Y/N	Y/N
PHYS/CHEM PROPERTIES							
Melting Point	Y(C8,C10)	N	Y	N	N	Y	N
Boiling Point	Y(M)	N	Y	N	N	Y	N
	E(B)	N	Y	Y	N	Y	N
Density	Y(C10)	Y	N	N	Y	Y	N
	Y(M)	N	Y	N	N	Y	N
Vapor Pressure	E(C8)	N	Y	Y	N	Y	N
	Y(C10)	Y	N	N	Y	Y	N
Partition Coefficient	Y(B)	Y	N	N	Y	Y	N
Water Solubility	Y(B)	Y	N	N	Y	Y	N
ENVIRONMENTAL FATE							
Photodegradation	Y(C10)	N	Y	N	Y	Y	N
Stability in Water	Y(C10)	N	Y	N	Y	Y	N
Biodegradation	Y(C10)	N	Y	N	Y	Y	N
Transport between Environmental Compartments (Fugacity)	E(B)	N	N	Y	N	Y	N
ECOTOXICITY							
Acute Toxicity to Fish	Y(M)	Y	N	N	Y	Y	N
Acute Toxicity to Aquatic Invertebrates	Y(M)	N	Y	N	Y	Y	N
Toxicity to Aquatic Plants	Y(M)	Y	N	N	Y	Y	N
Toxicity to Terrestrial (NR)	Y(M)	N	Y	N	Y	Y	N
TOXICOLOGICAL DATA							
Acute Toxicity	Y(M)	Y	N	N	Y	Y	N
Repeated Dose Toxicity	Y(M)	Y	N	N	Y	Y	N
Genetic Toxicity-Mutation	Y(M)	Y	N	N	Y	Y	N
Genetic Toxicity-Chromosomal Aberrations	Y(M)	Y	N	N	Y	Y	N
Toxicity to Reproduction	Y(M)[1]	Y	N	N	Y	Y	N
Developmental Toxicity	Y(M)	Y	N	N	Y	Y	N
OTHER TOXICITY DATA							
Skin Irritation (NR)	Y(M)	N	Y	N	Y/N	Y	N
Eye Irritation (NR)	Y(M)	N	Y	N	Y	Y	N
Sensitization (NR)	Y(M)	N	Y	N	Y	Y	N

Y = yes; N = no; E = estimated
(C8) = N,N-dimethyloctanamide only; (C10) = N,N-dimethyldecanamide only; (B) = both C8 and C10;
(M) = mixture containing C8 and C10
[1] Reproductive organ toxicity data from 91-day study

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1. Introduction

The C.P. Hall Company submits this test plan for N,N-dimethyloctanamide (CAS No. 1118-92-9) and N,N-dimethyldecanamide (CAS No. 14433-76-2) for hazard review under the Environmental Protection Agency High Production Volume Chemical Program. The technical contact at this company is:

Gary Wentworth
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5851 West 73rd Street
P. O. Box 910
Bedford Park Illinois 60499-0910
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2. Designation of Test Substance

Two chemical analogs are addressed in this test plan as follows:

$$CH_3CH_2CH_2CH_2CH_2CH_2CH_2(C{=}O)N(CH_3)_2$$

N,N-Dimethyloctanamide (CAS No. 1118-92-9)

and

$$CH_3CH_2CH_2CH_2CH_2CH_2CH_2CH_2CH_2(C{=}O)N(CH_3)_2$$

N,N-Dimethyldecanamide (CAS No. 14433-76-2)

These substances are chemical analogs with the same functionality, differing only in that N,N-dimethyldecanamide has two more carbons in its alkyl chain than N,N-dimethyloctanamide. N,N-dimethyldecanamide is available commercially as Hallcomid M-10®. N,N-dimethyloctanamide is not manufactured in pure form, but is commercially available as the major component in Hallcomid M-8-10®. Hallcomid M-8-10 contains (in weight %) 50-65% N,N-dimethyloctanamide and 37-50% N,N- dimethyldecanamide, with minor impurities N,N-dimethylhexanamide (0-5%) and N,N- dimethyldodecanamide (0-2%). This product will be referred to by its commercial name (Hallcomid M-8-10) for the remainder of this document. Both Hallcomid products are used principally as pesticide inert ingredients.

3. Criteria for Determining Adequacy of Data

All available studies were reviewed and assessed for adequacy according to the standards of Klimisch et al. (1997). Studies receiving a Klimisch rating of 1 or 2 were considered to be adequate.

4. Discussion of Available Test Information

The N,N- dimethyloctanamide and N,N- dimethyldecanamide test plan matrix (as shown in Table 1 on page 2) was constructed after a careful evaluation of all existing data (see below). This matrix is arranged by study type (columns) and screening data endpoints (rows), and indicates if data are provided for each end point in the sets of robust summaries. For the various endpoints data exist for one of the analogs, or for both analogs, or for the commercial product Hallcomid M-8-10. For endpoints where data are missing for one of the analogs, a structure activity relationship (SAR) approach is taken to use data for the other analog or for Hallcomid M-8-10 to predict behavior for the first analog.

4.1 Chemical and Physical Properties

The results of chemical/physical property testing are shown in Table 2.

Table 2. Chemical/physical properties of N,N-dimethyloctanamide and N,N-dimethyldecanamide

Endpoint	Value*	
	N,N-Dimethyloctanamide (CAS No. 1118-92-9)	N,N-Dimethyldecanamide (CAS No. 14433-76-2)
Molecular Weight grams/mol	171.28	199.34
Melting point (° C)	-27 to -22°C[a]	-11 to -7°C[a]
Boiling point (° C)	240 - 265.5 at 1015 hPa**,[b] *257.2 at 1016 hPa*	240 - 265.5 at 1015 hPa**,[b] *289.7 at 1016 hPa*
Relative Density	0.8835**,[b]	0.88 at 20°C[c]
Vapor pressure (hPa at 25° C)	*0 .026*	0.00114 [d] *0 .01*
Partition coefficient (Log Pow or Kow)	2.59 at 23° C[c] *2.46*	3.92 at 24°C[c] *3.44*
Water solubility (mg/l at 25 ° C)	4300 at 20°C[f] *372.3*	344 at 20°C[f] *19.8*

* Values shown in italics were estimated using the EPIWIN model program.
** Value is for Hallcomid M-8-10, a mixture containing 50-60% N,N-dimethyloctanamide and 35-45% N,N-dimethyldecanamide
[a]Internal communication from The C. P. Hall Company; [b] C. P. Hall Company MSDS ; [c]Krohn, 1995; [d]Krohn, 1994a; [e]Krohn, 1993; [f]Krohn, 1994b

4.1.1 Melting Point

Measured melting points were determined by the C. P. Hall Company using differential scanning calorimetry. The test materials were typical commercial Hallcomid M-10 (of =>98% purity) and Hallcomid M-8-10, which is a mixture containing 50-60% N,N-dimethyloctanamide and 35-45% N,N-dimethyldecanamide. Melting points were also estimated using EPIWIN MPBPWIN, but the values were much greater (40.1°C for N,N-Dimethyloctanamide and 60.8°C for N,N-

Dimethyldecanamide) than room temperature. Both products are known to be liquids at room temperature.

4.1.2 Boiling Point

A measured boiling point range of 240-265.5° C is available for Hallcomid M-8-10, a mixture containing 50-60% N,N-dimethyloctanamide and 35-45% N,N-dimethyldecanamide N,N-dimethyloctanamide (The C. P. Hall Company, 2002). Boiling points for the individual chemicals have been estimated by EPIWIN. These boiling points (257.2° C and 289.7° C for N,N-dimethyloctanamide and N,N-dimethyldecanamide, respectively) are in agreement with the measured boiling point for Hallcomid M-8-10, with an expected somewhat higher boiling point for N,N-dimethyldecanamide, which has a longer alkyl chain and higher molecular weight. These data are adequate for addressing this endpoint.

4.1.3 Vapor Pressure

The vapor pressure of 0.00114 hPa measured for N,N-dimethyldecanamide (Krohn, 1994a) is in close agreement with the EPIWIN estimate of 0.01 hPa. The EPIWIN estimate of 0.026 hPa for N,N-dimethyloctanamide is reasonable in comparison with the determinations for N,N-dimethyldecanamide, based on the expected somewhat higher volatility for the shorter chain, and lower molecular weight of N,N-dimethyloctanamide. These data are adequate for characterizing the vapor pressure for these substances

4.1.4 Octanol/Water Partition Coefficient

Log Pows of 2.59 and 3.92 have been determined for N,N-dimethyloctanamide and N,N-dimethyldecanamide (respectively), using ^{14}C-labeled test substance and following OECD Guideline No. 107 (Krohn, 1993). Values of ca. 2.46 and 3.44 (respectively) estimated by EPIWIN KOWWIN, are in the same ranges. These data are adequate for characterizing octanol/water partitioning for these substances.

4.1.5 Water Solubility

Water solubilities of 4.3 g/l and 344 mg/l have been determined for N,N-dimethyloctanamide and N,N-dimethyldecanamide (respectively), using ^{14}C-labeled test substance and following OECD Guideline No. 105 (Krohn, 1994b). EPIWIN WSKOW (v1.40) estimates somewhat lower respective values of 372.3 and 19.8 mg/l based on the estimated Log Kow values given above. It is likely that the measured values are more accurate than the estimated values. The data are adequate for characterizing water solubility of these substances.

4.1.6 Summary/Test Plan for Physical Properties

Both of the test substances are liquids with fairly high boiling points, low vapor pressures, limited water solubility, and positive partition coefficients. Measured data are available for both substances with respect to melting point, water solubility and partition coefficients. The measured density value for N,N-dimethyldecanamide is similar to the value measured for Hallcomid M-8-10, a mixture containing 50-60% N,N-dimethyloctanamide and 35-45% N,N-

dimethyldecanamide. EPIWIN appears to be a good model for estimating the vapor pressure for N,N-dimethyloctanamide, since the EPIWIN-estimated and measured values for dimethyldecanamide are in good agreement. Most measured values for the individual components and Hallcomid M-8-10 are similar to EPIWIN-estimated values, indicating that EPIWIN is a good model to predict physical properties of these materials, with the exception of melting points (see Section 4.1.1).

4.2 Environmental Fate/Pathways

Results of environmental fate modeling and studies are summarized in Table 3.

Table 3. Environmental fate parameters for N,N-dimethyloctanamide and N,N-dimethyldecanamide

Endpoint	**Value***	
	N,N-dimethyloctanamide (CAS No. 1118-92-9)	N,N-dimethyldecanamide (CAS No. 14433-76-2)
Photolysis (Atmospheric $T_{1/2}$, days) Direct Photolysis in air[a] Direct Photolysis in soil[b]	 No data No data	 >30 33
Indirect Photolysis (OH sensitizer) Hydroxyl Radical Rate Constant *cm^3/(molecule * sec)* Atmospheric $T_{1/2}$ (days)	 *2.7×10^{-11}* *0.4*	 *2.98×10^{-11}* *0.4*
Stability in Water**	*Half-life >1 year*	*Half-life >1 year* Insignificant hydrolysis after 30 days at 25°C at pH 5,7,9[c]
Biodegradation	No data	50 % after 0.5 - 6.5 hrs[d,e] 90% after 0.65 - 7.5 days[d,e]
Henry's Law Constant (atm-m^3/mol)	*2.95×10^{-7}*	*5.2×10^{-7}*
Koc	*118*	*1,130*
Environmental transport (Fugacity Level III mass percentages)	*Air 1.6%* *Water39%;* *Soil 59.5%* *Sediment 0.23%*	*Air 1.19%* *Water 37.8%* *Soil 58.9%* *Sediment 2.09%*

*Values given in italics are estimated by EPIWIN.
**The test substances do not possess functional groups generally recognized to be readily hydrolyzable in water under neutral ambient conditions.
[a]Burri, 1995a; [b]Burri, 1996; [c]Burri, 1995b; [d] Flueckiger,1995; [e] Wyss-Benz and Tschech, 1995

4.2.1 Photodegradation

Direct photolysis of N,N-dimethyldecanamide has been determined in water (Burri, 1995a) and in soil (Burri, 1996), following EPA Guide-line subdivision N 161-2 and EPA Guide-line subdivision N 161-3, respectively. The results of these studies indicate that this substance is not

rapidly photolyzed in either medium. Atmospheric hydroxyl radical-induced photodegradation rate constants of ca. 2.7 x 10^{-11} cm^3/(molecule*sec) and 2.98 x 10^{-11} cm^3/(molecule*sec) have been estimated for N,N-dimethyloctanamide and N,N-dimethyldecanamide using EPIWIN AOP (v1.90). The same program estimates half-lives of 0.4 days for both substances for atmospheric photodegradation with hydroxyl radical as a sensitizer. These results are consistent for both analogs, and indicate that hydroxyl radical-induced atmospheric photodegradation proceeds readily, whereas direct photolysis in water or soil proceeds very slowly. No additional testing is necessary.

4.2.2 Stability in Water

The hydrolysis rate of N,N-dimethyldecanamide has been determined (Burri, 1995b) following EPA Pesticide Assessment Guidelines, Subdivision N. The results of this study indicate insignificant hydrolysis after 30 days at 25°C at pH 5, 7, and 9. EPIWIN modeling of both substances suggests that the amide group is the functionality in the molecule that is most susceptible to hydrolysis, and that hydrolysis at this position is extremely slow (half-life greater than one year). This result is consistent with the measured result and with generally recognized knowledge that amide functions are resistant to hydrolysis under neutral, ambient conditions. Because both test substances contain identical functional groups that are recognized to be resistant to hydrolysis, no testing of this endpoint is recommended.

4.2.3 Fugacity

Level III fugacity modeling has been conducted on the test materials using EPIWIN. The results are nearly identical for both chemical analogs, and indicate that the test substances will partition preferentially to water and soil. The model predicts that the lower homolog, N,N-dimethyloctanamide has a very slightly greater affinity for water. The calculated Henry's Law Constants of 2.95 x 10^{-7} and 5.2 x 10^{-7} atm-m^3/mol suggest that neither analog will rapidly volatilize from water, which in each case is the result of low vapor pressure. Volatilization from soil or sediment is also strictly limited. A soil adsorption/desorption study with N,N-dimethyldecanamide indicates that this material has low or low to medium mobility in soil (Morgenroth, 1995). Water soil partition constants (Koc) of 118 and 1,130 have been estimated using EPIWIN PCKOC for N,N-dimethyloctanamide and N,N-dimethyldecanamide, respectively. These values suggest (as would be expected) that the lower homolog would have somewhat higher soil mobility than N,N-dimethyldecanamide. Additional fugacity testing is not recommended.

4.2.4 Biodegradation

Two well-conducted studies performed with C^{14} labeled N,N-dimethyldecanamide indicate that this material rapidly biodegrades in soil (Flueckiger,1995; Wyss-Benz and Tschech, 1995). The rates of degradation of 50% and 90% of the material in different types of soil ranged from 0.5 to 6.5 hours, and 0.65 to 7.5 days, respectively. Since N,N-dimethyloctanamide is closely related in structure and chemical physical properties to N,N-dimethyldecanamide, this material is also expected to rapidly degrade in soil. Measured data are not available for biodegradation in water. The EPIWIN BIOWIN (v 4.00) program predicts that both substances are readily biodegradable. In addition, aliphatic amides are generally known to readily undergo biodegradation; first to

carboxylic acids, followed by further microcosm-induced breakdown. Results of the well-conducted biodegradation tests in soil, together with estimates from the EPIWIN/BIOWIN program are adequate to characterize this endpoint for N,N-dimethyloctanamide and N,N-dimethyldecanamide.

4.2.5 Summary/Test Plan for Environmental Fate Parameters

Level III fugacity modeling indicates that N,N-dimethyloctanamide and N,N-dimethyldecanamide will tend to partition to water and soil when released to the environment. Although both substances have low vapor pressures and moderately low Henry's Law Constants, EPIWIN modeling predicts that molecules entering the atmosphere will readily undergo hydroxyl radical-induced photodegradation. Well-conducted photodegradation studies are available for N,N-dimethyldecanamide in both soil and water. These studies indicate that the test substance is highly resistant to direct sunlight-induced photolysis in both media. The identical functionality of N,N-dimethyloctanamide suggests that this analog is also resistant to photolysis in these media. The abiotic hydrolysis of N,N-dimethyldecanamide has been studied at pH 3,5, and 7, indicating that this substance is resistant to hydrolysis at ambient temperatures, as is generally recognized for simple aliphatic amides. This study would predict similar behavior for the shorter chain analog, N,N-dimethyloctanamide .

Water-soil partition constants measured for dimethyldecanamide and estimated for N,N-dimethyloctanamide by EPIWIN predict some (albeit limited) soil mobility. Biodegradation studies and modeling indicate that N,N-dimethyldecanamide is readily degraded in soil and water. Modeling results, together with measured determinations of photolysis, hydrolysis and biodegradation are sufficient to characterize environmental fate end points for N,N-dimethyloctanamide and N,N-dimethyldecanamide at the screening level; therefore no further testing for these endpoints is planned.

4.3 Ecotoxicity

4.3.1 Acute Toxicity to Fish

A static, OECD guideline study in rainbow trout was performed with Hallcomid M-8-10 (Dogerloh, 1993). The no observable effect concentration (NOEC) and lethal concentration in 50% of the organisms (LC50) in this 96-hour study were 5 and 21.1 mg/l, respectively. None of the fish exposed to ≤ 15.8 mg/l died by 96 hours.

4.3.2 Acute Toxicity to Aquatic Invertebrates

A static EPA guideline study in Daphnia magna was performed with Hallcomid M-8-10 (Forbis, 1990). The NOEC and LC50 values in this 48-hour study were 4 and 7.7 mg/l, respectively.

4.3.3 Acute Toxicity to Aquatic Plants

The toxicity of Hallcomid M-8-10 to Selenastrum capricornutum was tested according to OECD Guideline 201 (Anderson, 1993). For inhibition of growth rate, the NOEC, and effective

concentration in 50% of the organisms (EC50) were 1.80 and 16.06 mg/l for 72 hours, respectively. For inhibition of biomass, the NOEC and the EC50 were < 1.80 and 5.47 mg/l, respectively. Although the pH of the control flasks was slightly higher (0.10 units) at the end of the study than the recommended value, this did not appear to adversely affect the outcome of the test.

4.3.4 Toxicity to other Non-Mammalian Terrestrial Species

Although not required, an EPA guideline test with Hallcomid M-8-10 was performed in bobwhite quail (Grau, 1994). Five groups of 10 birds (five per sex) were given a single oral dose of 0, 200, 400, 800 or 1600 mg/kg Hallcomid M-8-10 by gelatin capsule and observed for 14 days. None of the birds exposed to 800 mg/kg or less Hallcomid M-8-10 died. Transient signs of toxicity (ptosis, loss of equilibrium and/or apathy) were observed in 5 animals treated with 800 mg/kg. Five animals exposed to 1600 mg/kg died and all exhibited convulsions, ptosis, loss of equilibrium and/or apathy on the day of treatment. The no observable effect level (NOEL), lowest observable effect level (LOEL) and lethal dose in 50% of the animals (LD50) values were therefore 400, 800 and 1600 mg/kg, respectively.

4.3.5 Summary/Test Plan for Ecotoxicity

Results of guideline studies in rainbow trout, Daphnia magna and Selenastrum capricornutum show that Hallcomid M-8-10 is of moderate toxicity to these species. An additional study indicates that Hallcomid M-8-10 is of low toxicity to bobwhite quail. The studies that have been performed adequately assess the toxicity of Hallcomid M-8-10 to fish, aquatic invertebrates, algae and birds. Since this material predominantly contains N,N- dimethyl octaneacidamide and N,N- dimethyl decaneacidamide (in approximately equal amounts), and the two materials are closely related in chemical structure and physical properties, the potential for ecotoxicity of the two chemical analogs is not expected to differ substantially from that of Hallcomid M-8-10. Therefore, additional testing with the individual analogs is not necessary.

4.4 Human Health Data

4.4.1 Acute Mammalian Toxicity

This endpoint is filled by sufficient oral, inhalation and dermal toxicity studies in rats performed with Hallcomid M-8-10 (Kreuzmann, 1990a, Pauluhn, 1991, Bomann, 1995). The LD_{50} and LD_{100} (lethal dose in 10%% of animals) values for the oral study were 1,250 mg/kg and 2,500 mg/kg, respectively. The NOEC and LC50 value for inhalation were 118.5 mg/m^3 and greater than 3551 mg/m^3, respectively. The dermal LD_{50} values were 2000 mg/kg for males and between 400 and 2000 mg/kg for females. The NOEL for systemic effects in the dermal study was 200 mg/kg.

Symptoms observed in rats orally treated with 1,250 to 5,000 mg/kg Hallcomid M-8-10 included ataxia, depression, and labored breathing prior to death. Piloerection, red stains around nostrils, brownish urine stains and/or hunched posture were noted up to study day 4 in surviving rats treated with 1.25 or 2.5 g/kg (3/4 and 1/4, respectively). Rats treated orally with 0.025 g/kg

exhibited signs of toxicity only on the day of dosing. Survivors appeared normal after approximately day 5, and had normal necropsies at study termination.

In rats exposed to 586.4 mg/m^3 Hallcomid M-8-10 for 4 hours by inhalation, signs of toxicity such as reddening of the nose, reduced motility and piloerection occurred on the day of exposure only. Most of the rats exposed to higher concentrations also exhibited additional signs and symptoms of respiratory irritation. Symptoms in rats exposed to 2007.6 or 3550.7 mg/m^3 persisted for up to 7 and 14 days, respectively. The necropsy of the one animal that died after exposure to 3550.7 mg/m^3 revealed distended, liver-like and edematous lungs, hydrothorax, and reddened and swollen rhinarium. Surviving rats exposed to 3550.7 mg/m^3 also had a higher incidence of distended lung. Animals exposed to lower concentrations did not exhibit any gross pathological changes with respect to controls.

In the dermal study, four out of 5 females exposed to 400 mg/kg and all rats exposed to higher concentrations exhibited clinical signs of toxicity. These signs generally occurred within 30 minutes of treatment and reversed within 6 days treatment. Skin irritation was noted at the site of administration of most animals exposed to 200 mg/kg, all animals exposed to 400 mg/kg, and all males exposed to 2000 mg/kg. The skin effects lasted from day 2 until the end of the study. One female treated with 50 mg/kg had some squamation at the treatment area. Since none of the others treated with 50 mg/kg had skin reactions, this dose was chosen as the threshold level for local effects.

Since Hallcomid M-8-10 predominantly contains N,N-dimethyloctanamide and N,N-dimethyl decanamide (in approximately equal amounts), and the two materials are closely related in chemical structure and physical properties, the potential for acute mammalian toxicity of the two chemical analogs is not expected to differ substantially from that of Hallcomid M-8-10. Therefore, additional acute toxicity testing with the individual materials is not necessary.

4.4.2 Repeated Dose Mammalian Toxicity

Four repeated dose toxicity studies have been performed with Hallcomid M-8-10. The critical study for the endpoint was a 91-day oral dietary study performed according to OECD guideline 408 (Wirnitzer and Ruhl-Fehlert, 1993). The no observable adverse effect level (NOAEL) for Hallcomid M-8-10 in this study was 2,000 ppm (136.8 mg/kg/day for males and 178.5 mg/kg/day for females), and the lowest observable adverse effect level (LOAEL) was 10,000 ppm (787.6 mg/kg/day for males and 894.6 mg/kg/day for females). Effects noted at 10,000 ppm included emaciation (5/10 males), decreased body weight gain (which normalized during a 28 day recovery period), increased serum cholesterol, increased liver weight, and pathological changes in the kidneys (males only). Similar findings were observed in rats ingesting 10,000 ppm Hallcomid M-8-10 in a 28-day range finding study (Wirnitzer, 1993).

In dogs treated orally by gavage with 20, 100, or 500/1000 mg/kg Hallcomid-M-10 for 6 weeks, no effects were noted at 20 mg/kg/day (Vliegen, 1996). The study personnel set the NOAEL at 100 mg/kg/day; however, the data suggested that there were some treatment-related effects at this dose (i.e. increased vomiting, salivation, and liver, kidney and pancreas weights). Dogs dosed with 500 mg/kg/day for two weeks and 1000 mg/kg/day for the remainder of the study

exhibited vomiting, salivation, increases in some liver enzymes, and increased liver, kidney and pancreas weights.

A five day inhalation study of Hallcomid M-8-10 in rats was conducted according to OECD guidelines (Pauluhn, 1992). In this study, rats were exposed (head and nose only) to an aerosol containing 24.6, 111.2 and 521.2 mg/m^3 material with an average MMAD (and GSD) of 1.4 (1.5) microns. The NOAEL and LOAEL in this study were 111.2 and 521.2 mg/m^3, respectively. Effects noted at 521.2 mg/m^3 included difficulties in breathing, reduced motility, hypothermia and weight loss during treatment, and pathological changes in the nasal and paranasal cavities (females only) after a 15-day recovery period. Lesions in other organs were not observed at necropsy.

Since Hallcomid M-8-10 predominantly contains N,N-dimethyloctanamide and N,N-dimethyl decanamide (in approximately equal amounts), and the two materials are closely related in chemical structure and physical properties, the potential for repeated dose mammalian toxicity of the two analogs is not expected to differ substantially from that of Hallcomid M-8-10. Therefore, additional repeat dose toxicity testing with the individual materials is not necessary.

4.4.3 Genetic Toxicity

4.4.3.1 Mutagenicity

Hallcomid M-8-10 tested negative for mutagenicity in an Ames test (OECD 471) involving *S. typhimurium* strains TA98, TA100, TA1535, and TA1537 in the absence and presence of a metabolic activation system (Herbold, 1992) and a HGPRT assay (OECD 476) conducted with V79 Chinese hamster lung cells in the absence and presence of a metabolic activation system (Brendler-Schwaab, 1994).

The potential for mutagenicity of N,N-dimethyloctanamide and N,N-dimethyldecanamide is not expected to differ substantially from that of Hallcomid M-8-10, since they are the predominant ingredients. Therefore, mutagenicity testing with the individual materials is not necessary.

4.4.3.2 Chromosomal aberration

An OECD Guideline 473 study has been conducted with Hallcomid M-8-10 in Chinese Hamster Ovary Cells in the absence and presence of a metabolic activation system (Gahlmann, 1995). In this study, incubation with up to 160 micrograms/ml (without activation) and 180 micrograms/ml (with activation) did not lead to an increase in the number of aberrants with respect to historical controls. The finding of an increased number of aberrants at 8 hours for cells treated with 180 micrograms/ml in the presence of a metabolic activation system with respect to the solvent control was considered by study personnel to be due to the unusually low number of solvent control cells with aberrations (0.5%).

Based on the fact that N,N-dimethyloctanamide and N,N-dimethyldecanamide are the predominant ingredients of Hallcomid M-8-10 and have similar structures and physical properties, the results of the study with Hallcomid M-8-10 are likely to be predictive of those

with the individual chemical substance analogs. Therefore, additional chromosomal aberration testing with the individual analogs is not necessary.

4.4.3.3 Additional Studies

The ability of Hallcomid M-8-10 to cause unscheduled DNA synthesis in rat primary hepatocytes in the absence of metabolic activation was tested according to OECD Guideline 402 (Brendler-Schwab, 1994). At concentrations up to 98.8 micrograms/ml (the highest concentration that did not cause excessive toxicity), there was no increase in nuclear labeling or the percentage of cells in repair.

4.4.4 Reproductive Toxicity

No mating studies with the individual chemical analogs or Hallcomid M-8-10 have been performed. However, the 91-day rat dietary study that was conducted with Hallcomid M-8-10 included examination of reproductive organs (Wirnitzer and Ruhl-Fehlert, 1993). In this study, the NOAEL for reproductive effects was 10000 ppm, which was higher than the NOAEL for systemic effects. Changes in the testes, prostate and/or epididymis that were noted in 1-2 males from the control, low and high dose groups were not considered to be related to treatment since the incidences and degrees of severity of the lesions in were low (with the exception of one low dose animal that had a high degree of tubular atrophy in the testes) and not dose-dependent.

Results of the developmental toxicity studies (see Section 4.4.5 below) indicate that treatment with up to 450 mg/kg/day Hallcomid M-8-10 in rats or 1000 mg/kg/day of Hallcomid M-8-10 in rabbits during organogenesis has no effect on the number of resorptions, implantations, corpora lutea or viable or nonviable fetuses. At the clearly maternally toxic dose of 450 mg/kg/day, rats had a small increase in post-implantation (embryonic) loss (9.4% vs. 5.6% in controls).

Altogether, the results of the repeated dose and developmental studies suggest that the potential for reproductive toxicity of Hallcomid M-8-10 is low. Therefore, reproductive toxicity testing with N,N-dimethyloctanamide and N,N-dimethyldecanamide is not necessary.

4.4.5 Developmental Toxicity

Results of two OECD guideline studies show that Hallcomid M-8-10 is not a developmental toxicant at non-maternally toxic doses. In a study in rats treated with 50, 150 or 450 mg/kg/day Hallcomid M-8-10 from Days 5 though 15 of gestation (Becker and Biedermann, 1991a), 50 mg/kg/day was the NOAEL for maternal toxicity. Reduced food consumption was observed in dams treated with 150 mg/kg/day (the LOAEL), and more severe signs of toxicity (ventral recumbancy, dyspnea, apathy, coma, and weight loss) were noted in dams treated with 450 mg/kg. Treatment with 50 or 150 mg/kg/day had no effect on any reproductive or fetal parameter. Treatment with 450 mg/kg/day was associated with increased post-implantation (embryonic) loss, reduced fetal weight, and an increased incidence of fetuses (and litters) with skeletal abnormalities (eg. wavy ribs and dumbbell-shaped thoracic bodies) and variations (e.g. non-ossified or incompletely ossified vertebrae, sternebrae or metatarsala). Study personnel did not consider the abnormal skeletal findings in fetuses from dams treated with the high dose to be

indicative of a specific teratogenic effect of the test article because they are commonly found in Wistar rats and correlated with reduced fetal weight.

The results of the OECD study in rabbits (Becker and Biedermann, 1991b) show that Hallcomid M-8-10 is not a developmental toxicant at doses up to 1000 mg/kg/day, which was a maternally toxic dose. Although a number of skeletal variations were observed in this study, there appeared to be no clear-cut, dose-dependent differences in the incidences of variants between treated and control animals. Therefore, study personnel did not consider them to be related to administration of test material.

As the results of the developmental studies with Hallcomid M-8-10 are likely to be predictive of results for N,N-dimethyloctanamide and N,N-dimethyldecanamide, no additional testing is necessary.

4.4.6 Additional Data

4.4.6.1 Skin and Eye Irritation

The results of a DOT corrosivity potential study performed in 6 rabbits indicate that Hallcomid M-8-10 causes moderate-severe skin irritation but is not corrosive (Harris, 1990). An additional skin irritation study performed in one rabbit indicates that the material is corrosive (Kreuzmann, 1990b). Altogether, these results suggest that Hallcomid M-8-10 is severely irritating to the skin. Due to the suspected irritation potential of Hallcomid M-8-10, the material was tested for eye irritation in a single young adult male New Zealand White rabbit (Kreuzmann, 1990c). The total irritation scores ranged from 26 (at 1 hr) to 66 (at Day 4), indicating that the material was highly irritating.

Based on the fact that the two chemical analogs are the predominant ingredients of Hallcomid M-8-10 and have similar structures and physical properties, the results of the study with Hallcomid M-8-10 are likely to be predictive of those with the individual analogs. No additional testing is necessary.

4.4.6.2 Sensitization

The ability of Hallcomid M-8-10 to produce sensitization has been tested in a GLP study in guinea pigs (Kreuzmann, 1990c). After initiation with the highest dose that did not cause irritation (5% test material in 80% ethanol/20% distilled water), challenge with 2.5% test material in acetone did not produce skin irritation. Therefore, Hallcomid M-8-10 did not cause sensitization in the guinea pig. Based on the rational presented above, the results of this study are likely to be predictive of results with N,N-dimethyloctanamide and N,N-dimethyldecanamide. Therefore, testing of these chemical analogs is not necessary.

4.4.7 Summary/Test plan for mammalian toxicity

Adequate studies with Hallcomid M-8-10 have been conducted for all required endpoints. Acute oral, inhalation and dermal toxicity studies show that exposure to fairly large amounts of Hallcomid M-8-10 is required to produce acute toxicity. Inhalation of a very high concentration

(521 mg/m^3) for 5 days causes toxicity to the respiratory system of rats (but not other organs). Results of an OECD guideline, 91-day oral study show that repeated ingestion of doses up to approximately 800 mg/kg/day for 91 days is well tolerated in rats. The material is irritating to the skin and eyes, and is not a sensitizer. Repeated exposure to doses equal to or greater than 100 mg/kg/day also appears to be irritating to the GI tract of dogs, as evidenced by vomiting and increased salivation after dosing. Adequate studies show that Hallcomid M-8-10 is not mutagenic or clastogenic. Results of the 91-day test indicate that the material is not toxic to reproductive organs, and developmental studies in rats and rabbits indicate that the material is not a developmental or reproductive toxicant.

Since Hallcomid M-8-10 predominantly contains N,N-dimethyloctanamide and N,N-dimethyl decanamide (in approximately equal amounts), and the two materials are closely related in chemical structure and physical properties, the potential for mammalian toxicity of the two chemical analogs is not expected to differ substantially from that of Hallcomid M-8-10. Therefore, additional mammalian toxicity testing with the individual materials is not necessary.

5. Summary

In summary, valid data are present to satisfy all physical/chemistry, environmental, aquatic and mammalian toxicity endpoints. In general, measured physical chemistry values for N,N-dimethyloctanamide, N,N-dimethyldecaneacidamide and Hallcomid M-8-10 are similar to each other and to EPIWIN-estimated values for the individual components, indicating that EPIWIN is a good model to predict physical properties and environmental fate of these materials, that data for one analog will be predictive of the other, and those data for Hallcomid M-8-10 can be used to predict behavior of the individual components. No additional testing is necessary.

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201-14154B

Robust Summaries and Dossier for N,N-Dimethyloctanamide (CAS No. 1118-92-9)

Existing Chemical	:	ID: 1118-92-9
CAS No.	:	1118-92-9
Producer Related Part		
Company	:	The C.P. Hall Company, Inc.
Creation date	:	19.09.2002
Substance Related Part		
Company	:	The C.P. Hall Company, Inc.
Creation date	:	19.09.2002
Memo	:	
Printing date	:	12.11.2002
Revision date	:	12.11.2002
Date of last Update	:	12.11.2002
Number of Pages	:	63
Chapter (profile)	:	Chapter: 1, 2, 3, 4, 5, 7
Reliability (profile)	:	Reliability: without reliability, 1, 2, 3, 4
Flags (profile)	:	Flags: without flag, confidential, non confidential, WGK (DE), TA-Luft (DE), Material Safety Dataset, Risk Assessment, Directive 67/548/EEC, SIDS

2002 DEC 20 PM 2:15

1.0.1 OECD AND COMPANY INFORMATION

Type	:	cooperating company
Name	:	The C. P. Hall Company
Partner	:	
Date	:	19.09.2002
Street	:	5851 West 73rd Street
Town	:	60499 Bedford Park, Illinois
Country	:	United States
Phone	:	
Telefax	:	
Telex	:	
Cedex	:	
Reliability	:	(1) valid without restriction

19.09.2002

1.0.2 LOCATION OF PRODUCTION SITE

1.0.3 IDENTITY OF RECIPIENTS

1.1 GENERAL SUBSTANCE INFORMATION

Substance type	:	organic
Physical status	:	liquid
Purity	:	% w/w
Remark	:	CAS No. 1118-92-9 is a component of the C.P. Hall Company commercial product known as Hallcomid M-8-10.

19.09.2002

1.1.0 DETAILS ON TEMPLATE

1.1.1 SPECTRA

1.2 SYNONYMS

N,N-dimethyl caprylamide
26.09.2002

N,N-Dimethyloctanamide
19.09.2002

octanoic acid dimethylamide
26.09.2002

1.3 IMPURITIES

1.4 ADDITIVES

1.5 QUANTITY

1.6.1 LABELLING

1.6.2 CLASSIFICATION

1.7 USE PATTERN

1.7.1 TECHNOLOGY PRODUCTION/USE

1.8 OCCUPATIONAL EXPOSURE LIMIT VALUES

1.9 SOURCE OF EXPOSURE

1.10.1 RECOMMENDATIONS/PRECAUTIONARY MEASURES

1.10.2 EMERGENCY MEASURES

1.11 PACKAGING

1.12 POSSIB. OF RENDERING SUBST. HARMLESS

1.13 STATEMENTS CONCERNING WASTE

1.14.1 WATER POLLUTION

1.14.2 MAJOR ACCIDENT HAZARDS

1.14.3 AIR POLLUTION

1.15 ADDITIONAL REMARKS

1.16 LAST LITERATURE SEARCH

1.17 REVIEWS

1.18 LISTINGS E.G. CHEMICAL INVENTORIES

2.1 MELTING POINT

Value	:	-27 to -22° C
Sublimation	:	
Method	:	Other : Differential scanning Calorimetry (DSC)
Year	:	2002
GLP	:	no
Test Condition	:	The heating/cooling rate was 10C/min. The lower temperature given is the onset of the melting curve and the higher temperature is the peak.
Test substance	:	The test substance is Hallcomid M-8-10 (tradename), which is a mixture of 50-60% N,N-dimethyloctanamide (CAS No. 1118-92-9) and 35-45% N,N-dimethyldecanamide (CAS No. 14433-76-2).
Reliability	:	(2) Valid with restrictions. Study details not documented.
Reference	:	Internal company data from The CP Hall Company

Value	:	ca. 40.1 ° C
Sublimation	:	
Method	:	other
Year	:	2002
GLP	:	no
Test substance	:	as prescribed by 1.1 - 1.4
Reliability	:	(3) invalid The reliability of this calculation is limited. EPIWIN MPBPWIN has used the same method to calculate a melting point of 60.83 degrees C for decanamide, N,N-dimethyl (CAS No. 14433-76-2), which is known to be a liquid at room temperature. Decanamide, N,N-dimethyl is a closely related, 2-carbon higher homolog of the test material (octanamide, N,N-dimethyl).

19.09.2002 (13)

2.2 BOILING POINT

Value	:	240 - 265.5 at 1015 hPa
Decomposition	:	
Method	:	other
Year	:	2002
GLP	:	no
Test substance	:	The test substance is Hallcomid M-8-10 (tradename), which is a mixture of 50-60% N,N-dimethyloctanamide (CAS No. 1118-92-9) and 35-45% N,N-dimethyldecanamide (CAS No. 14433-76-2).
Reliability	:	(2) valid with restrictions Data are for a commercial material containing approximately 50-60% of the material.

05.11.2002 (29)

Value	:	ca. 257.2 ° C at 1016 hPa
Decomposition	:	
Method	:	other
Year	:	2002
GLP	:	no
Test substance	:	as prescribed by 1.1 - 1.4
Method	:	EPIWIN MPBPWIN (v1.40) uses the adapted Stein and Brown method to estimate boiling point. The input into the EPIWIN program was the CAS No. of the test substance.
Reliability	:	(2) valid with restrictions Data were obtained by modeling.

19.09.2002 (13)

2.3 DENSITY

Type	:	relative density
Value	:	= .8835 at ° C
Method	:	
Year	:	
GLP	:	no data
Test substance	:	The test substance is Hallcomid M-8-10 (tradename), which is a mixture of 50-60% N,N-dimethyloctanamide (CAS No. 1118-92-9) and 35-45% N,N-dimethyldecanamide (CAS No. 14433-76-2).
Reliability	:	(2) valid with restrictions Data are for a commercial material containing approximately 50-60% of the material, with most of the remainder CAS No. 14433-76-2, which has a density of 0.88.

21.09.2002 (29)

2.3.1 GRANULOMETRY

2.4 VAPOUR PRESSURE

Value	:	ca. .026 hPa at 25° C
Decomposition	:	
Method		other (calculated)
Year	:	2002
GLP	:	no
Test substance	:	as prescribed by 1.1 - 1.4
Method	:	EPIWIN MPBPWIN (v1.40) used the Modified Grain Method for estimating vapor pressure. Input to the EPIWIN program was the CAS No. for the test substance.
Reliability	:	(2) valid with restrictions Data were obtained by modeling.

19.09.2002 (13)

2.5 PARTITION COEFFICIENT

Log pow	:	= 2.59 at 23° C
Method		OECD Guide-line 107 "Partition Coefficient (n-octanol/water), Flask-shaking Method"
Year	:	1993
GLP	:	yes
Test substance	:	as prescribed by 1.1 - 1.4
Method	:	Shaking method according to OECD Guidelines No. 107(corresponding to EEC Guidelines A8).
Test condition	:	A preliminary test was performed according to the shaking method with the partition coefficient determined to be 370 (log Pow 2.57). For the studies, demineralized water was used, the purity of which was equivalent to that of bidistilled water from a quartz distillation apparatus. The water and the n-octanol (purity >99%) were mutually saturated by stirring with a sufficient quantity of the other component of the partition system. The test vessels containing stock solution, water and n-octanol were rotated 100 times, through 180 degrees to thoroughly mix the contents.

The solutions from both phases were analyzed using an HPLC chromatograph, Model 5000 with spectrophotometric detector. It became evident from the chromatograms that no degradation of the test substance occurred under test conditions.

Calibration solutions of the test substances at different concentration levels were measured in connection with the determinations of the partition coefficients in order to establish reproducibility and linearity of the analytical HPLC methods used.

Test substance : Test substance was characterized by GLC and the contents certified to be 97.0% pure. The mass spectra and H-NMR-spectra complied with the appropriate chemical identity. Test substance was designated as Hallcomid C8 (tradename) Batch 930129ELB01.

Reliability : (1) valid without restriction
The study was performed according to GLP and standard guidelines. There were no deviations that could affect the outcome.

20.09.2002 (26)

Log pow : ca. 2.46 at ° C
Method other (calculated)
Year : 2002
GLP : no
Test substance : as prescribed by 1.1 - 1.4
Method : EPIWIN KOWWIN calculates Log Kow by summing individual contributions to Log Kow for each fragment in the molecule, based on values assigned in the program for each fragment.

Reliability : (2) valid with restrictions
Data were obtained by modeling.

20.09.2002 (11)

2.6.1 WATER SOLUBILITY

Value : = 4.3 g/l at 20 ° C
Qualitative :
Pka : at 25 ° C
PH : = 7 at and ° C
Method : OECD Guide-line 105 "Water Solubility"
Year : 1994
GLP : yes
Test substance : as prescribed by 1.1 - 1.4
Method : Flask method according to OECD-Guidelines No. 105 (corresponding to EC Guidelines A6).

Remark : Although the solubility was established only for neutral water in equilibrium with atmospheric carbon dioxide, solubilities will be similar in the cases of slightly acidic or alkaline solutions (pH 3-9), because salt formation by deprotonation or protonation in this pH range can be ruled out due to the chemical structure of an aliphatic tertiary carboxylic acid amide of the compound. The dissociation constant and pH value of Hallcomid M-8-10 (trademark) was conducted according to OECD Guideline No. 112. Hallcomid M-8-10 is the trade name for a mixture of 50-60% N,N-dimethyloctanamide (CAS No. 1118-92-9) and 35-45% N,N-dimethyldecanamide (CAS No.14433-76-2). On the basis of this test, the test substance does not show basic or acidic properties in water. It is not possible to specify a pK value of the test substance in aqueous systems. The pH value of a suspension of approx. 1 g. of the test substance in water was pH 4.8. The study reference is Bayer AG, Leverkusen Germany, H.P. Stupp, Dissociation Constant and pH Value of Hallcomid M-8-10, Study Number 15400 0809, July 22, 1993.

Test condition : For the study, demineralized water was used, the purity of which was

equivalent to that of bidistilled water from a quartz distillation apparatus. The water used was not buffered and in equilibrium with atmospheric carbon dioxide The water and the n-octanol (purity >99%) were mutually saturated by stirring with a sufficient quantity of the other component of the partition system.

1.4 grams of test substance were weighed into a 100 ml Erlenmeyer flask and added with 100 ml water. After a magnetic bar had been introduced, the flasks were put into a water bath thermostated at 20 degrees C. The test substance was suspended by intensively stirring by means of a magnetic stirrer below the water-bath. In order to estimate the rate of establishment of the solubility equilibrium, approx. 10 ml of suspension were sampled after increased stirring times, filled into a polyethylene beaker and centrifuged in a thermostatically controlled centrifuge at 18000 rpm and 20 degrees C for 50 min. The upper layer of the centrifuged sample was removed and discarded using a Teflon tube and applying reduced pressure. Portions from the clear solutions of the middle layer were diluted 1:100 and transferred into sampler bottles for concentration by HPLC

The solutions from both phases were analyzed using a HPLC chromatograph, Model 5000 with spectrophotometric detector, Model Uvikon LC 720. The concentration of samples resulting from the saturation procedure was measured in a sequence after the 24 hours sample had been drawn and again after further 24 hours of standing at ambient temperature. By comparing relative responses with that of freshly prepared calibration solutions, it became evident that no degradation of the test substance occurred under test conditions.

It became evident from the concentration measurements that the solubility equilibrium was reached after 30 minutes of stirring.

Test substance : The test substance was Hallcomid C8 (trade name), Batch 930129ELB01, chemical identity confirmed by mass spectra and H-NMR-spectra, and purity determined by GLC to be 97.0%.

Reliability : (1) valid without restriction
The study was performed according to GLP and standard guidelines. There were no deviations that could affect the outcome.

20.09.2002 (25)

Value : ca. 372.3 mg/l at ° C
Qualitative :
Pka : at 25 ° C
PH : at and ° C
Method : other
Year : 2002
GLP : no
Test substance : as prescribed by 1.1 - 1.4
Method : EPIWIN WSKOW calculates water solubility based on Log Kow, using the equation Log S (mol/L) = 0.796 - 0.854 Log Kow - 0.00728 MW + correction. A measured value (2.59) was inputted for the Log Kow.

Reliability : (2) valid with restrictions
Data were obtained by modeling.

20.09.2002 (14)

2.6.2 SURFACE TENSION

2.7 FLASH POINT

Value	:	= 118.3 ° C
Type	:	
Method	:	other
Year	:	
GLP	:	no data
Test substance	:	other TS
Test substance	:	The test substance is The C.P. Hall Company Hallcomid (trade name) M-8-10, which is a mixture of N,N-dimethyloctanamide (CAS No. 1118-92-9) and N,N-dimethyl decanamide (CAS No. 13322-76-2).
Reliability	:	(2) valid with restrictions Data are for a commercial material containing approximately 50-60% of the material, with the remainder CAS No. 14433-76-2, which is a related material.

20.09.2002 (29)

2.8 AUTO FLAMMABILITY

2.9 FLAMMABILITY

2.10 EXPLOSIVE PROPERTIES

2.11 OXIDIZING PROPERTIES

2.12 ADDITIONAL REMARKS

3.1.1 PHOTODEGRADATION

Type	:	air
Light source	:	Sun light
Light spect.	:	nm
Rel. intensity	:	based on Intensity of Sunlight
Indirect photolysis		
Sensitizer	:	OH
Conc. of sens.	:	
Rate constant	:	ca. .000000000027 cm3/(molecule*sec)
Degradation	:	ca. 50 % after .4 day
Deg. Product	:	
Method	:	other (calculated)
Year	:	2002
GLP	:	no
Test substance	:	as prescribed by 1.1 - 1.4
Method	:	EPIWIN AOP calculates the overall OH radical rate constant by summing up individual rate constants assigned in the program to reactions of OH radicals with individual bonds in the molecule. The half life is then calculated assuming first order kinetics with a constant concentration of OH radical.
Reliability	:	(2) valid with restrictions Data were obtained by modeling

20.09.2002 (8)

3.1.2 STABILITY IN WATER

Type	:	abiotic
t1/2 pH4	:	at degree C
t1/2 pH7	:	> 1 year at degree C
t1/2 pH9	:	at degree C
Deg. Product	:	
Method	:	other (calculated)
Year	:	2002
GLP	:	no
Test substance	:	as prescribed by 1.1 - 1.4
Method	:	EPIWIN HYDROWIN identifies the amide group as the only group in the molecule for which a half-life can be estimated. The remainder of the molecule is a saturated long-chain alkyl group that is not normally subject to hydrolysis.
Remark	:	The molecule is not expected to hydrolyze appreciably under neutral ambient conditions, because it does not contain functional groups expected to readily undergo hydrolysis.
Reliability	:	(2) valid with restrictions Data were obtained by modeling.

20.09.2002 (10)

3.1.3 STABILITY IN SOIL

3.2 MONITORING DATA

3.3.1 TRANSPORT BETWEEN ENVIRONMENTAL COMPARTMENTS

Type	:	fugacity model level III
Media	:	water - air
Air (level I)	:	1.6
Water (level I)	:	39
Soil (level I)	:	
Biota (level II / III)	:	.23
Soil (level II / III)	:	59.5
Method	:	other
Year	:	2002
Method	:	Inputs to run this program are: CAS No. 1118-92-9 mol. wt. = 171.29 Henry's Law Constant = 2.95E-7 atm-m3/mol (Henrywinprogram) vapor Pressure = 0.0194 mm Hg (Mpbpwin program) liquid vapor pressure = 0.0274 mm Hg melting pt = 40.1 degrees C (Mpbpwin program) octanol-water partition coefficient (Kow) = 288.403 log Kow = 2.59 (measured/user entered) soil Koc = 118 KOC program water solubility = 4300 mg/l ((measured/user entered) air-water partition coefficient 1.20646E-5 biomass to water partition coefficient = 58.4806 temperature = 25 degrees C
Reliability	:	(2) valid with restrictions Data were obtained by modeling

20.09.2002 (12)

3.3.2 DISTRIBUTION

3.4 MODE OF DEGRADATION IN ACTUAL USE

3.5 BIODEGRADATION

Type	:	aerobic
Inoculum	:	
Deg. Product	:	
Method	:	other: calculated
Year	:	2002
GLP	:	no
Test substance	:	as prescribed by 1.1 - 1.4
Remark	:	The EPIWIN/BIOWIN program estimates biodegradabilty of the test substance using a mathematical algorithm that sums up individual chemical bond fragment valuations for biodegradation. The result is consistent with general knowledge that intermediate length aliphatic hydrocarbon chains having a terminal amide function are generally recognized to biodegrade readily.
Result	:	EPIWIN/BIOWIN model predicts that the test substance will biodegrade fast.
Reliability	:	(2) valid with restrictions A reliability rating of 2 is assigned, because the determination is estimated by modeling.

20.09.2002 (9)

Type	:	aerobic
Inoculum	:	
Contact time	:	50 day

Degradation : = 50 % after .3 day
> 70 % after 4 days
Result : readily biodegradable
Deg. Product : yes
Method : other
Year : 1995
GLP : yes
Test substance : other TS
Method : The following guideline was followed:

Richtlinie Teil IV, 4-1 BBA der Bundesrepublik Deutschland: Verbleib von Pflanzenschutzmitteln im Boden - Abbau, Umwandlung and Metabolismus, Dezember, 1986.

Result : Based on data collected during a 50 day incubation period, DT-50 values of 0.02 day (Soil A) to 0.27 days (Soil C) were calculated. The DT-90 values amounted to 0.65, 1.14 and 2.46 days for soils A, B and C respectively. The test substance was mineralized to a very high degree. Totally, >= 83% of the applied radioactivity was found in the form of 14CO2 at the end of the 50 day incubation period. Two metabolites were found - N,N-dimethylsuccinic acid monoamide and N,N-dimethylmalonic acid monoamide. These metabolites rapidly degraded further to eventually form 14CO2.

Test condition : The rate of decline (DT-50 and DT-90 values) of the test substance was determined in three soils incubated in the dark for 50 days at 20 degrees C under aerobic conditions. The three soils were [A (silt loam), B (loamy sand) and C (silt loam) were treated with the radiolabeled test substance at a rate of 81 ug/100g of soil.

The soil samples were extracted with acetonitrile, acetonitrile/water (1/1) and water.

The extracted radioactive residues were analyzed by TLC and confirmed by HPLC. The amount of both parent substance and radioactive fractions was calculated.

Test substance : The test substance was N,N-dimethyldecanoic acid amide (CAS No. 14433-76-2), Batch No. 930129ELB02, 98.8% purity. The 14C radiolabeled material was labeled at the carbonyl carbon and was of 100% radiochemical purity.

Conclusion : The study author concluded that the rate of mineralization under the test condition was very high in all three soil types studied, and amounted to > 70% of the applied radioactivity after 4 days.

Reliability : (1) valid without restriction
The study was performed according to GLP and standard guidelines. There were no deviations that could affect the outcome.

(15)

26.09.2002

Type : aerobic
Inoculum :
Contact time : 154 day
Degradation : = 50 % after 2.2 hour(s)
Result : other: rapidly biodegraded
Deg. Product : yes
Method : other
Year : 1995
GLP : yes
Test substance : other TS
Method : The following guidelines were followed:

(U.S.) EPA 540/9-82-021: Pesticide Assessment Guidelines, Subdivision N: Chemistry: Environmental Fate, Section 162-1: Aerobic Soil Metabolism

Studies, Section 162-2: Anaerobic Soil Metabolism Studies, October 18, 1982.

(U.S.) EPA Pesticide Assessment Guidelines, Subdivision N, Environmental Fate, Section 162-1, Aerobic Soil Metabolism Studies. Standard Evaluation Procedure for Aerobic Soil Metabolism Studies, 1985.

(U.S.) EPA Pesticide Assessment Guidelines, Subdivision N, Environmental Fate, Section 162-1, Aerobic Soil Metabolism Studies. Standard Evaluation Procedure for Aerobic Soil Metabolism Studies, 1985.

(U.S.) EPA Pesticide Assessment Guidelines, Subdivision N, Environmental Fate, Section 162-1, Aerobic Soil Metabolism Studies. Addendum 5 on Data Reporting, 1987.

(U.S.) EPA Pesticide Assessment Guidelines, Subdivision N, Environmental Fate, Section 162-1, Aerobic Soil Metabolism Studies, Acceptance Criteria, 1989.

Result : The mean recovery over the whole incubation period was 102.9% of the radioactivity applied. The test article was mineralized very fast and to a very high degree. After 1 day 33.5% of the radioactivity of the labeled test material was found as 14CO2, after 2 days this portion amounted to 63.5%. At the end of the incubation (154 days) 83.3% of the applied radioactivity was found as 14C02. Negligible amounts of volatiles other than 14CO2 were observed. Based on the data collected, a DT-50 value of 2.2 hours and a DT-90 value of 7.5 days were calculated. Metabolites like N,N-dimethylsuccinic acid monoamide and N,N-dimethylmalonic acid monoamide that were formed in the soil on day 1 were rapidly mineralized during further incubation.

Test condition : The aerobic degradation and metabolism of the test substance was investigated in one agricultural soil of the U.S. (sandy loam) at 20 +- degrees C and 75% of 1/3 bar moisture in the dark for 154 days. The labeled test material was applied at an initial concentration of 40.07 ug/100 g dry soil equivalent (8939485 dpm) corresponding to 400.7 ug/kg soil. The study was performed in duplicate in metabolism flasks. The sampling days were 0, 1, 2, 3, 4, 7, 14, 28, 77, and 154 days.

The soil samples were extracted with acetonitrile and acetonitrile/water (1/1).

The extracted radioactive residues were analyzed by TLC and confirmed by HPLC. The amount of both parent substance and radioactive fractions was calculated.

Test substance : The test substance was N,N-dimethyldecanoic acid amide (CAS No. 14433-76-2), Batch No. 930129ELB02, 98.8% purity. The 14C radiolabeled material was labeled at the carbonyl carbon and was of >98% radiochemical purity as determined by TLC and HPLC analysis.

Reliability : (1) valid without restriction
The study was performed according to GLP and standard guidelines. There were no deviations that could affect the outcome.

26.09.2002 (33)

3.6 BOD5, COD OR BOD5/COD RATIO

3.7 BIOACCUMULATION

3.8 ADDITIONAL REMARKS

4.1 ACUTE/PROLONGED TOXICITY TO FISH

Type	:	static
Species	:	Oncorhynchus mykiss (Fish, fresh water)
Exposure period	:	96 hour(s)
Unit	:	mg/l
Analytical monitoring	:	yes
NOEC	:	m = 5
LC0	:	m = 15.8
LC50	:	m = 21.1
Method	:	other: OECD Guideline 203; EEC Directive 79/831, Annex V, Method C1; EPA Pesticide Assessment Guideline, Subdivision E, 1982
Year	:	1993
GLP	:	yes
Test substance	:	other TS
Remark	:	The slight symptoms of adaptation in 5 fish exposed to 5 mg/l for 4 hours were dismissed by study personnel because this was the only time point that they exhibited this behavior. Therefore, this concentration was chosen at the no observable effect concentration.
Result	:	None of the fish exposed to 15.8 or less test material died by 96 hours. Mortality of fish exposed to 28.1 mg/l was 9/10 at 24 hours and 10/10 at 48 hours. All fish exposed to 50.0 mg/l died by 4 hours. The LC50 values (with confidence intervals) were 37.5 (28.1-50.0) for 4 hours, 22.4(15.8-28.1) for 24 hours, and 21.1(15.8-28.1) for 48, 72 and 96 hours. There were no symptoms of intoxication in controls. Half of the fish exposed to 5 mg/l were observed near the water surface at 4 hours. All fish exposed to this concentration appeared normal at all other time points. Four or five of the fish exposed to 8.89 mg/l were observed near the surface at all time points except 96 hours. Most fish (9 to 10/10) exposed to 15.8 mg/l had slightly irregular swimming behavior at all time points (except 24 hours), which included tumbling at 72 and 96 hours. At 96 hours, all fish exposed to 15.8 mg/l had changed coloration. All fish exposed to 28.1 mg/l exhibited convulsions and/or were lying on their side at the bottom at 4 hours. The lowest lethal concentration, the no observed lethal effect concentration, the lowest observed effect concentration, the effect threshold and the no observed effect concentration for 96 hours were 28.1, 15.8, 8.89, 6.67 and 5.0 mg/l test material, respectively. At all times, the test material was distributed homogeneously in the medium and did not precipitate out of solution. The dissolved oxygen and pH ranged from 10.0-11.1 and 7.4-8.0, respectively. The average concentration of C6, C8 and C10 isomers in the medium were 93.9-96.8, 90.5-95.8, and 79.1-92.8% of nominal values. The concentrations at the end of the test did not differ significantly from the beginning of the test. Since the concentrations of the isomers were 79% or greater than nominal, results are listed based on nominal concentrations. None of the isomers were detected in the control aquarium.
Test condition	:	Fish: The rainbow trout used in the study were obtained as eye eggs and hatched in the testing facility. All fish were observed for at least 14 days before testing. No injured or deformed fish were used. Less than 3% mortality was noted prior to the test. Fish were fed a commercial trout diet up to 48 hours from the start of the study, and were not fed during the test. The mean body weight and length (+/- SD) of the fish at the beginning of the test were 1.4 +/- 0.4 g and 5.0 +/- 0.5 cm, respectively. Test medium: Reconstituted water was prepared by adding salt stock

solution to demineralized water (conductivity 0.2 micromhos/cm). The final ionic concentrations were 0.015 mM K+, 0.384 mM Ca++, 0.096 mM Mg ++ and SO4--, 0.148 mM Na+ and HCO3-, and 0.783 mM Cl-. The hardness was 40-60 mg CaCO3/l. The water was aerated to oxygen saturation with air (dissolved oxygen was 10.1- 11.1 mg/l). The water was analyzed for impurities approximately 5 and 2 months before the beginning of the test. Concentrations of 24 common organochlorine contaminants and 54 common pesticides were < 0.01 and 0.05 micrograms/liter, respectively. Concentrations of common inorganic contaminants were normal. Water from the same source was used to breed Daphnia. The pH and temperature were 7.4-8.0 and 12.1 +/- 1 degrees C, respectively.

Test conduct: Fish (10/ concentration) were placed in glass aquaria (32 x 36 x 38 cm) containing 40 liters of medium containing nominal concentrations of 0 (control), 5.00, 8.89, 15.8, 28.1 and 50.0 mg/l test material. One aquarium was used per concentration. The loading was 0.4 g fish/liter of test medium. Water samples were taken immediately before fish were added from the center of the aquaria and at the end of the study for analysis of the C6, C8 and C10 isomers by HPLC with UV-detection. The limit of detection was 0.1 mg/l for each isomer.

Fish were examined 4 hours after addition to the tanks, and then daily for the remainder of the 96 hour test. Dissolved oxygen and pH were determined daily, and water temperature was measured hourly.

LC50 values (with 95 % confidence intervals) for 24, 48, 72 and 96 hours were calculated with a computer program that estimated the LC50 value using one of three statistical techniques: moving average, binomial probability, or probit. The appropriate method was determined based on the characteristics of the data (the criteria were not listed).

Test substance : The test material (Hallcomid M-8-10) was a commercial product containing 4.43% N,N-dimethyl-hexanoic amide, 52.2% N,N-dimethyl-octanoic amide (CAS No. 1118-92-9), 37.2% N,N-dimethyl-decanoic amide (CAS No. 14433-76-2), and 0.59% N,N-dimethyl-dodecanoic amide (according to the manufacturer).

Reliability : (1) valid without restriction
The study was performed according to GLP and standard guidelines. There were no deviations that could affect the outcome.

30.09.2002 (7)

4.2 ACUTE TOXICITY TO AQUATIC INVERTEBRATES

Type	:	static
Species	:	Daphnia magna (Crustacea)
Exposure period	:	48 hour(s)
Unit	:	mg/l
Analytical monitoring	:	no
NOEC	:	m = 4
LC50	:	m = 7.7
Method	:	EPA OTS 797.1300
Year	:	1990
GLP	:	yes
Test substance	:	other TS
Remark	:	The light intensity in the culture chamber containing adult Daphnids fell slightly below the intended value of 50-70 footcandles. According to study personnel, this did not affect health or reproduction.
Result	:	None of the organisms exposed to concentrations < = 4.0 mg/l or controls died or had abnormal behavior. At 24 hours, 2/10 and 5/10 Daphnia exposed to 8.0 mg/l died. Three of the organisms in one flask and one in

another were observed alive on the bottom at 24 hours. There were no deaths at 24 hours in organisms exposed to 16 mg/l. However, all of the organisms exposed to this concentration were on the bottom of the vessels at 24 hours. At 16 mg/l, 5/10 and 7/10 of the organisms on the bottom of the vessels were coated with extraneous material. At 48 hours, 7/10 and 9/10 deaths occurred at 8.0 mg/l and 8/10 and 10/10 occurred at 16 mg/l.

The LC50 values (with confidence intervals, if appropriate) were > 4.0 mg/l (estimated) at 24 hours and 7.7 (6.2 and 10) mg/l at 48 hours. The values at 24 and 48 hours were calculated using the binomial method and the moving average method, respectively. The no effect concentration at 48 hours was 4.0 mg/l. The slope of the dose-response curve at 48 hours was 6.0.

All solutions were clear and a precipitate was not observed. Dissolved oxygen concentrations ranged between 7.9 and 8.3 mg/l (94 and 98% of saturation, respectively). The pH and temperature of the solutions ranged from 8.3 to 8.4, and 21 to 22 degrees C, respectively.

Test condition : Test material: A standard solution of 32 mg/l test material in dimethylformamide (DMF) solvent was prepared. A working standard was prepared by mixing 1 ml of this solution in 2 liters of hard blended water. A solvent control solution was made of 0.5 ml DMF in 1 liter of hard blended water. Hard blended water is a combination of well water and reverse-osmosis water blended to a hardness of 160-180 mg/l $CaCO_3$.

Test water: Test water had a hardness, alkalinity, pH, conductivity, total organic carbon and suspended solid content of 160 mg/l (as $CaCO_3$), 156 mg/l (as $CaCO_3$), 8.3, 320 micromhos/cm, < 1.0 ppm and 0.3 ppm. It contained < 0.01 ppm unionized ammonia, < 1.0 ppb toxaphene, < 0.5 ppb Vapona, Thimet, Diazinon, Methyl Parathion, Parathion, Ronnel, Malathion, and total PCBs, < 0.10 ppb Mirex and Methoxychlor, < 0.05 ppb Endrin, DDE, DDD, DDT, and Dieldrin, and < 0.01 ppb HCB, HE and alpha, beta, gamma and delta BHC. Elemental analyses were within normal limits.

Organisms: All daphnids were cultured in 2-liter glass containers in hard blended water at 20 +/- 2 degrees C. Lighting was maintained at 50-70 footcandles on a 16-hour daylight photoperiod. Adult daphnids were fed algae and a supplement of trout chow and active dry yeast at least every 3 days. The adults were subcultured for 39 days prior to the study and had no signs of stress, disease or physical damage. First-instar daphnids (< 24 hours old) were used in the test.

Test conduct: Tests were conducted in 250-ml glass beakers containing 200 ml of test water. All vessels were covered with loose-fitting petri dish covers to minimize evaporation and prevent contamination. The vessels were kept at 20 +/- 2 degrees C, under the same light conditions as described above. An initial range-finding study was conducted with 10 Daphnia magna per concentration of test material (10 and 100 mg/l). Based on the finding of 80% and 100% mortalities at 10 and 100 mg/l, groups of 10 Daphnia were exposed to 1.0, 2.0, 4.0, 8.0 and 16.0 mg/l test material, a solvent control and an untreated control (in duplicate). Daphnia were added to the vessels within 30 minutes of adding test material. Daphnia were observed for abnormal behavior and mortality 24 and 48 hours after being added to the vessels. Temperature, dissolved oxygen and pH were measured in one vessel/concentration.

LC50 values (and 95% confidence limits) were calculated with a computer program based on the binomial, moving average and probit tests. The method of calculation selected for presentation in the report was the one that gave the narrowest confidence limits for the LC50 value. The 48-hour dose-response slope was calculated by transferring the percent mortality to probit values and performing a linear regression.

Test substance	:	Dimethyl hexaneacidamide, 50-65% N,N- dimethyl octaneacidamide, 37-50% N,N- dimethyl decaneacidamide, and 0-2% N,N- dimethyl dodecaneacidamide. The exact composition of the test material was not specified. [This specification was not listed in the study. It was derived from data G. Wentworth of the C.P. Hall Company supplied and from specs listed in studies that were conducted around 1990].
Reliability	:	(2) valid with restrictions The exact composition of the test material was not listed.

30.09.2002 (16)

4.3 TOXICITY TO AQUATIC PLANTS E.G. ALGAE

Species	:	Selenastrum capricornutum (Algae)
Endpoint	:	growth rate
Exposure period	:	72 hour(s)
Unit	:	mg/l
Analytical monitoring	:	yes
NOEC	:	m = 1.8
LOEC	:	m = 3.2
EC50	:	m = 16.06
Method	:	other: OECD Guideline 201;EEC Directive 79/831/EWG, Annex V, C3; ISO Guideline No. 8692: 1989(E)
Year	:	1993
GLP	:	yes
Test substance	:	other TS
Remark	:	Historical data for K2Cr2O7 and validity criteria for the test were not provided.
Result	:	For inhibition of growth rate, the EC50 value (with 95% confidence limits) was 16.06 (7.95 to 32.45) mg/l. The lowest observed effect concentration (LOEC) for growth rate at 72 hours was 3.20 mg/l, and the no observed effect concentration (NOEC) at 72 hours was 1.80 mg/l. All concentrations of test material inhibited the growth rate at 24 hours. All concentrations tested caused a significant decrease in biomass by 72 hours. Therefore, the NOEC and LOEC for inhibition of biomass were < 1.80 mg/l, and 1.80 mg/l, respectively. The EC50 value for inhibition of biomass at 72 hours (with 95% confidence limits) was 5.47 (2.64 to 11.34) mg/l. Some (number not stated) deformed cells were noted after treatment with concentrations greater than or equal to 3.20 mg/l. Inhibition of biomass was not noted in cells treated with any concentration of test material at 24 hours. At the start of the test, the pH of cultures ranged from 8.28 to 8.34. By 72 hours, the pH of cultures containing 0 to 10.0 mg/l increased due to rapid growth. pH values varied inversely with test material concentration. The highest pH (9.88) was observed in the control flask. Although slightly higher (0.10 units) than suggested, this did not appear to adversely affect the test. The analytical concentrations of N,N-dimethyl-hexanoic amide, N,N-dimethyl-octanoic amide, and N,N-dimethyl-decanoic amide (CAS No. 14433-76-2) in cell-free cultures were an average of 98.4%, 97.6%, and 88.9% of nominal. Altogether, this suggested that the test material concentrations in each flask were approximately 95% of nominal. The lower value for the C-10 isomer may have been due to the lower than nominal concentration of this amide in the stock solution of the test material (94.1%, compared to 97.7% and 103.8% for the C-8 and C-6 isomers, respectively).
Test condition	:	Stock cultures of algae were grown at 23 +/- 2 degrees C under a 16-hour light/day cycle in cotton-plugged, 300-ml Erlenmeyer flasks containing 50

ml of nutrient solution (as described by Bringmann and Kuhn, Water Res. 14:231-241, 1980). Fresh stock cultures were prepared once a week. Pre-cultures were prepared by inoculating a growth solution containing 15.0 mg NH4Cl, 12.0 mg MgCl2 x 6H2O, 18.0 mg CaCl2 x 2 H2O, 15.0 mg MgSO4 x 7 H2O, 1.6 mg KH2PO4, 50.0 mg NaHCO3, 100.0 micrograms Na2EDTA x 2H2O, 185.0 micrograms H3BO3, 415.0 micrograms MnCl2 x 4H2O, 3.0 micrograms ZnCl2, 1.5 micrograms CoCl2 x 6H2O, 0.01 micrograms CuCl2 x 2 H2O, 7.0 micrograms Na2MoO4 x 2H2O, and 80.0 micrograms FeCl3 x 6H2O per liter H20 with 1 x 10E4 cells/ml and allowing the cells to grow for 2-3 days in an incubator.

For the growth inhibition test, 1 x 10E4 cells/ml of the incubated pre-culture were added to flasks containing 150 ml growth medium and 0, 1.80, 3.20, 5.60, 10.0, 18.0, 32.0 or 56.0 mg/l test material. The flasks were then sealed with cotton wool plugs and placed in an incubator (23 +/- 2 degrees C). Flasks containing all test concentrations without algae were also prepared for quantitative analyses (see below). Flasks were illuminated at 8000 lux 24 hours/day. In the incubator, flasks were suspended by their necks from a series of plastic disks supported in the middle by a central pole. The pole was turned intermittently (6.5 thrust per revolution, 3 revolutions per minute) to prevent sedimentation of the cells or test material. Ph of the cultures was measured at 0, 24, 48 and 72 hours. Cell numbers at 24, 48 and 72 hours were determined photometrically (578 nm), from extinction values. The EC50 for growth of biomass and algal growth rates were calculated using Finney probit analyses and the slopes of the regression lines were calculated following methods described by Litchfield and Wilcox. Calculations were carried out using commercial software. The NOEC and LOEC were calculated using an analysis of variance and Dunnett's test (comparing values obtained for treated cells versus controls).

The sensitivity of the test system was checked approximately 6 months before the assay with the test material by testing a known reference chemical (K2Cr2O7) at 0.18, 0.56, 1.00 and 1.80 mg/l. In this test, the 72-hour EC50s for inhibition of biomass and growth rate were 0.70 mg/l and 1.34 mg/l, respectively.

Test material concentrations were analytically verified by measuring the individual concentrations of the 3 major amides present in the test material in cell-free cultures containing all concentrations of test material on Day 0, using HPLC with UV-detection. The limit of detection was 0.1 mg/l.

Test substance : The test material (Hallcomid M-8-10) was a commercial product containing 4.4% N,N-dimethyl-hexanoic amide, 52.2% N,N-dimethyl-octanoic amide (CAS No. 1118-92-9), 37.2% N,N-dimethyl-decanoic amide (CAS No. 14433-76-2), and 0.6% N,N-dimethyl-dodecanoic amide.

Reliability : (1) valid without restriction
The study was performed according to GLP and standard guidelines. There were no deviations that could affect the outcome.

30.09.2002 (1)

4.4 TOXICITY TO MICROORGANISMS E.G. BACTERIA

4.5.1 CHRONIC TOXICITY TO FISH

4.5.2 CHRONIC TOXICITY TO AQUATIC INVERTEBRATES

4.6.1 TOXICITY TO SOIL DWELLING ORGANISMS

4.6.2 TOXICITY TO TERRESTRIAL PLANTS

4.6.3 TOXICITY TO OTHER NON-MAMM. TERRESTRIAL SPECIES

Species	:	Colinnus virginianus (avian)
Endpoint	:	mortality
Exposure period	:	14 day
Unit	:	mg/kg bw
LD50	:	m = 1600
Method	:	EPA OPP 71-1
Year	:	1994
GLP	:	yes
Test substance	:	other TS
Result	:	None of the birds exposed to 0, 200, or 400 mg/kg died or exhibited toxic signs. At 800 mg/kg, 4 females and 1 male showed transient (less than one day) signs (ptosis, loss of equilibrium and/or apathy). There were no deaths at 800 mg/kg. At the 1600 mg/kg dose, three males and two females died and all exhibited signs of toxicity (apathy, convulsions, ptosis, loss of equilibrium and/or diarrhea) on the day of treatment. Survivors recovered after one to three days. All birds treated with 3200 mg/kg died within 2-9 hours of treatment. Necropsies of animals exposed to 800, 1600 or 3200 mg/kg showed no compound-related lesions. Birds (predominantly females) treated with 1600 mg/kg test material had significantly higher body weights than controls at termination (but not on Day 7). Feed consumption of the group of animals exposed to 1600 mg/kg was lower than the other groups at all time intervals (0-3, 3-7 and 7-14 days). On an individual basis, food consumption of birds exposed to 400 and 1600 mg/kg was higher than controls from days 0-3 and 7-14, respectively. Food consumption of other groups and individual birds within groups was similar to control. The acute oral LD50 value was 1600 mg/kg. According to study personnel, the no observable and lowest observable effect level (NOEL and LOEL) were 400 and 800 mg/kg, respectively.
Test condition	:	Adult Bobwhite Quail (17 weeks of age) were acclimated for 14 days before treatment. Injured or deformed birds were not utilized. The mortality rate during acclimation was < 5%. The quail were given feed and water ad libitum (except during an 18-hour fasting period just prior to dosing). Five groups of 10 birds (five per sex) were given a single oral dose of 200, 400, 800, 1600 or 3200 mg/kg test material by gelatin capsule (without any carrier). The doses were not corrected for purity. One additional control group of ten birds (five/sex) were dosed with an empty capsule only. Animals were observed for mortality and toxic signs continuously for the first hour after dosing, hourly for the first day, and then daily for 14 days (except on weekends if no symptoms were noted the day before). Animals were weighed the day before dosing, on Study Day 7, and prior to termination (if animals were still alive). Feed consumption of each group was recorded on Study Days 3, 7, and 14. Necropsies were conducted at termination on all birds in the 800 and 1600 mg/kg groups that survived to termination and all birds that died during the study. The LD50 value was calculated with a computer program that estimated the value based on moving average, binomial probability, or probit. The appropriate method was selected based on characteristics of the data

(criteria were not listed). Body weight and growth data were first analyzed using Bartlett's test to determine if the groups had equal variances. Parametric data were analyzed using a one way analysis of variance (ANOVA). Bonferroni's test was used to determine differences from control. Nonparametric data were analyzed using the Kruskal-Wallis test. The criterion for significance was $P < 0.05$.

Test substance : The test material (Hallcomid M-8-10) was a commercial product containing 4.4% N, N-dimethyl hexane acid amide, 52.2% N,N-dimethyl octane acid amide (CAS No. 1118-92-9), 37.2% N,N-dimethyl decane acid amide (CAS No. 14433-76-2), and 0.6% N,N-dimethyl dodecane acid amide. The purity was 94.4%.

Reliability : (1) valid without restriction
The study was performed according to GLP and standard guidelines. There were no deviations that could affect the outcome.

30.09.2002 (18)

4.7 BIOLOGICAL EFFECTS MONITORING

4.8 BIOTRANSFORMATION AND KINETICS

4.9 ADDITIONAL REMARKS

5.1.1 ACUTE ORAL TOXICITY – THIS ONE IS NEW

Type	:	LD50
Species	:	Rat
Strain	:	Sprague-Dawley
Sex	:	male/female
Number of animals	:	22
Vehicle	:	
Value	:	= 1250 mg/kg
Method	:	other: 40/ CFR
Year	:	1990
GLP	:	yes
Test substance	:	other TS
Result	:	All animals exposed to 5.0 ml/kg died and three animals (2/2 females and 1/2 males) exposed to 2.5 g/kg died between days 0 and 1 of treatment. One female given 1.25 g/kg died between days 1 and 2 of treatment. All other animals survived. Based on these data, an LD50 value of 1.25 g/kg was calculated. Symptoms of intoxication before death included ataxia, depression, and labored breathing. Symptoms observed in rats treated with any concentration included rapid and shallow breathing, cool to the touch, ataxia and depression on the day of dosing. These symptoms persisted to day 1 in rats treated with 2.5 g/kg. Piloerection, red stains around nostrils, brownish urine stains and/or hunched posture were noted up to study day 4 in surviving rats treated with 1.25 or 2.5 g/kg. Survivors appeared normal after approximately day 5. All survivors gained weight normally over the 14-day period. Gross necropsies of animals that died revealed intestines and stomach yellowish in color, white viscous material in stomach, stomach and/or intestines enlarged and bloated with gas, mottled liver, kidneys congested, and urinary bladder filled with reddish brown fluid. Gross necropsies of surviving rats were normal.
Test condition	:	Animals (249-293 g males and 215-249 g females) were acclimated to the laboratory for at least 4 days until use. They were supplied food and water ad libitum (except for withholding food overnight prior to dosing) and maintained on a 12 hour light/dark cycle. A group of 5 animals/sex were given test material by gavage at a concentration of 5.0 g/kg. Three additional groups of 2 animals/sex were given test material at 0.625, 1.25 and 2.5 g/kg. Animals were observed closely for gross sings of systemic toxicity and mortality several times during the day of dosing, and at least twice daily thereafter for a total of 14 days. Body weights were measured on the day of dosing, and on days 7 and 14 (just prior to termination). At day 14, animals were euthanized and gross necropsies were performed. The LD50 value and 95% confidence limits were calculated by the method of Gad and Weil, 1982, Statistics for Toxicologists, Raven Press.
Test substance	:	The test material was Hallcomid M-8-10. This material contains 0-5% N,N-dimethyl hexaneacidamide, 50-65% N,N- dimethyl octaneacidamide, 37-50% N,N- dimethyl decaneacidamide, and 0-2% N,N- dimethyl dodecaneacidamide. The exact analytical composition was not specified. [This specification was not listed in the study. It was derived from data G. Wentworth of the C. P. Hall Company supplied and from specs listed in studies that were conducted around 1990].
Reliability	:	(2) valid with restrictions The results may have been influenced by the relatively few animals (2/sex)

treated with doses less than 5 g/kg.

01.11.2002 (21)

5.1.2 ACUTE INHALATION TOXICITY

Type	:	LC50
Species	:	rat
Strain	:	Wistar
Sex	:	male/female
Number of animals	:	50
Vehicle	:	
Exposure time	:	4 hour(s)
Value	:	> 3551 mg/m³
Method	:	other: OECD Guide-line 403;EEC Directive 84/449
Year	:	1991
GLP	:	yes
Test substance	:	other TS
Remark	:	Study personnel stated that the respiratory symptoms were due to a primary irritant effect of the material on the respiratory tract. Hypothermia was considered to be related to this irritation. Study personnel also stated that lower air humidity readings at the high concentrations were due to damage to sensors caused by the test material.
Result	:	Concentrations of material in the chambers were stable throughout the study. At target concentrations of 1000, 5000, 20000 and 50000 mg/m3, average analytical concentrations were 118.5, 586.4, 2007.6 and 3550.7 mg/m3, respectively. The average MMAD (and GSD) of the aerosols at each concentration ranged from 1.14-1.37(1.37- 1.49) microns. The mass fraction of respirable particles (< 3 microns) was 99-100% for test material and 96% for control material. Data were based on actual concentrations (rather than target) due to the large difference in the two values. One male rat exposed to 3550.7 mg/m3 died. All other animals survived to 14 days. None of the animals exposed to 118.5 mg/m3 exhibited any signs of toxicity. Rats exposed to 586.4 mg/m3 had exhibited reddening of the nose (1 female, all males), reduced motility (all males) and piloerection (all males) on the day of exposure only. Most of the rats exposed to 2007.6 mg/m3 exhibited effects seen at 586.4 mg/m3, along with ungroomed fur, and symptoms of respiratory irritation such as swollen rhinarium, serous nasal discharge, and/or slow and labored respiration. These symptoms, plus dyspnea, stridor, purulent and severely swollen rhinarium, sniffing noises, steppage, prostation, atony, and cyanosis were observed in rats exposed to 3550.7 mg/m3. Whereas symptoms in rats exposed to 586.4 mg/m3 were only observed on the day of exposure, symptoms in rats exposed to 2007.6 or 3550.7 mg/m3 persisted for up to 7 and 14 days, respectively. Neurological examinations performed within the first 3 days of the post-treatment period revealed no differences between animals exposed to test material and controls. Reduced rectal temperatures were found in animals exposed to all concentrations except 118.5 mg/m3. Animals exposed to 2007.6 and 3550.7 mg/m3 had decreased body weights. The necrospy of the animal that died revealed distended, liver-like and edematous lungs, hydrothorax, reddened and swollen rhinarium, pale spleen, marbled kidneys and slimy-yellow duodenal contents. Surviving rats exposed to the high concentration also had a higher incidence of distended lung. Animals exposed to lower concentrations did not exhibit any gross pathological changes with respect to controls. The temperatures in the chambers ranged from 20.8 to 24.3 degrees C, with higher temperatures generally towards the end of the study. The relative humidities were generally approximately 10% higher at the

beginning than the end of exposures, and varied according to concentration. The highest relative humidity was 37.0 (for the low concentration at the beginning of exposure) and the lowest was 4.8 (for the highest concentration approximately 3.5 hours into the exposure). The temperatures and relative air humidities inside the inhalation chambers were within the tolerance ranges specified by the OECD Guideline.

Test condition : Animals: Healthy, young, adult SPF-bred Wistar rats (Bor:WISW SPF-Cpb) were acclimated for at least 4 days before exposure. The rats had a mean weight of 170 to 210 g. The animals received food and water ad libitum (except during exposure).

Generation of aerosol/Exposure conditions: The aerosol was generated with a nozzle and conditioned compressed air. The compressed air was produced with two in-parallel Boge compressors. The air was automatically conditioned by an in-line VIA compressed air dryer that removed water, dust and oil. The compressors operated at a pressure of 800 to 1000 kPa. The operating pressure for each compressor was set using reduction valves. Two aerosols were used for the study. For high concentrations (20000 and 50000 mg/m3), test material was nebulized under dynamic conditions into the baffle of the inhalation chamber in undiluted form (at 200 or 500 microliters spray solution/10 liters air/min for 200000 or 50000 mg/m3, respectively. The dispersion pressure was approximately 600 kPA. At low concentrations (1000 and 5000 mg/m3), solutions of test material (5% and 25%, respectively) were nebulized as a 1:1 mixture with polyethylene glycol 400-ethanol, which enhanced the formation of smaller particles. At all concentrations, solutions were passed to the nozzle by means of a continuous infusion pump with a 50-ml ground glass syringe. The aerosol (200 microliters/10 liters of air per min) was sprayed under dynamic conditions into a cylindrical inhalation chamber with a baffle, which increased the efficiency of aerosol formation and removed larger particles. The dispersion pressure was approximately 600 kPa. The aerosol generation conditions ensured approximately 30 air exchanges per hour. A steady state concentration was reached within approximately 6 minutes of operation. The nominal concentrations were calculated from the quotient of the test article (mg) nebulized into the baffle and the total air in the inhalation chamber (20 liters). The analytical concentration of material in the test atmosphere in the breathing zone of the rats was determined by gas chromatography. Where technically feasible, samples were taken from the inhalation chamber just after equilibration, at the mid-point, and towards the end of the study. The total air volume per analysis was 10 liters air (sampling rate 1 liter/min). Samples for particle distribution analyses also were taken from the immediate breathing zone of the rats. Particle analyses were performed with an aerodynamic particle sizer with a laser velocimeter run at two dilution states. The NMAD (number median aerodynamic diameter) and GSD (geometric standard deviation) were determined from the probit-transformed particle-related cumulative frequency distribution and the logarithmized effective cutoff diameters of the individual measurement capillaries of the laser velocimeter using liner regression. The MMAD (mass median aerodynamic diameter) was calculated from the NMAD according to the following equation: ln (MMAD) = ln(NMAD x density) + 3(ln(GSD))squared. The GSD was calculated from the regression curve (percentile 84/percentile 50). The apertures of the sampling apparatus complied with those required for representative sampling of the test atmosphere.

Five animals/sex/concentration (100, 500, 20000 and 50000 mg/m3) were exposed head/nose-only to the aerosol for 4 hours in plexiglass exposure tubes. The PVC inhalation chamber had a diameter of 30 cm, height of 28 cm, and volume of approximately 20 liters. During testing, the ratio of inlet to outlet air was selected so that approximately 80% of the dynamic inlet air was extracted by a filter (cylinder containing cotton wool). An air

flow in the direction of the rats was set up within the exposure system. During exposure the air flows were continuously monitored with a rotameter and adjusted when necessary. The inhalation chambers were operated in fume hoods. The outlet air was purified with a cotton wool filter. Chamber temperature and humidity were recorded over 10 minute intervals.

Body weights of the rats were taken before exposure, on Days 3, 7, and 14. Appearance and behavior were monitored several times on the day of exposure and then twice daily for the remainder of the study (including weekends). The animals in the tubes were examined closely if obvious signs occurred. Parameters examined after exposure were gross appearance of the mucous membranes of the eyes and respiratory tract, general state of muzzle skin and pinna, state of fur and grooming activity, respiration, cardiovascular activity (where possible), somato-motor system and behavior pattern, central nervous and autonomic signs, visual placing response and grip strength, tone of abdominal muscles, pupil, cornea, righting, startle and pinna reflexes, and tail-pinch response. Rectal temperature was measured within 10-25 minutes after exposure was terminated. The animals were euthanized on Day 14 and subjected to a gross necropsy.

Additional rats (5 per sex) were exposed every 3 months to the solvents used in the study (air, water/aerosol (nominal 50000 microliters/m3 air) and polyethylene glycol 400-ethanol (1:1) aerosol (nominal 20000 microliters/m3 air). The body weights, rectal temperatures and gross pathology of the test rats were compared to those of the last relevant control group exposed. For this study, the polyethylene glycol 400-ethanol (1:1) aerosol group was the control.

Necropsy findings were evaluated using Fisher's Pairwise Test with a preceding RxC chi square test. Body weight and body weight gain data were tested for normal distribution by comparing mean and median values. If an F-test showed that the spread within the group was greater than between groups, there was no significant difference between the groups. If the spread within groups was less than between groups, data were compared using Games and Howell's modification of the Tukey-Kramer Significance Test. The criterion for significance was $p < 0.05$. Rectal temperatures were compared using analysis of variance (ANOVA). The LC50 value was calculated with computer program based on the maximum likelihood method.

Test condition : The test material (Hallcomid M-8-10) contained 3.7% N,N-dimethyl hexane acid amide, 54.1% N,N-dimethyl octanoic acid amide (CAS No. 1118-92-9), 38.5% decanoic acid amide (CAS No. 14433-76-2), and 1.3% N,N-dimethyl dodecanoic acid amide (according to the MSDS provided with the study report). The purity was not analytically verified.

Reliability : (1) valid without restriction
The study was performed according to GLP and standard guidelines. There were no deviations that could affect the outcome.

30.09.2002 (27)

5.1.3 ACUTE DERMAL TOXICITY

Type : LD50
Species : rat
Strain : Wistar
Sex : male/female
Number of animals : 40
Vehicle : other: cellulose
Value : = 400 - 2000 mg/kg bw

Method : other: OECD No. 402; EEC Directive 67/548, Annex V, Part B3 as amended by EEC 92/69;Pesticide Assessment Guidelines, Subdivision F, Hazard Evaluation Series 81-2, 1984

Year : 1995

GLP : yes

Test substance : other TS

Result : None of the animals exposed to 50 or 200 mg/kg died or exhibited signs of toxicity (with the exception of skin irritation). None of the females exposed to 400 mg/kg died. Two out of 5 males and all females exposed to 2000 mg/kg died within 2 days. All males exposed to 5000 mg/kg died within 5 hours of treatment. The LD50 values for males and females were 2000 mg/kg (approximate), and between 400 and 2000 mg/kg, respectively.

Four out of 5 females exposed to 400 mg/kg and all rats exposed to higher concentrations exhibited clinical signs such as piloerection, labored breathing, decreased motility and reactivity, abdominal position, poor reflexes, spastic gait, temporary tremor, pallor, cyanosis, increased salivation and lacrimation, hypothermia, chromodacryorrhea, red incrusted margin of eye, narrowed palpebral fissure and/or red colored urine. These signs generally occurred within 30 minutes of treatment and reversed within 6 days treatment. The no effect level (NOEL) for systemic effects was 200 mg/kg.

Local effects such as reddening, dark color, scarring, squamation, incrustation, dark color, partial hardening of the skin and/or scab formation were noted at the site of administration of most animals exposed to 200 mg/kg, all animals exposed to 400 mg/kg and all males exposed to 2000 mg/kg. The skin effects lasted from day 2 until the end of the study. One female treated with 50 mg/kg had some squamation at the treatment area. None of the others treated with 50 mg/kg had skin reactions. Therefore, this dose was chosen as the threshold level for local effects.

Transient reductions in body weight (on Day 4) were observed in surviving males in the 2000 mg/kg groups.

None of the survivors had any adverse pathology. Brownish-red fluid in the urinary bladder and discoloration of the liver were noted in animals that died.

Test condition : SPF-bred Wistar rats (strain Hsd Win:Wu) were acclimated for 7 days before treatment. Only healthy animals were used. The males and females were approximately 10-11 and >= 16 weeks old and weighed 242-286 and 228-260 grams at study commencement (respectively). Groups of 5 animals per sex were randomly assigned to 4 different treatment groups (50, 200, 2000 and 5000 mg/kg for males and 50, 200, 400 and 2000 mg/kg for females). For each dose and animal, the test material was weighed onto a piece of aluminum foil and mixed to a paste with cellulose (1 g test material plus 450 mg cellulose) and applied to the intact dorsal skin (shaved on the previous day). The size of the foil was 4 x 5 cm for the low dose and 5.5 x 5.5 cm for the high dose (sizes for other doses were not listed). The foil was covered with an occlusive dressing for 24 hours. Dressings were then removed, and the skin was cleaned with water. Stability of the material in the paste was analytically confirmed.

Appearance and behavior were recorded several times on the day of treatment and at least once/day for the remainder of the 14-day study. Body weights were recorded one day before treatment and on days 4, 8 and 15 (prior to necropsy). Animals were euthanized and subjected to a gross necropsy 14 days after treatment. Animals that died before study termination also were necropsied.

The LD50 value was calculated with a computer program. The approximate

LD50 value was assessed without slope and confidence interval when 2 dose groups caused mortality > 0 and < 100%, and another caused 0% or 100% mortality.

Test substance : The test material was Hallcomid M-8-10, which was defined as a mixture of 4.68% N,N-dimethyl hexane acid amide, 54.1% N,N-dimethyl octane acid amide (CAS No. 1118-92-9), 39.0% N,N-dimethyl decane acid amide (CAS No. 14433-76-2) and 0.55% N,N-dimethyl dodecane acid amide. The purity of the material was 98.03%.

Reliability : (1) valid without restriction
The study was performed according to GLP and standard guidelines. There were no deviations that could affect the outcome.

30.09.2002 (4)

5.1.4 ACUTE TOXICITY, OTHER ROUTES

5.2.1 SKIN IRRITATION- BOTH OF THESE ARE NEW

Species : rabbit
Concentration : undiluted
Exposure : occulsive
Exposure time : 4 hours
Number of animals : 6
PDII : 4.625
Result : irritating
EC classification : irritating
Method : other: DOT corrosivity potential study in rabbits (49 CFR)
Year : 1990
GLP : no data
Test substance : other TS
Remark : The primary irritation score (PII) was not calculated. Based on the results, the PII was 4.625. This result would lead to a classification of potential for moderate-severe irritation.

The study was audited for quality assurance.

Result : The total average erythema and eschar scores in all animals were 1 or 2 (slight to well-defined) at 4 hours and 3 (moderate to severe erythema) at 24 and 48 hours. Edema scores at all time points were 3 or 4 (moderate to severe). At 24 and 48 hours, spreading of erythema beyond the site, blanching, light or dark brown coloration on the site and/or coriaceousness also were noted. Hair was present on the site at 24 and 48 hours in 2 animals. Necrosis was not observed.

Based on the results, it was concluded that the material was not corrosive.

Test condition : Due to the suspected irritation potential, the material was first tested in a single, young adult male New Zealand white rabbit (weight was not stated). Due to the absence of extreme irritation, 5 additional animals (2 males and 3 females) were added to the study. All animals were acclimated to the laboratory for at least one day before use. They were given tap water and feed ad libitum. The hair on the application site (dorsal surface) was clipped one day prior to dosing. Test material (0.5 ml, undiluted) was applied to the site under a 1" x 1" gauze square. Each patch was held in place with adhesive tape. The trucks of the rabbits were then wrapped with rubber dental dam and secured with staples. An outer layer of gauze was then wrapped around the trunk of each animal and secured with tape. The animals were fitted with an appropriate restrainer to prevent them from removing the dressings. All dressings were removed after 4 hours.

The test was scored according to the method of Draize. The 1) erythema

and eschar and 2) edema scores were based on a scale of 1-4. The scores at 1/2-1, 24, 48 and 72 hours after removal of the dressings were totaled (for each endpoint and time) and averaged. The animals was terminated after the last skin evaluation.

The material was considered to be corrosive if it caused destruction (ulceration or necrosis) or irreversible alteration of tissue.

Test substance : The test material was Hallcomid M-8-10. This material contains 0-5% N,N-dimethyl hexaneacidamide, 50-65% N,N- dimethyl octaneacidamide, 37-50% N,N- dimethyl decaneacidamide, and 0-2% N,N- dimethyl dodecaneacidamide. The exact analytical composition was notspecified. [This specification was not listed in the study. It was derived from data G. Wentworth of the C. P. Hall Company supplied and from specs listed in studies that were conducted around 1990].

Reliability : (2) valid with restrictions.
The animals were not allowed to recover for a long enough period to determine if there was irreversible alteration of the skin (one of the criteria for assigning a designation of corrosive).

(19)

01.11.2002

Species : rabbit
Concentration : undiluted
Exposure : occulsive
Exposure time : 4 hours
Number of animals : 1
PDII : 7.0
Result : corrosive
EC classification : corrosive (causes burns)
Method : other
Year : 1990
GLP : yes
Test substance : other TS
Remark : Due to the effects exhibited in the animal, the study was terminated without testing in additional animals (the standard protocol recommended using 6).

Result : The total average 1) erythema and eschar and 2) edema scores at all time points were 3.00 (moderate to severe erythema) and 4.00 (severe edema raised more than 1 mm which extended beyond the area of exposure). The primary irritation index (PII) was 7.0. Changes noted in the skin after 1-24 hours after exposure included blanching, light and dark brown coloration on the site and coriaceousness. These symptoms (with the exception of blanching) also were noted at 48 and 72 hours. Necrosis and slight fissuring also were noted at 72 hours.

Test condition : Due to the suspected irritation potential, the material was tested in a single, young adult male New Zealand white rabbit (weight was not stated). The rabbit was acclimated for at least one day before use. The hair on the application site (dorsal surface) was clipped one day prior to dosing. Test material (0.5 ml, undiluted) was applied to the site under a 1" x 1" gauze square. Each patch was held in place with adhesive tape. The truck of the rabbit was then wrapped with rubber dental dam and secured with staples. An outer layer of gauze was then wrapped around the trunk of the animal and secured with tape. The animal was fitted with an appropriate restrainer to prevent the animal from removing the dressings. All dressings were removed after 4 hours.

The test was scored according to the method of Draize. The 1) erythema and eschar and 2) edema scores were based on a scale of 1-4. The scores at 1/2-1, 24, 48 and 72 hours after removal of the dressings were totaled (for each endpoint and time) and averaged. The animal was terminated after the last skin evaluation. The primary irritation index was calculated by adding the 8 average scores together and dividing them by 4.

Test substance : The test material was Hallcomid M-8-10. This material contains 0-5% N,N-dimethyl hexaneacidamide, 50-65% N,N- dimethyl octaneacidamide, 37-50% N,N- dimethyl decaneacidamide, and 0-2% N,N- dimethyl dodecaneacidamide. The exact analytical composition of the test material was not specified. [This specification was not listed in the study. It was derived from data G. Wentworth of the C. P. Hall Company supplied and from specs listed in studies that were conducted around 1990].

Reliability : (2) valid with restrictions.
Only one animal was tested.

(22)

01.11.2002

5.2.2 EYE IRRITATION-THIS IS NEW

Species : rabbit
Concentration : undiluted
Dose : 0.1 ml
Exposure Time : 24 hour(s)
Comment :
Number of animals : 1
Result : highly irritating
EC classification : irritating
Method : other
Year : 1990
GLP : yes
Test substance : as prescribed by 1.1 - 1.4

Remark : Due to the effects exhibited in the single animal, the study was terminated without testing in additional animals. The author remarked that "although this eye irritation test was not allowed to progress to a point where formal classification could be applied, the eye irritation that resulted from exposure to the test material strongly suggests classification in Toxicity Category I (corrosive or corneal involvement or irritation persisting for more than 21 days)."

The methods section and the raw data sheet stated that the eye was rinsed after 24 hours and the summary/conclusions section stated that the material was applied without rinsing.

Result : The test material produced corneal opacity, iritis and conjunctival irritation persisting for the duration of the test (4 days). Corneal opacity scores ranged from 1 (at 1 and 24 hours) to 3 (at Day 4). A corneal opacity score of 3 was consistent with the finding of opalescent areas, no details or iris visible, and size of pupil barely discernable. The scores for the area of corneal opacity ranged from 1 (at 1 hr) to 4 (at 48 hours). The scores with fluorescein were similar to those without (with the exception of one area score increasing from 2 to 4 with fluorescein). A score of 4 for area of corneal opacity was indicated that 3/4 to to whole area of the cornea was involved. Scores for the iris were 1 (sluggish reaction to light and folds above normal, congestion, swelling and/or circumcorneal injection) at all time points. Vascularization of the iris was present at Day 4. Conjunctival erythema and discharge scores ranged from 1-3 (with higher scores at the end of the study) and 0-3 (with higher scores early on in the study), respectively. Redness and discharge scores of 3 were consistent with beefy red conjuctivae and discharge with moistening of the lids, hairs and considerable area around the eye. All chemosis scores were 4 (swelling with lids about half closed to completely closed). Total irritation scores ranged from 26 (at 1 hr) to 66 (at Day 4). No evidence of corrosion was noted.

Test condition : Due to the suspected irritation potential of the test material, a single young adult male New Zealand White rabbit (weight was not stated) was used. The animal was acclimated to the laboratory for at least one day before

use. Food and water were supplied ad libitum. Results of a fluorescein test taken approximately 24 hours prior to testing showed that the animal did not have any preexisting corneal defects.

The test material (0.1 ml) was applied undiluted to one eye, and the eye was rinsed after 24 hours. The untreated eye served as the control. The treated eye was scored 1, 24, 48, 72 and 96 hours after instillation of test material. Scores were obtained before and after staining with fluorescein. Corneas stained with fluorescein were visualized under ultraviolet illumination.

The A) degree of corneal opacity and B) area of cornea involved were scored on a 0-4 point scale. The total corneal score equaled A x B x 5. The total maximum corneal score was 80. The degree of injury to the iris was scored on a 0-2 point scale, and the product of this score x 5 was the total score for the iris (maximum of 10). The conjunctivae were scored for redness (0-3 point scale), chemosis (0-4 point scale) and discharge (0-3 point scale). The total conjunctival score was the sum of these scores times 2 (total maximum conjunctival score was 20). The maximum total score was the sum of all the total scores for the cornea, iris and conjunctivae (maximum was 110).

Test substance : The test material was Hallcomid M-8-10. This material contains 0-5% N,N-dimethyl hexaneacidamide, 50-65% N,N- dimethyl octaneacidamide, 37-50% N,N- dimethyl decaneacidamide, and 0-2% N,N- dimethyl dodecaneacidamide. The exact analytical composition of the test material was not specified. [This specification was not listed in the study. It was derived from data G. Wentworth of the C. P. Hall Company supplied and from specs listed in studies that were conducted around 1990].

Reliability : (2) valid with restrictions.
Only one animal was used.

30.09.2002 (23)

5.3 SENSITIZATION-THIS IS NEW

Type : other
Species : guinea pig
Concentration : induction 5%
challenge 2.5%
Number of animals : 46
Vehicle : other: 80% ethanol/20% distilled water (induction) and acetone (challenge)
Result : not sensitizing
Classification : not sensitizing
Method : other
Year : 1990
GLP : yes
Test substance : as prescribed by 1.1 - 1.4

Result : Irritation study: In pilot study 1, an erythema score of 1 was noted in one female treated with 5% test material in 80% ethanol/20% distilled water and one female treated with 2.5% test material in 80% ethanol/20% distilled water. All other scores in animals given 5% material or less in 80% ethanol/20% distilled water were +/- (slight, patchy erythema) or 0 (no reaction). Most scores for higher concentrations of test material in 80% ethanol/20 distilled water or undiluted test material (Pilot 2) were 1 (slight but confluent or moderate patchy erythema) or 2 (moderate erythema). All scores of animals given 5% test material or less in acetone (Pilot 3) were +/- or 0. Higher concentrations of test material in acetone produced scores of 1 or 2 in most animals. None of the animals tested had a score of 3 (severe erythema with or without edema). Based on the results of this study, animals were induced with 5% test material in 80% ethanol/20% distilled water.

: Sensitization Study: Following primary challenge with 2.5% test material in acetone, none of the animals received test grades of 1 or higher. Seven and 12 out of twenty test animals and 3/10 and 5/10 controls received scores of 0 at 24 and 48 hours, respectively. The incidences of grade +/- responses at 24 and 48 hours in the test group (13/20 and 8/20, respectively) were similar to those of the naive control group (7/10 and 5/10, respectively). Therefore, a rechallenge was not conducted.

The mean severity scores of test animals at 24 and 48 hours (0.3 and 0.2) were not different from those of naive controls (0.4 and 0.3 at 24 and 48 hours, respectively). Animals gained weight during the study.

Test condition : Young adult male and female Hartley guinea pigs weighing between 374-623 g were used in the study. All animals were quarantined for at least 4 days prior to use. Food and water were supplied ad libitum during the quarantine and test periods. The animals were divided into 3 separate groups as follows: Primary irritation (8/sex), test (10/sex) and naive control (5/sex). The test was conducted according to the method of Buhler (Arch Dermatol 91:171-175, 1965) and Ritz and Buehler (Current Concepts in Cutaneous Toxicity (V.A. Drill and T. Lazar, eds., Academic Press, New York, pp. 25-40).

Primary irritation (pilot) phase: The primary irritation test was performed to determine the proper level of test material to use in the induction and challenge phases. Four separate tests with 2 animals/sex were conducted. In pilot 1, 0.5, 1.0, 2.5 and 5% test material in 80% ethanol/20% distilled water were tested on each animal. In pilot 2, test material was applied to each animal undiluted and at 10, 25 and 50% in 80% ethanol/20% distilled water. For pilot 3, 0.5, 1.0, 2.5 and 5% test material in acetone. For pilot 4, 10, 15, 25 and 50% test material in acetone were tested on each animal. The position of the different concentrations on the back of each animal was varied to adjust for possible site-to-site variation in response. The day prior to exposure, hair was removed from the animal's backs using a small animal clipper. Each concentration of test material was applied (0.3 ml) was placed into a 25 mm Hill Top Chamber. Animals were placed into restrainers and the chambers were applied to the clipped backs as quickly as possible. The chambers were covered with rubber dental dam pulled taut and fastened to the bottom of the restrainers with clips. Restrainers were adjusted to minimize movement of animals during exposure. The dressings and animals were removed from the restrainers 6 hours later. The day after the primary challenge, all animals were depilated for no more than 15 minutes with a commercial depilatory. The depilatory was removed with warm, running water and the skin was dried. The test sites were graded a minimum of 2 hours after depilation.

Induction phase: The concentration selected for induction (5% in 80% ethanol/20% distilled water) caused mild to moderate irritation. The left shoulder of each animal was clipped the day before exposure. The animals were treated with test material applied to chambers as described above under "irritation phase". This procedure was repeated at the same site once a week (from 5-9 days) for the next two weeks for a total of 3 approximately 6-hour exposures. The animals were then untreated for approximately 2 weeks (12-16 days) before the challenge.

Challenge phase: Chambers containing 2.5% test material in acetone were applied to skin sites of induced animals at sites that had not been previously exposed (using the same exposure procedure defined above). Ten naive animals (5/sex) that were never exposed to test material were concurrently treated with 2.5% test material in acetone. All animals were depilated the day after the challenge as described above under "primary irritation phase". The test sites were graded a minimum of 2 hours after depilation, and the following day. For reporting purposes the first and second gradings were designated as the 24 and 48 hour readings.

Test condition : Grades of 1 (slight, but confluent, or moderate patchy edema) were considered to be indicative of sensitization (provided that the naive controls had grades of less than 1). If grades of 1 or greater were noted on the control animals, then reactions of test animals that exceeded the most severe control reaction were presumed to be due to sensitization. If the test animals had similar scores but a higher incidence of +/- (slight, patch erythema) skin reactions, a rechallenge was recommended.

Body weights were measured just prior to the first exposure (with the exception of naive controls that were weighed concurrently with the others at time of challenge. Final body weighs were taken at termination (except for pilot animals, which were not weighed at termination).

Test substance : The test material was Hallcomid M-8-10. This material contains 0-5% N,N-dimethyl hexaneacidamide, 50-65% N,N- dimethyl octaneacidamide, 37-50% N,N- dimethyl decaneacidamide, and 0-2% N,N- dimethyl dodecaneacidamide. The exact analytical composition of the test material was not specified. [This specification was not listed in the study. It was derived from data G. Wentworth of the C. P. Hall Company supplied and from specs listed in studies that were conducted around 1990].

Reliability : (1) valid without restriction

The test conduct and documentation were robust.

04.11.2002 (24)

5.4 REPEATED DOSE TOXICITY

Species : rat
Sex : male/female
Strain : Wistar
Route of admin. : oral feed
Exposure period : 91 days
Frequency of treatment : continuously
Post obs. period : 28 days
Doses : 400, 2000, 10000 ppm (27.4, 136.8, 787.6 mg/kg/day for males and 35.2, 178.5, 894.6 mg/kg/day for females)
Control group : yes, concurrent no treatment
NOAEL : = 2000 ppm
LOAEL : = 10000 ppm
Method : other:OECD 408; EPA Pesticide Assessment Guideline Subdivision F, Series 82-1; EEC Directive 87/302, Part B.
Year : 1992
GLP : yes
Test substance : other TS
Remark : The no effect level set by the histopathologist was 2000 ppm for males and 10000 ppm for females.
Result : Overall: One control male and female and a female treated with 2000 ppm died as a result of blood sampling. No abnormalities were found in these animals at necropsy. All other animals survived to necropsy. There was no effect of treatment on the mortality rate, body surfaces and orifices, general behavior, posture, breathing, excretion, feed or water consumption, opthalmological examination, or gross pathology. The mean amount of test material ingested by the animals in the 400, 2000 and 10000 ppm groups (both main and recovery) was 27.4, 136.8, 787.6 and 726.7 mg/kg/day for males and 35.2, 178.5, 894.6 and 907.7 mg/kg/day for females, respectively. Traumatic changes in the region of the eye and Hardarian gland were seen in some animals as a result of retrobulbar blood sampling. Phagocytic cell foci in the liver were found in 2 controls and 3-5 treated animals (with no relationship to concentration).

10000 ppm: Emaciation was observed in 5/20 males (4/10 at week 11 and 1/10 in weeks 11 and 12). Appearance and general behavior of females was normal. Males in the main group had decreased body weight gain (7-11%) from week 3 on and females in the recovery period had decreased weight gain (6-12%) from weeks 2-13. Weight gains normalized during the recovery period. Mean corpuscular hemoglobin concentration was decreased in males during week 4/5 (326 vs. 332 g/l in control). Erythrocyte count (8.83 vs. 9.30 x 10E12/l in control), hematocrit (0.452 vs. 0.466 l/l in control), and thromboplastin time (31.2 vs. 34.2 sec in control) were decreased in males at week 13. Thromboplastin time also was decreased in females at week 13 (29.9 vs. 31.3 sec in controls). The change in thromoplastin time was attributed to the higher than normal value in controls. Differential blood counts revealed increased monocytes in males (4.8% vs. 2.3% in control), and decreased lymphocytes (87.3% vs. 92.5% in controls) in females at weeks 4/5. At week 13, males had increased lymphocyte count (91.4% vs. 88.1% in control) and decreased segmented cells (7.0% vs. 9.0% in control) and females had increased lymphocytes (91.7% vs. 88.1% in control). Males that recovered had decreased lymphocyte count (88.2% vs. 91.5% in control) and increased segmented cells (9.5% vs. 6.1% in control). None of the hematological changes were attributed to be due to study material since they were slight and not dose-dependent.

At week 4/5, cholesterol concentrations in plasma were increased in both males (2.60 vs. 2.15 mmol/l in control) and females (2.47 vs. 1.82 mmol/l in control). Cholesterol values increased with time, so that at 13 weeks the values were 3.27 mmol/l in males (vs. 2.61 in controls) and 2.93 mmol/l in females (vs. 2.15 mmol/l in controls). Bilirubin was higher than control in males and females at weeks 4/5 (1.0 micromoles/l in males and females vs. 0.8 micromoles/l and 0.7 micromoles/l in male and female controls, respectively) and week 13 in females (1.5 micromoles/l vs. 1.3 micromoles/l in control). Alanine aminotransferase was increased in females at weeks 4/5 (47.4 vs. 36.7 U/ml in control) and aspartate aminotransferase was decreased in males (34.5 vs. 38.4 U/l in control) and females (39.2 vs. 45.4 U/l in control) at 13 weeks. The only change observed in recovery animals was decreased alanine transaminase in males (44.2 vs. 51.1 U/ml in control). Males and females had slightly increased serum sodium at 4/5 weeks (143 and 142 mmol/l, respectively, vs. 141 and 139 mmol/l in controls). Males also had increased serum phosphorus (2.40 vs. 2.13 mmol/l in control) and females had decreased potassium (4.8 vs. 5.2 mmol/l) at 4-5 weeks. At 13 weeks, there was increased serum chloride in males (104 vs. 101 mmol/l in control) and increased serum phosphorus in females (1.40 vs. 1.08 mmol/l in control). Serum chloride also was increased in recovered males (102 vs. 99 mmol/l in controls). Recovered females had decreased serum potassium (4.5 vs. 4.9 mmol/l in controls). Study personnel did not consider any of the changes in clinical chemistry (with the exception of changes in cholesterol) to be due to test material. The only change noted in the urinalysis was increased protein in males at week 12 (0.65 vs. 0.41 in control).

Increased absolute (13%, females only) and relative liver weights (16% for males and 10% for females) were found in main study animals. Relative liver and spleen weights of females that recovered also were increased (by 8.5% and 18%, respectively). Absolute, but not relative brain weight was decreased in main study males (1991 vs. 2103 g in control). Relative, but not absolute brain weight was increased in recovered females (882 vs. 836 mg/100 g bw in control). The changes in brain weights were attributed to lower body weights of treated animals vs. controls.

No pathological changes were found in the liver. Males had an increased incidence of basophilic regenerative tubuli in the renal cortex (9 vs. 3 in control). In recovered males, the incidence and severity of basophilic

regenerative tubuli in previously treated animals (9) was similar to control (7). A small number of protein casts in medullary tubuli were found in 6 main study animals (0 in controls). Two control animals (and no treated animals) in the recovery group had casts. There was no evidence of increased hyalin deposition. There were no other effects on any parameter measured.

2000 ppm: Body weight gain among males was 6-8% lower than controls (from week 3). Females had decreased erythrocyte counts (8.20 vs. 8.46 x 10E12/l in control), hemoglobin (145 vs. 152 g/l in control), hematocrit (0.434 vs. 0.457 l/l in control), and thromboplastin time (29.2 vs. 31.3 sec in control) at week 13. Cholesterol was increased in females at weeks 4/5 (2.09 vs. 1.82 mmol/ liter in control) and 13 (2.56 vs. 2.15 mmol/l in control). Bilirubin was increased in males (1.1 vs. 0.8 micromoles/l in control) and alanine transaminase in females (43.9 vs. 36.7 U/l in control) at week 4-5. Males and females had slightly increased serum sodium at 4/5 weeks (142 in both sexes vs. 141 in male controls and 139 mmol/l in female controls). Since the differences were within a 2s scatter range, study personnel did not consider any of the changes to be indicative of toxicity.

The only changes noted in the urinalysis were increased density (1018 vs. 1011 g/l in control) and increased protein in males at week 12 (0.72 vs. 0.41 g/l in control). The increase in protein was due to a single high value in one animal.

There was no effect of treatment on organ weights or histopathology.

400 ppm: Males exhibited decreased leukocyte concentrations (7.5 vs. 9.4 x 10E9/l in control), and thromboplastin time (31.7 vs. 34.2 sec in control). The change in thromboplastin time was attributed to the higher than normal value in controls. Males exhibited decreased aspartate aminotransferase (31.0 vs. 36.6 U/ml in control) and females had decreased urea concentration (8.56 vs. 10.27 mmol/l in control) and increased bilirubin (0.9 vs. 0.7 micromoles/l in control) at weeks 4-5. Aspartate aminotransferase in males and urea in females also were decreased at 13 weeks (33.0 vs. 38.4 U/l in control and 8.34 vs. 9.32 mmol/l in control, respectively). Study personnel did not consider any of the changes to be indicative of toxicity.

The actual concentrations of test material in diets designed to contain 400, 2000 and 10000 ppm were an average of 401, 1980 and 9770 ppm, respectively. Values for analyses performed after a storage period of 7 days were similar to fresh diets. The standard deviation of results from 3 different sampling areas within diets formulated to deliver 100 and 20000 mg/kg differed by less than 3%. Diets containing nominal concentrations of 100 or 20000 ppm contained 111 and 21200 ppm at time 0 and 112 and 21000 ppm at day 14 (1% deviation from initial value). Therefore, the material was stable in feed over 14 days.

Test condition : Test material was mixed with the feed (Altromin 1321 with 1% peanut oil) using a mixing granulator. Fresh diets were prepared weekly. A purity of 100% test material was assumed when preparing the diets. Feed mixtures containing test material at 400, 2000 and 10000 ppm were analyzed before the study and 3 times within the study period for concentration of the test material. The test material was extracted with ethylacetate in a Soxtec apparatus and the concentration analyzed by gas chromatography with NP detection. Results of a previous study (T 941022) were included to show that the material remained stable and homogeneously distributed in feed at concentrations of 100 and 20000 ppm over a period of 14 days (see next record).

Five to 6 week-old animals (Wistar BOR:WISW (SPF-Cpb) were acclimated for one week before treatment. Healthy animals were randomly

allocated to 6 groups of 10 animals/sex. Four groups were given diet containing 0, 400, 2000 or 10000 ppm test material over a period of 91 days. Two additional groups of 10 animals/sex were given 0 or 10000 ppm test material for 91 days and then control diet for 28 days (recovery animals). Doses were chosen based on results of a 28-day range finding study. Mean body weights (ranges) of males and females at the beginning of treatment were 130 g (116-145 g) and 120 g (103-135 g). Animals were housed individually during the study. Food and water were available ad libitum. Contaminant levels of the food were within accepted limits. Water quality complied with the Drinking Water Ordinance of Dec 5, 1990, Federal Law Gazette No. 66, p. 2612-2629).

Animals were inspected at least twice daily (once on weekends or holidays) for clinical signs or mortality. A detailed examination of the body surfaces, orifices, posture, general behavior, breathing and excretion was performed once weekly. Body weights were measured before treatment commenced, weekly until week 13, and at necropsy on day 91 (main groups). Body weights of recovery animals continued to be recorded weekly during the 28-day post treatment period, and at necropsy on day 120. Weekly feed and water consumption was determined for each rat. From these data the mean daily feed consumption per animal and kg body weight, cumulative feed consumption per animal and kg body weight, mean water consumption per animal and kg body weight and cumulative water consumption per animal and kg body weight were calculated. Cumulative food and water consumption for the main study and recovery period were calculated separately. Opthalmologic examinations were performed on all control and high dose animals in the main study groups before treatment and at necropsy on day 91. The pupil reflexes of both eyes were tested in a darkened room and the frontal regions of the eye examined. The refractive parts of the eye and fundus were examined by indirect opthalmoscopy following dilation with a mydriatic. At necropsy, the animals were also examined under a Zeiss slit lamp.

Blood samples were collected during week 4, 13 (main animals only) and 17 (recovery animals only) from tail veins (for determination of glucose in deprotinized whole blood) and from the retroorbital vein. Hematological parameters examined were differential blood count, erythrocyte morphology and count, blood hemoglobin concentration, hematocrit, leukocyte count, mean corpuscular hemoglobin and hemoglobin concentration, mean corpuscular cell volume, thrombocyte count and thromboplastin time. Plasma was analyzed for alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase, albumin, bilirubin, cholesterol, total protein, urea, creatinine, inorganic phosphate, chloride, calcium, potassium and sodium. All analyses were performed using standardized methods subject to a continuous quality control.

Urine was collected over approximately 16 hour periods (overnight) a few days before taking blood (weeks 4 and 12 for the main groups and week 17 for the recovery groups). While drinking water was available during the collection period, feed was withheld. Urine volume, pH, specific weight (density), sedimentation, and protein, blood glucose, ketone body, bilirubin and urobilinogen were determined using standardized methods subject to a continuous quality control.

Any animals that died during the study were dissected as soon as possible after death and the organs/ tissues were subjected to a detailed gross pathological assessment. Animals in the main study were euthanized on day 91 (males) and 92 (females). Those in the recovery study were euthanized on day 120. The brain, heart, testes, liver, lung, spleen and kidneys were excised and weighed. The adrenals, aorta, bone marrow (femur and sternum), brain, ears, epididymus, esophagus, extraorbital lacrimal glands, eyes, eyelids, femur with knee joint, Hardarian glands,

heart, head, intestine (caecum, colon, duodenum, ileum, jejunum and rectum), kidneys, larynx, liver, lymph nodes (mesenteric and mandibular), lung, mammary gland, muscle (femoral), optic nerve, ovaries, ovarian tubes, pancreas, pituitary, prostate gland, salivary glands, sciatic nerve, seminal vesicles, skin, spine with spinal medulla (cervical, thoracic, lumbar), spleen, sternum, stomach, testes, tooth, tongue, thymus (where present), thyroid with parathyroid, trachea, ureter, urethra, urinary bladder, uterus, vagina and Zymbal gland were fixed. All organs from the control and high dose groups (main animals) and the liver, kidney and gross changes in the low and mid dose groups (main animals) and all recovery animals were examined histologically.

Values for body and organ weights, food and water consumption, hematologies and clinical chemistries were compared using the Mann-Whitney U or Wilcoxon test. Levels of significance were $p < 0.05$ and $p < 0.01$.

Test substance : The test material contained 4.59% N,N-dimethyl-hexaneacidamide, 53.4% N,N-dimethyl-octaneacidamide (CAS No. 1118-92-9), 39.6% N,N-dimethyl-decaneacidamide (CAS No. 14433-76-2) and 0.58% N,N-dimethyl-dodecaneacidamide. The purity was 98.17%.

Conclusion : The increased cholesterol concentrations at the high concentration were regarded by test personnel as being due to impaired hepatic fat metabolism, which was reversible upon cessation of treatment. As there were no histological findings, the increases in liver weight were regarded as a corollary of the impaired fat metabolism of a non-specific adaptation due to higher metabolic demand. The increased incidence of basophilic regenerated tubuli in the renal cortex, with a corresponding increase in protein excretion at the high dose was regarded as a toxicological effect (which was reversible).

Reliability : (1) valid without restriction
The study was performed according to GLP and standard guidelines. There were no deviations that could affect the outcome.

Flag : Critical study for SIDS endpoint

30.09.2002 (31)

Species : rat
Sex : male/female
Strain : Wistar
Route of admin. : oral feed
Exposure period : 28 days
Frequency of treatment : continuously
Post obs. period : none
Doses : 1000, 3000, 10000 ppm (82.9, 250.6, and 965.0 mg/kg for males; 93.7, 293.2 and 1075.7 mg/kg for females)
Control group : yes, concurrent no treatment
NOAEL : = 3000 ppm
LOAEL : = 10000 ppm
Method : other:OECD 407; EEC Directive 84/449, Annex V, Letter B7
Year : 1992
GLP : no
Test substance : other TS
Remark : A dose of 20000 ppm (instead of 10000 ppm) was inadvertently fed to the animals during the first week. In deviation with the guidelines, no differential blood counts, urinalyses or histological examinations were carried out.

Study personnel did not assign NOAEL and LOAEL values, but implied that there were no significant findings at 3000 ppm. However, the summary preparer assigned a NOAEL of 1000 ppm, based on a dose dependent increase in relative liver weight, which was significantly different from control at 3000 and 10000 ppm.

Based on results of this study, doses chosen for a 90-day study were 400, 2000 and 10000 ppm.

Result : Overall: Appearance, general behavior and mortality rate were not affected by treatment with the test material. One animal in the 1000 ppm group died as a result of blood sampling. The necropsy of this animal was normal. No clinical signs of toxicity occurred in treated animals. Feed and water consumption of controls and treated animals were similar. The mean amount of test material ingested by the animals in the 1000, 3000 and 10000 ppm groups was 82.9, 250.6, and 965.0 mg/kg/day for males and 93.7, 293.2 and 1075.7 mg/kg/day for females.

10000 ppm: Body weight gain of female rats treated with 10000 ppm was depressed by 7% during week one, but not at other time points. Reduced body weight gain was observed throughout the study in males. Thromboplastin time was reduced in females treated with 1000 ppm (26.3 vs. 29.1 sec in control), but was within the range of historical controls. Both males and females had increased relative liver (24% and 22%, respectively) and kidney weights (27% and 13%, respectively) and cholesterol concentrations in plasma (2.93 vs. 1.94 mmol/l in control females and 2.71 vs. 2.02 mmol/l in control males). The relative brain weight of males was increased (766 vs. 675 mg in controls). Absolute liver weights increased by 21% in females and absolute lung weight was decreased in males (1219 vs. 1360 mg in controls). Creatinine was decreased in females (39 vs. 47 micromoles/ liter in controls), but was within the range of historical controls. There was no effect of treatment on any other parameter measured.

3000 ppm : The erythrocyte count in males (7.66 vs. 8.03 x 10E12/l in control) and females (7.76 vs. 8.23 x 10E12/l in control) was significantly less than control. The hematocrit in both males (0.448 vs. 0.473 l/l in control) and females (0.436 vs. 0.458 l/l in control) also was significantly less than control. Creatinine was decreased in females (41 vs. 47 micromoles/liter in controls), but was within the range of historical controls. The relative liver weight was increased in males (4258 vs. 3885 mg/100 g bw in control). There was no effect of treatment on any other parameter.

1000 ppm : The erythrocyte count in females (7.76 x 10E12/l) was significantly less than control (8.23 x 10E12/l). Hemoglobin concentration was decreased in females (143 vs. 152 g/l in controls). The hematocrit in females (0.433 l/l) also was significantly less than control (0.458 l/l). There was no effect of treatment on any other parameter.

The actual concentration of test material in diets designed to contain 1000, 3000 and 10000 ppm were an average of 1100, 3330 and 11000 ppm, respectively. Values for analyses performed after a storage period of 7 days were similar to fresh diets. The standard deviation of results from 3 different sampling areas within diets formulated to deliver 100 and 20000 mg/kg differed by less than 3%. These diets were stable over a period of 14 days.

Test condition : The test material was mixed with feed for final concentrations of 100, 3000 and 10000 ppm. A purity of 100% was assumed when weighing. The stability of the material in the feed was assessed by determining the analytical concentration of the test material in feed before the study was started and twice during the study period. The stability (over 14 days) and homogeneity of diets designed to deliver nominal concentrations of 100 and 20000 mg/kg also were tested. The test material was extracted with ethylacetate in a Soxtec apparatus and the concentration analyzed by gas chromatography with NP detection.

Seven to eight week-old SPF-bred Wistar rats were acclimated for four days before treatment. At the beginning of treatment, average weights of

males and females were 152 g (143-166g) and 141 g (129-155 g), respectively. Groups 5 of animals/sex were given feed containing 0, 1000, 3000 or 10000 ppm (approximately 50, 150 and 500 mg/kg) test material continuously for 28 days. The doses were based on results of a previously conducted developmental toxicity study in rats. Tap water was available ad libitum.

Animals were inspected at least twice daily (once on weekends or holidays) for clinical signs or mortality. Body weights were measured before treatment commenced, weekly until study termination, and at termination. Weekly feed and water consumption was determined for each rat. From these data the mean daily feed consumption per animal and kg body weight, cumulative feed consumption per animal and kg body weight, mean water consumption per animal and kg body weight and cumulative water consumption per animal and kg body weight were calculated.

Blood samples were collected during week 4 from tail veins (for determination of glucose in deprotinized whole blood) and from the retroorbital vein at necropsy (for all other parameters). Hematological parameters examined were differential blood count, erythrocyte count, blood hemoglobin concentration, hematocrit, leukocyte count, mean corpuscular hemoglobin and hemoglobin concentration, mean corpuscular cell volume, thrombocyte count and thromboplastin time. Plasma/serum was analyzed for alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase, albumin, bilirubin, cholesterol, total protein, urea, creatinine, inorganic phosphate, chloride, calcium, potassium and sodium.

The animal that died spontaneously was dissected as soon as possible after death and the organs/tissues were subjected to a detailed gross pathological assessment. All animals were euthanized on day 28 and subjected to gross necropsies. The brain, heart, testes, liver, lung, spleen and kidneys were excised and weighed. The adrenals, aorta, bone marrow (femur and sternum), brain, epididymus, extraortbital lacrimal glands, eyes, eyelids, femur with knee joint, Hardarian glands, heart, intestine (caecum, colon, duodenum, ileum, jejunum and rectum), kidneys, larynx, liver, lymph nodes (mesenteric and mandibular), mammary gland, muscle (femoral), optic nerve, ovaries, ovarian tubes, pancreas, pituitary, prostate gland, salivary glands, sciatic nerve, seminal vesicles, skin, spine with spinal medulla (cervical, thoracic, lumbar), spleen, sternum, stomach, ears, testes, tongue, thymus (where present), thyroid with parathyroid, trachea, ureter, urethra, urinary bladder, uterus, vagina and Zymbal gland, plus other organs/tissues with conspicuous changes were fixed and retained (but were not examined).

Values for body and organ weights, food and water consumption, hematologies and clinical chemistries were compared using the Mann-Whitney U or Wilcoxon test. Levels of significance were $p < 0.05$ and $p < 0.01$.

Test substance : The test material contained 4.59% N,N-dimethyl-hexaneacidamide, 53.4% N,N-dimethyl-octaneacidamide (CAS No. 1118-92-9), 39.6% N,N-dimethyl-decaneacidamide (CAS No. 14433-76-2) and 0.58% N,N-dimethyl-dodecaneacidamide. The purity was 98.3%.

Reliability : (2) valid with restrictions
The study was not run according to GLP. Histological examination, urinalyses and differential blood counts were not carried out.

30.09.2002 (32)

Species : dog
Sex : male/female
Strain : Beagle
Route of admin. : gavage

Exposure period	:	6 weeks
Frequency of treatment	:	daily
Post obs. period	:	none
Doses	:	20, 100, 500 mg/kg (1000 mg/kg from week 3)
Control group	:	yes
NOAEL	:	= 100 mg/kg bw
LOAEL	:	= 1000 mg/kg bw
Method	:	other
Year	:	1994
GLP	:	no
Test substance	:	other TS
Remark	:	The study pathologist did not consider the effects on the jejunum or ileum to be related to treatment since similar changes had been observed in control animals of other species. The NOAEL set by the pathologist was 500/1000 mg/kg/day. Study personnel set the NOAEL at 100 mg/kg/day. They did not consider the changes observed at 100 mg/kg/day to be treatment-related. However, the data suggest that there are some treatment related effects at this dose (e.g. increased vomiting, salivation). The study results may have been influenced by the presence of infection.
Result	:	Overall: There was no effect of treatment on reflexes, heart rate, heart and lung sounds, differential blood cell counts, blood pressure, ECG, body weight, opthalmic findings, urinalyses (volume, specific gravity, pH, glucose, blood, protein, bilirubin, urobilinogen, ketone bodies or sediment). The histopathological examination of the trachea of animals in all groups showed an increased number of goblet cells and stratified squamous epithelium. Nearly all animals had inflammatory changes in the renal parenchyma and pelvis, which study personnel thought were due to infection. 500/1000 mg/kg/day: All animals had a defense reaction during treatment. The incidences of vomiting and salivation were 24 and 88 incidences/129 observations, respectively. Two dogs (329 and 300) were temporarily in the lateral or prone position and had disturbed coordination one hour after treatment with 1000 mg/kg/day. Three animals (329, 300, and 328) had a yellowish/ greenish nasal discharge from days 17 to 37. All dogs had reduced food consumption shortly after each treatment. All dogs had reduced food consumption sporadically from days 24 to 43. The leukocyte count in female 300 was elevated at weeks 4 (22.4 x 10E9/l) and 6 (27.4 x 10E9/l) and in female 328 at week 3 (26.3 x 10E9/l), compared to initial values (13.6 and 12.9 10E9/l, respectively). Alanine aminotransferase activity was elevated in one female (300) at week 2 (53.6 vs. 16.9 U/ml at baseline). Lactate dehydrogenase in the same animal was elevated at weeks 5 and 6 (100 and 103 vs. 51 U/ml at baseline, respectively). One male and one female (329 and 328) had distinctly increased N-demethylase in the liver (119.9 and 175.3 vs. an average of 64.7 and 68.75 mU/g in controls, respectively). Animal 328 also had marginally increased cytochrome 450 in the liver (37.1 vs an average of 16.55 nmol/g in control). The relative brain (300), lung (300, 328), kidney (300,329, 328), liver (328, 300, 329) and pancreas (300, 328) weights were outside of the s-scattering range of historical controls in the listed animals. Compared to study controls, the relative weight of the lungs of animal 300, the spleen of rat 329, and the liver of rats 328, 300, and 329 were elevated. Females of the high dose group had surface changes and discolorations of the lungs, correlating histopathologically with severe purulent pneumonia associated with intrabronchial foreign material. Study personnel stated that these effects were due to aspiration from gavage. There was moderate vacuolization of the mucosal epithelium in the jejunum of both sexes.

100 mg/kg/day: One animal died before the end of treatment due to gavage error. All animals had a defense reaction during treatment. Two animals had a nasal discharge without fever on days 19 and 30 (321 and 322). The incidences of vomiting and salivation were 7 and 66 incidences/168 observations, respectively. The leukocyte count of female animal 206 was elevated at week 2 compared to its baseline (21.1 vs. 17.0 x 10E9/l). Two female animals (206, 322) had increased creatine kinase at week 6 relative to baseline (179 and 399 vs. 49 and 42 U/ml, respectively). The LDH of female 322 also was elevated at week 6 (105 vs. 40 U/l at baseline). The relative kidney (206, 322), liver (322, 206, 321) and pancreas (321, 206) weights were outside of the s-scattering range of historical controls in the listed animals. Compared to study controls, the relative weight of the liver of rat 322 was increased. There was moderate vacuolization of the mucosal epithelium in the jejunum of one male and ileum of one female.

20 mg/kg/day: Two animals had a nasal discharge without fever. The incidences of vomiting and salivation were 2 and 1 incidences/168 observations, respectively. One animal (322) had marginally elevated lactate dehydrogenase at week 6 and another (321) had marginally increased N-demethylase. The relative brain (330), kidney (327, 331, 316), lung (327, 330), liver (330, 316, 327) and pancreas (316, 327) weights were outside of the s-scattering range of historical controls in the listed animals.

control: None of the animals vomited or salivated after treatment. The leukocyte count of one animal (237) was elevated at week 2 (18.9 vs. 12.0 x 10E9/l). The relative brain (237), lung (237, 317) and liver weights (320) were outside of the s-scattering range of historical controls in the listed animals.

The concentrations of test material in the 4 mg/ml, 20 mg/ml and 200 mg/ml gavage preparations before and after treatment were 96.4-104% of target. Homogeneity analyses of the 4 mg/ml and 200 mg/ml gavage preparations from the upper, middle and lower segments of the preparation were 94.9 to 104% of target immediately and 8 days after the preparations were made.

Test condition : Twenty male and female thoroughbred beagles were quarantined for a period of approximately 3 weeks before transfer to the treatment facility. The animals underwent parasitological testing twice for helminth larvae and once for helminth eggs (flotation and sedimentation methods), and bacterial testing for Salmonella. Coccidien oocytes were detected in four samples analyzed using the flotation method. Other analyses were negative. After acclimation for days, 8 healthy animals/sex were chosen for use in the study. They were randomly allocated to groups of 2 animals/sex after being weighed. The dogs were 20-29 weeks of age and 6.8 -11.3 kg at the time of randomization. All study dogs were individually housed in a force-ventilated room kept at 20.0 -23.0 degrees C. The day/night cycle was 12 hr day, 12 hr night). All animals were allowed to exercise daily (separated by sex) for approximately 30 minutes. The cages and stall were cleaned during this period.

The test material was dissolved in 0.5% Tylose once weekly with a magnetic mixing apparatus. Analyses performed before the beginning of the study demonstrated that the test material was stable for a minimum of 8 days and that it was homogeneously distributed in the emulsion. The amount of material in the emulsion was analytically monitored throughout the study.

Test material was given daily by gavage for 6 weeks (43 total days) to 2 animals per sex at 20, 100 or 500 mg/kg. The dose for the high dose animals was increased at week 3 to 1000 mg/kg/day because there were

no signs of toxicity at 500 mg/kg/day. A control group received 0 mg/kg/day test material. Whether or not these dogs were gavaged with the vehicle was not stated. All dogs were given a 350 g/day ration of quality monitored standard diet one hour after treatment during weeks 1-6. The nutritive composition and contaminant content were routinely spot-checked and found to be within acceptable limits. Tap water (drinking water as defined in the German Drinking Water Statue of May 22, 1986) was available free choice. The quality of the water was not expected to have an effect on the study.

The appearance and behavior of the dogs was monitored during feeding and the exercise period. The amount of drinking water in the water bowls also was recorded at these times. Individual feed intake was determined daily. Body weight was determined weekly (generally at intervals of 7 days). Each animal's reflexes (pupillary, corneal, patellar, extensor, postural and flexor) was carried out 2 weeks before the beginning of treatment and in treatment weeks 4 and 6. Body temperatures, electrocardiograms (ECG), blood pressure (at the femoral artery of supine animals) and condition of the eyes (with a Zeiss ophthalmoscope) also were determined at these times. The eyeground of all animals was also photographed at these times (with the exception of week 4). Heart rates were determined in the context of blood pressure measurements. Pulse rate, as well as systolic, diastolic and mean arterial pressures were calculated from at least 5 recorded blood pressure profiles.

Blood was collected from the jugular vein 2 weeks before the beginning of the study and in weeks 2, 4, and 6 for standard hematology and clinical chemistry analyses. Blood for hematologies or other analyses was collected in EDTA- or heparin-coated tubes, respectively. Glucose was measured in deprotinized whole blood and electrolytes were measured in serum. All other parameters were measured for serum. Urine was collected for standard urinalyses (time of collection was not stated).

All animals were euthanized a day after the last treatment and necropsied. The brain, heart, liver, lungs, spleen, adrenals, kidneys, pancreas, thyroid, parathyroid glands, pituitary, testes, prostate gland and ovaries were weighed. The adrenal glands, aorta, brain (cerebrum, cerebellum, pons/medulla, bone marrow, epididymides, esophagus, eyes, femur, gallbladder, heart, intestine (duodenum, jejunum, ileum, cecum, colon, rectum), kidneys, liver, lungs, lymph nodes (mandibular and mesenteric), mandibular gland, optic nerves, ovaries (with oviducts), pancreas, parotid, pituitary gland, prostate, sciatic nerve, skeletal muscle (thigh), skin (mammary region), spinal cord (cervical, thoracal, lumbar), spleen, sternum, stomach, testes, thymus, thyroid (with parathyroids), tonsils, tongue, trachea, urinary bladder, uterus, vagina and all organs with macroscopic findings were fixed, stained and examined histologically. Osseous tissues were first decalcified by EDTA. Bone marrow smears were prepared. Activities of lactate dehydrogenase, N-demethylase, o-demethylase and triglycerides in liver also were analyzed.

Statistical analyses could not be performed due to the small number of animals/group. Analyses were descriptive in nature.

Test substance : The test material is described as Hallcomid M-8-10, which contained 4.81% N,N-diemthylcaproamide, 54.30% N, N-dimethylcaprylamide (CAS No. 1118-92-9), 38.70% N,N-dimethylcapramide (CAS No. 14433-76-2) and 0.54% N, N-dimethylauramide. The purity was 100%.

Reliability : (2) valid with restrictions
The number of animals used for the study was too small for the data to be analyzed statistically.

30.09.2002 (30)

Species	:	rat
Sex	:	male/female
Strain	:	Wistar
Route of admin.	:	inhalation
Exposure period	:	5 consecutive days
Frequency of treatment	:	6 hours/day
Post obs. period	:	none
Doses	:	24.6, 111.2, 521.2 mg/m3
Control group	:	yes, concurrent vehicle
NOAEL	:	= 111.2 mg/m³
LOAEL	:	= 521.2 mg/m³
Method	:	other:OECD 403, 412; EEC Directive 84/449; FIFRA Guideline 81-3 and 82-4
Year	:	1991
GLP	:	yes
Test substance	:	other TS
Remark	:	Study personnel did not consider the findings observed at 24.6 and 111.2 mg/m3 to be due to the test material. Therefore, the summary preparer assigned a no observable effect level of 111.2 mg/m3.
Result	:	Concentrations of material in the chambers were stable throughout the study. At target concentrations of 100, 500, and 2500 mg/m3, average analytical concentrations in the breathing zone were 24.6, 111.2, and 521.2 mg/m3, respectively. The average MMAD (and GSD) of the aerosols at each concentration was approximately 1.4 (1.5) microns. Ninety seven percent of the particle mass was respirable (< 3 microns). Data were based on actual concentrations (rather than target) due to the large difference in the two values. Overall: None of the animals died. Animals exposed to 24.6 and 111.2 mg/m3 exhibited no clinical signs or significant changes in body weight. There was no effect of treatment on any reflex test. The temperatures in the chambers ranged from 24 to 26 degrees C. The relative humidity was 18-30%. The relative humidity was occasionally slightly lower than that required by the guideline. This deviation had no apparent influence on the study. 521 mg/m3: Most animals exposed to 521.2 mg/m3 exhibited labored breathing and reduced motility from days 2 to 7 of the test. Approximately half exhibited wheezing and serous nasal discharge from days 2-7. Redness of the rhinarium and bradypnea were noticed in a few animals from days 2-8. The breathing-related signs increased in severity over the treatment period. Weights of males and females were lower than initial values at days 4 and 7. Rectal temperatures of males were slightly lower than control on the first day of the test (35.3 vs. 37.8 degrees C, respectively). Those of females were lower than control on the first day of the test (33.8 vs. 37.2 degrees C, respectively) and on day 7 (38.0 vs. 38.8 degrees C, respectively). Increases in leukocyte counts (6.0 vs. 2.5 x 10E9/l) and mean corpuscular hemoglobin concentration (315 vs. 304 g/l) were observed in females at day 7, but not at day 22. Females had elevated aspartate (57.0 vs. 47.6 U/l in control, not significant) and alanine transaminase activities (53.5 vs. 35.9 U/l in control, significant) at 7 days. Males euthanized on day 7 had increased relative brain weights (817 vs. 668 mg/100 g bw in control). Females had marginally increased absolute liver weights at 7 days (6630 vs. 5727 mg in control, not significant). Females (but not males) had an increased incidence of goblet cell hyperplasia in the nasal and paranasal cavities at days 7 (5/5) and 22 (4/5) compared to control (0/5 and 1/5, respectively). 111.2 mg/m3: Mean corpuscular volume was decreased (60 vs. 63 fl) in males at day 7 and mean corpuscular hemoglobin concentration was

increased (304 vs. 296 g/l) in males at day 14.

24.6 mg/m3: Increased leukocyte counts (4.9 vs. 2.5 x 10E9/l in control) were observed in females at week 7. A significant increase in hyperemia of the lungs was noted in females at day 7 (4/5 vs. 0/5 in control).

Test condition : Animals: Healthy, young, adult SPF-bred Wistar rats (Bor:WISW SPF-Cpb) were acclimated for at least 1 week before exposure. The rats had a mean weight of 180 to 200 g. The animals received food and tap water ad libitum (except during exposure). The nutritive and contaminant content of the diet were routinely spot-checked. The water was of drinking water quality and contaminant levels were within prescribed limits.

Generation of aerosol/Exposure conditions: The aerosol was generated with a nozzle and conditioned compressed air. The compressed air was produced with two in-parallel Boge compressors. The air was automatically conditioned by an in-line VIA compressed air dryer that removed water, dust and oil. The compressors operated at a pressure of 600 to 700 kPa. The operating pressure for each compressor was set using reduction valves. The test atmosphere was generated by nebulizing the test material (1%, 5% and 25%) in a polyethylene glycol 400-ethanol vehicle (1:1), which enhanced the formation of smaller particles. At all concentrations, solutions were passed to the nozzle by means of a continuous infusion pump with a 50-ml ground glass syringe. The aerosol was sprayed under dynamic conditions into a cylindrical inhalation chamber with a baffle, which increased the efficiency of aerosol formation and removed larger particles. The aerosol generation conditions ensured approximately 45 air exchanges per hour. A steady state concentration was reached within approximately 4 minutes of operation. The nominal concentrations were calculated from the quotient of the test article (mg) nebulized into the baffle and the total air in the inhalation chamber (5.4 m3). The analytical concentration of material in the test atmosphere in the breathing zone of the rats was determined by gas chromatography. Where technically feasible, samples were taken from the inhalation chamber just after equilibration, at the mid-point, and towards the end of the study. The total air volume per analysis was 150-70 liters for the 100 mg/m3 group, 20 liters for the 500 mg/m3 group and 10 liters for the 2500 mg/m3 group (sampling rate 1 liter/min). Samples for particle distribution analyses also were taken from the immediate breathing zone of the rats. Particle analyses were performed with an aerodynamic particle sizer with a laser velocimeter. The NMAD (number median aerodynamic diameter) and GSD (geometric standard deviation) were determined from the probit-transformed particle-related cumulative frequency distribution and the logarithmized effective cutoff diameters of the individual measurement capillaries of the laser velocimeter using linear regression. The MMAD (mass median aerodynamic diameter) was calculated from the NMAD according to the following equation: ln (MMAD) = ln(NMAD x density) + 3(ln(GSD))squared. The GSD was calculated from the regression curve (percentile 84/percentile 50). The apertures of the sampling apparatus complied with those required for representative sampling of the test atmosphere.

Ten animals/sex/concentration (100, 500, and 2500 mg/m3) were exposed head/nose-only to the aerosol for 4 hours in plexiglass exposure tubes. The PVC inhalation chamber had a diameter of 30 cm, height of 28 cm, and volume of approximately 20 liters. During testing, the ratio of inlet to outlet air was selected so that approximately 70% of the dynamic inlet air was extracted by a filter (cylinder containing cotton wool). An air flow in the direction of the rats was set up within the exposure system. During exposure the air flows were continuously monitored with a rotameter and adjusted when necessary. The inhalation chambers were operated in fume hoods. The outlet air was purified with a cotton wool filter. Chamber temperature and humidity were recorded over 10 minute intervals.

Body weights of the rats were taken before exposure, on Days 4, 7, and 14 and 22 (14 days after the last treatment). Appearance and behavior were monitored several times on the day of exposure and then twice daily for the remainder of the study (including weekends). The animals in the tubes were examined closely if obvious signs occurred. Parameters examined after exposure were gross appearance of the mucous membranes of the eyes and respiratory tract, general state of muzzle skin and pinna, state of fur and grooming activity, respiration, cardiovascular activity (where possible), somato-motor system and behavior pattern, central nervous and autonomic signs, visual placing response and grip strength, tone of abdominal muscles, pupil, cornea, righting, startle and pinna reflexes, and tail-pinch response. Rectal temperature of 5 rats/group/sex was measured on the first day of treatment (Day 0) and on Days 4 and 7. Half of the animals were euthanized on Day 7 (three days after the last exposure) and the other half on Day 22 and subjected to a gross necropsy. The brain, heart, liver, lungs and kidneys were weighed. The eyes, heart, head (nasopharynx, oropharynx, nasal and paranasal cavities), larynx, liver, lung (with main bronchi), lymph nodes (mediastinal and lung-associated), kidneys, and trachea were fixed, sectioned and examined histologically.

General clinical chemical tests were performed at each necropsy. Blood sampling was performed by heart puncture after rats had been anaesthetized. Blood was analyzed for hematocrit, hemoglobin, leukocytes, erythrocytes, mean corpuscular volume, mean erythrocyte hemoglobin concentration and content, thrombocyte count, and thromboplastin formation time. Serum was analyzed for aspartate aminotransferase, alanine aminotransferase, and glutamate and lactate dehydrogenase activities.

Necropsy findings were evaluated using Fisher's Pairwise Test with a preceding RxC chi square test. Organ weight and rectal temperature data were analyzed using one-way analysis of variance (ANOVA). Body weight and body weight gain data were analyzed with the Mann and Whitney Rank U test and ANOVA, respectively. Clinical chemistry and hematological data were analyzed using the Rank U test. Means of data analyzed by ANOVA were compared using Games and Howell's modification of the Tukey-Kramer Significance Test. The criterion for significance was $p < 0.05$ for data analyzed by ANOVA and $p < 0.05$ or 0.01 for data analyzed with the U test.

Test substance : The test material contained 3.7% N, N-dimethyl hexane acid amide, 54.1% N, N-dimethyl octane acid amide (CAS No. 1118-92-9), 38.5% N, N-dimethyl decane acid amide (CAS No. 14433-76-2) and 1.3% N, N-dimethyl dodecane acid amide.

Reliability : (2) valid with restrictions
The duration of the test is too short to adequately determine the NOAEL for repeated dose inhalation exposure.

30.09.2002 (28)

5.5 GENETIC TOXICITY 'IN VITRO'

Type : Ames test
System of testing : S. typhimurium strains TA98, TA100, TA1535 and TA1537
Concentration : up to 5000 micrograms/plate
Cytotoxic conc. : 200 micrograms/plate (strains TA1535 and 1537), 400 micrograms/plate (strain TA98), 800 micrograms/plate (strain TA100)
Metabolic activation : with and without
Result : negative
Method : other:OECD471;EEC 84/449;USEPA PB 84-233295
Year : 1999

GLP : yes
Test substance : other TS
Remark : Strain 1538 was not included because others had shown that it overlapped considerably with TA98. It was mentioned that testing in 1538 would be performed if results from strain TA98 were questionable.
Result : The test material did not cause a dose-related and at least a 2-fold increase in the number of mutants in any of the strains (with or without S-9). In the first test, the average number of mutants in control TA535, TA100, TA1537 and TA98 cultures without S-9 were 11, 57, 6 and 22, respectively. In the presence of test material (8-1000 micrograms/plate) without S-9, the number of mutant colonies for each of these strains (respectively) ranged from 4-9, 14-50, 1-8 and 6-28. With S-9, the average number of mutants in control TA535, TA100, TA1537 and TA98 cultures were 24, 80, 11 and 36, respectively. With 30% S-9 and test material (8-1000 micrograms/plate), the number of mutant colonies for each of these strains (respectively) ranged from 16-21, 49-81, 8-14 and 34-42.

In test 2, bacteriotoxicity was observed in strains TA1535 and TA1537 at 200 micrograms/plate, strain TA98 at 400 micrograms/plate, and 800 micrograms/plate in strain TA100. In the second test, the average number of mutants in control TA535, TA100, TA1537 and TA98 cultures were 17, 81, 10 and 23, respectively. In the presence of test material (25-800 micrograms/plate) without S-9, the number of mutant colonies for each of these strains (respectively) ranged from 2-16, 48-94, 5-13 and 3-26. With 4% S-9, the average number of mutants in control TA535, TA100, TA1537 and TA98 cultures were 12, 83, 13 and 47, respectively. With 4% S-9 and test material (25-800 micrograms/plate), the number of mutant colonies for each of these strains (respectively) ranged from 5-13, 55-98, 8-16 and 14-44. With 10% S-9, the average number of mutants in control TA535, TA100, TA1537 and TA98 cultures were 13, 101, 12 and 32, respectively. With 10% S-9 and test material (25-800 micrograms/plate), the number of mutant colonies for each of these strains (respectively) ranged from 6-14, 63-100, 6-14 and 7-35.

The positive controls induced at least a 3.9-fold increase in the number of mutants in the absence or presence of S-9. All criteria for validity were met.
Test condition : S. typhimurium strains TA98, TA100, TA1535 and TA1537 were tested for crystal-violet and UV sensitivity. Cultures that did not produce satisfactory results were not used. A special test for ampicillin resistance was not necessary since strains TA100 and TA98 were incubated on ampicillin-containing nutrient agar and formed individual colonies. In each test, histidine dependence of the cultures was automatically checked by the accompanying negative controls.

S9 mix was prepared from the livers of at least 6 adult, male Sprague Dawley rats (200-300 g). The animals received a single ip injection of Aroclor 1254 in corn oil (500 mg/kg) 5 days prior to liver removal. The liver was homogenized and centrifuged at 9000 g (4 degrees C) for 10 minutes. The supernatant (S-9 fraction) was stored at -80 degrees C. Protein content was 25.9 mg/ml. Cofactor mix containing 162.6 mg $MgCl_2$ x 6 H_2O, 246.0 mg KCl, 179.1 mg glucose-6-phosphate (disodium salt), 315.0 mg NADP (disodium salt), and 100 mM phosphate buffer (total volume of 70 ml) was prepared right before use. The S-9 mix contained 4, 10 or 30% S-9, 70% cofactor solution, and 26, 30 or 0% 0.15 M KCl (depending on the percentage of S-9 used). Prior to use, each batch of S-9 mix was checked for metabolizing capacity using reference mutagens. Appropriate activity was demonstrated. At the beginning of each experiment, 4 aliquots of the S9 mix were plated (0.5 ml/plate) to assess sterility. No contamination was found.

In the first test, 0.1 ml of test material (8, 40, 200, 1000 or 5000 micrograms/plate), negative control (ethanol), or positive control (or DMSO

solvent), 0.1 ml of bacteria, 0.5 ml of 30% S-9 mix (for the test with activation) or buffer (for the test without activation), and 2.0 ml soft agar were mixed in a test tube and incubated for 30 sec (45 degrees C). The positive controls for tests without S-9 were sodium azide (10 micrograms/plate) for strain TA1535, nitrofurantoin (0.2 micrograms/plate) for strain TA100, and 4-nitro-1,2-phenylene diamine (4-NPDA) for strains TA1537 (10 micrograms/plate) and TA98 (0.5 micrograms/plate). The positive control for all strains incubated with S-9 was 2-aminoanthracene (3 micrograms/plate). The mixture was plated onto solid agar and incubated for 48 hours (37 degrees C). Four plates were prepared per test tube. Resulting colonies were counted using an automatic colony counter.

Titers of bacterial suspensions (diluted 1:1,000,000) were determined under the same conditions as mutations, except that the histidine concentration in the soft-agar was increased five-fold to permit complete growth of bacteria.

Since the results of the first test indicated that concentrations of 1000 and 5000 micrograms/ml were toxic to all strains (based on a marked reduction in the mutant count and/or cell titer), tests were repeated using 0, 25, 50, 100, 200, 400 and 800 micrograms/plate in the presence or absence of 4% or 10% S-9.

A negative test was considered valid if the negative controls were within historical ranges, the positive controls showed significant effects (as defined by the laboratories' experience), and the titers were sufficient. Even if these criteria were not met, an assay was accepted if it showed mutagenic activity of the test material. A reproducible and dose-related increase in the number of mutants in at least one strain was considered to be a positive result. At least a two-fold increase for strains TA1535, TA100 and TA98, and a 3-fold increase for strain TA1537 should occur. Otherwise, the test was considered negative. The data were confirmed by 2 additional experiments.

Test substance : The composition of the test material (Hallcomid M-8-10) was analytically confirmed on two separate occasions approximately six months apart. The test material contained 4.71-4.73% N,N-dimethylhexanoic acid amide, 53.9-54.0% N,N-dimethyloctanoic acid amide (CAS No. 1118-92-9), 38.9-39.0% N,N-dimethyldecanoic acid amide (CAS No. 14433-76-2), and 0.55% N,N-dimethyldodecanoic acid amide.

Reliability : (1) valid without restriction
The study was performed according to GLP and standard guidelines. There were no deviations that could affect the outcome.

Flag : Critical study for SIDS endpoint

30.09.2002 (20)

Type : HGPRT assay
System of testing : V79 Chinese hamster lung cells
Concentration : 25, 50, 100, 125, 150, 200 and 250 micrograms/ml
Cytotoxic conc. : 200 micrograms/ml (without S-9), 250 micrograms/ml (with S-9)
Metabolic activation : with and without
Result : negative
Method : other:OECD 476;EEC Directive 87/302;USEPA PB 84-233295
Year : 1994
GLP : yes
Test substance : other TS
Remark : Although the authors mentioned the result at 100 micrograms/ml in test 2 without S-9 was greater than control, they did not mention the results at 50 micrograms/ml or 150 micrograms/ml in test 2 without S-9 or at 200 micrograms/ml with S-9 as being greater than control. However, these concentrations induced at least a 2-fold increase in the number of mutants with respect to controls. Since none of these increases were reproducible, the summary writer concluded that they were not relevant.

Result : Concentrations of 200 and 250 micrograms/ml were toxic to all cells in both experiments without S-9. In the presence of S-9, 250 micrograms/ml was toxic in test 1, and neither concentration was toxic in test 2.

No biologically significant increase of the mutant frequency was observed in the two assays (in the absence or presence of S-9). In the tests without S-9, the mutant frequencies of controls ranged from 2.2 to 4.9 x 10E-6 (test 1) and 0.6 to 3.0 x 10E-6 (test 2), and the frequencies of treated cells ranged from 0.0 to 6.2 x 10E-6 (test 1) and 0.0 to 9.4 x 10E-6 (test 2). In test 2 without S-9, three concentrations caused greater than 2-fold increases in mutants in one test (6.2 x 10E-6 at 50 micrograms/ml, 9.4 x 10E-6 at 100 micrograms/ml and 7.6 x 10E-6 at 150 micrograms/ml). The result at 100 micrograms/ml was not considered by study personnel to be relevant because it was not duplicated in the parallel cultures or in the first test. In the tests with S-9, the mutant frequencies of controls ranged from 3.7 to 4.3 x 10E-6 (test 1) and 1.2 to 2.9 x 10E-6 (test 2), and the frequencies of treated cells ranged from 0.0 to 5.1 x 10E-6 (test 1) and 0.0 to 6.6 x 10E-6 (test 2). In test 2 with S-9, one concentration caused greater than 2-fold increase in mutants in one test (6.6 x 10E-6 at 200 micrograms/ml). A joint statistical assessment of the 2 trials showed that there was no statistically significant increase in mutants at any of the tested concentrations.

The test was valid, since absolute cloning efficiencies for the vehicle controls were greater than 50% (varied from 64.3% to 96.3% without activation and from 66.3% to 71.8% with activation), the mutant frequencies of the vehicle control were within historical background ranges, at least 5 plates were scored per parallel experiment, and the positive controls were clearly mutagenic in both experiments (EMS and DMBA induced mutant frequencies of between 552 and 881 x 10E-6 and 47.2 to 125.3 x 10E-6, respectively).

Test condition : To reduce the number of spontaneous mutants, V79 cell cultures were subcloned by plating approximately 1,000 cells per culture vessel every 2 weeks. If necessary, the spontaneous frequency of HGPRT-mutants was additionally reduced by supplementing the culture medium with thymidine (9 micrograms/ml), hypoxanthine (10 micrograms/ml), glycine (22.5 micrograms/ml) and methotrexate (0.3 micrograms/ml). A 6-thioguanine sensitive subclone was used for the assay. Cultures were periodically checked for karyotype stability and mycoplasma contamination.

S-9 from the liver of Aroclor-induced, male Wistar rats was stored at -80 degrees C until use. Total protein was 42.0 mg/ml. S-9 was thawed and tested for contamination and cytotoxicity prior to use. S-9 mix containing 8 mM $MgCl_2$ x 6 H_2O, 33 mM KCl, 5 mM glucose-6-phosphate, 1 mM NADP, and 40% S-9, diluted with sodium phosphate buffer (volume not stated) was prepared on the day of the test and kept on ice until use.

Culture medium contained hypoxanthine-free Eagle's Minimal Essential Medium (MEM) containing L-glutamine (2 mM), MEM-vitamins, $NaHCO_3$, penicillin (50 U/ml), streptomycin (50 micrograms/ml) and heat-inactivated fetal calf serum (10%). During treatment with test material, the concentration of fetal calf serum was reduced to 2%. 6-thioguanine (10 micrograms/ml) was added to the medium for mutant selection. The test material was dissolved in ethanol so that the final concentration of ethanol in the test medium was 1% or less.

Hallcomid M-8-10 was tested for toxicity by plating exponentially growing V79 cells (4 x 10E6/250 ml flask) in culture medium, allowing them to attach (16-24 hours), and exposing them to vehicle or 9 concentrations of test material (ranging from 7.9 to 1000 micrograms/ml in the presence and absence of 5% S-9 mix) for 5 hours in culture medium containing 2% fetal calf serum. Test material concentrations greater than or equal to 1500

micrograms/ml precipitated in the test medium. Cells were then washed with phosphate buffered saline (PBS), trypsinized and replated in culture medium (200 cells per each of 3 Petri dishes). These dishes were incubated for 7 days. Cells were then fixed with 95% methanol, stained with Giemsa, and counted (excluding colonies with < 50 cells). Cytotoxicity was expressed by comparing cells treated with test material to controls. Concentrations used in the test were those that caused a 0-90% reduction in colony forming ability. Concentrations equal to or greater than 250 micrograms/ml were toxic.

The incubation conditions for the HGPRT assay (in the presence or absence of S-9) were similar to those described above for the toxicity test (up to the point of trypsinization). Cells (4 x 10E6/250 ml flask) were incubated with 7.9, 15.7, 31.3, 62.5, 125, 200 and 250 micrograms/ml, negative control (medium), the vehicle control (ethanol), or a positive control [900 micrograms/ml ethylmethanesulfonate (EMS) without S-9 and 20 micrograms/ml dimethylbenzanthracene (DMBA) with S-9] for 5 hours. After trypsinization, cells were replated in culture medium at a density of 1.5 x 10E6 cells/250 ml flask (2 flasks/concentration) and 200 cells/60 mm Petri dish (3 dishes/concentration). The Petri dishes were incubated to allow colony development and determine cytotoxicity (generally for 7 days). The large flasks were incubated to permit growth and expression of mutations. They were subcultured on days 4 and 7. At each subculture, the 2 cultures for each dose level were reseeded at a density of 1.5 x 10E6 cells/250 ml flask (in duplicate). After 6 days, the cultures were reseeded at 3 x 10E5 cells per 100 mm dish (8 dishes per culture) in selection medium. Three dishes (60 mm) were prepared with 200 cells each in culture medium to determine the cloning efficiency for each dose level. After incubation for approximately 7 days, the colonies were fixed, stained with Giemsa and counted. Those with 50 cells or less were excluded. The mutant frequency was calculated by dividing the total number of colonies by the number of cells seeded (corrected for the cloning efficiency). Tests were repeated at least once.

The assay was considered to be valid if the cloning efficiency of the controls was at least 50%, the highest concentration of test material killed at least 70% of the cells, the background mutant frequency was less than 25 x 10E-6 cells (if all other criteria were met and this was not, the assay was not necessarily invalid), the cloning efficiency was at least 10%, a minimum of five dishes per concentration were scored, and the positive control induced an average mutant frequency of at least three times that of the vehicle control. The assay was considered positive if a dose-dependent increase (at least 3 doses) in mutants in the parallel cultures was observed. At least a 2 to 3-fold increase in the number of mutants with respect to control was significant. The positive results also had to be obtained in the repeat test for a material to be considered mutagenic. If a reproducible increase of greater than 2 times control was observed for a single dose near the highest concentration tested, the material also was considered to be mutagenic. An equivocal result was one in which there is no dose-dependency but one or two doses caused a reproducible, significant increase in mutants. An assay was negative if none of the doses tested caused a reproducible, significant increase in mutants. If a positive result occurred, the osmolality of the tested concentrations was determined. The material was only judged to be mutagenic if there was no change in osmolality compared to the vehicle control.

Pooled data from both studies were analyzed using a weighted analysis of variance followed by the Dunnett test. A regression analysis was performed on data from each concentration (omitting the positive and negative controls). The level of significance was $p < 0.05$.

Test substance : The composition of the test material (98.26%, 98.08% and 98.17%) was analytically confirmed on three separate occasions approximately six

months apart. The test material (Hallcomid M-8-10) contained 4.59% N,N-dimethylhexaneacidamide, 53.4% N,N-dimethyloctaneacidamide (CAS No. 1118-92-9), 39.6% N,N-dimethyldecanacidamide (CAS No. 14433-76-2), and 0.58% N,N-dimethyldodecanacidamide.

Reliability : (1) valid without restriction
The study was performed according to GLP and standard guidelines. There were no deviations that could affect the outcome.

30.09.2002 (5)

Type : Chromosomal aberration test
System of testing : Chinese Hamster Ovary Cells
Concentration : 10, 40, 160 micrograms/ml (without S-9) and 7.2, 36 and 180 micrograms/ml (with S9)
Cytotoxic conc. :
Metabolic activation : with and without
Result : negative
Method : other: OECD Guideline 473; EEC Directive 79/831, Annex V; EPA, CFR Title 40, subpart F
Year : 1995
GLP : yes
Test substance : other TS
Remark : The finding of an increased number of aberrants (excluding, but not including gaps) at the 8 hour harvest for cells treated with 180 micrograms/ml in the presence of S9 mix (with respect to the solvent control) was judged by study personnel to be due to the unusually low number of solvent control cells with aberrations (0.5%). Historical values for cells treated with ethanol and S9 mix for 4 hours and harvested at 8 hours ranged from 0.0 to 1.5% of cells (excluding gaps).

Result : The mitotic indices for cells treated with 160 micrograms/ml without S9 mix and 180 micrograms/ml with S9 mix were reduced at 8 hours (43.2% and 66.7 of control, respectively), but not at 24 or 30 hours.

With one exception, no statistically significant increases in the number of aberrations were detected 8, 24 or 30 hours after the 4 hours of treatment with test material in the absence or presence of S9 mix. A statistically significant increase in the number of cells with aberrations (excluding gaps) was noted in cells exposed to 180 micrograms/ml in the presence of S9 at the 8 hour harvest time (3.5% compared to 0.5% for the solvent control). The incidence of cells with aberrations including gaps also was 3.5% at this dose. This was not significantly different from the solvent control incidence of 1.5%.

The positive controls had no effect on mitotic index. The incidences of aberrations in cells treated with the positive controls mitomycin C (without S9 mix) and cyclophosphamide (with S9 mix) and harvested at 24 hours were at 35% and 31% (including gaps) and 23.5% and 33% (excluding gaps), respectively.

Test condition : Cultured Chinese Hamster Ovary (CHO) cells (line WB-1) were grown in Ham's F12 medium containing 5 or 10% fetal calf serum (fcs), 200 mM L-glutamine, and penicillin/streptomycin (5000 IU/ml / 5000 micrograms/ml) at 37 degrees C in a CO2 incubator (air to CO2 ratio of 95:5). They were checked for mycoplasma contamination before use.

S9 was a commercial preparation isolated from the livers of Wistar rats (sex not stated) after treatment with Aroclor 1254. The protein content was 40.0 mg/ml. The S9 was frozen until S-9 mix was prepared on the day of the experiment. S9 mix contained 162.6 mg MgCl2 x 6H2O, 246.0 mg KCl, 152.0 mg glucose-6-phosphate (disodium salt), 78.8 mg NADP (disodium salt), 60.0 ml sodium phosphate buffer and 40.0 ml S-9.

Test material (10, 50, 100, 250, 500, 750 and 1000 micrograms/ml) was tested for cytotoxicity in the absence and presence of S9 mix (1 ml) by

treating the cells (1 x 10E6/20 total ml medium containing 5% fcs/75 cm2 flask) for 4 hours, washing the cells with phosphate buffered saline (37 degrees C), and incubating them in 20 ml of medium containing 10% fcs for an additional 20 hours. The solvent for the pretest was DMSO (in contrast to other studies that used ethanol). Both cell survival and mitotic index were determined. In this test, no cytotoxicity was observed at concentrations < = 100 micrograms/ml and complete toxicity was observed at >= 250 micrograms/ml. Based on this result, a second pretest was performed with 100, 130, 190, 220 and 250 micrograms/ml. The highest dose selected for use in the main study was one that caused a 50% reduction in mitotic index. The mitotic index was determined by counting 100 cells per culture. The number of mitotic and non-mitotic cells were noted. Duplicate cultures were processed and examined.

The mitotic index also was determined within the main study, after metaphases from treated and control cells had been prepared. The number of mitotic cells among 1000 cells/culture was determined. Duplicate cultures were evaluated in the pre-test and the main study. All cells that were not in interphase were defined as mitotic.

Based on the result of the second pre-test, doses selected for use in the main study were 10, 40 and 160 micrograms/ml without S9 mix and 7.6, 38 and 190 micrograms/ml with S9 mix. Due to an incorrect calculation, the doses used in the study with S9 mix were 7.2, 36 and 180 micrograms/ml. The conditions for the tests with and without S9 mix were identical to those described above for the pretests (with the exception that ethanol was the solvent for the test material). Positive controls (2 micrograms/ml mitomycin C without S9 mix and 10 micrograms/ml cyclophosphamide with S9 mix), solvent controls (0.2 ml per culture) and negative controls (no additions) were set up in parallel. Tests also were run (with the solvent control and highest dose of test material only) using an incubation time of 8 or 30 hours. For all tests, duplicate cultures were prepared per treatment.

Two hours before the incubation was terminated, 0.2 ml of colcemid (40 micrograms/ml water) was added to each flask. Two hours later, cells were removed from the flasks by trypsinization, spun in a centrifuge and resuspended in hypotonic solution (0.56% KCl, 37 degrees C). The cells were again spun in a centrifuge and carefully resuspended in cold ethanol/acetic acid fixative (3:1). The cells were incubated at room temperature for 20-30 min, pelleted, washed with fixative, repelleted, and resuspended in fixative. This suspension was dropped onto cooled slides. At least 2 slides were prepared from each flask. The slides were dried for 2 hours, stained with Giemsa, and covered. Alternatively, slides were submerged in methanol before staining with Giemsa. Slides were rinsed with water and then acetone and were kept in xylene. Slides were dried and coded before scoring.

Chromosomes for approximately 200 metaphases per concentration (100 from each of 2 parallel cultures) were examined for structural changes. Only metaphases containing the modal chromosome number (21) were analyzed (unless exchanges were detected). A light microscope at 1000-fold magnification with planachromatic lenses was used for the evaluation. Both chromosomal and chromatidal aberrations were assessed. This distinction was not made for exchanges. The numbers of aberrations of each type, aberrations including and excluding gaps, and exchanges were recorded for the metaphases of individual cultures. Data were analyzed using the Fisher exact test. The level of significance was $p < 0.05$.

A test was considered to be positive if a dose-dependent and statistically significant increase of aberrants was observed that was outside the range of historical solvent controls. A test was negative if there was no evidence of an increase in aberrants at any concentration tested. A test was

considered equivocal if there was a statistically significant increase that was not concentration-dependent (or vice-versa). An increased incidence of gaps without a concomitant increase in another type of aberration was not considered to be indicative of clastogenicity. An assay was acceptable if there was an increase in aberrations in positive controls and if numbers of aberrations in the negative controls were within the historical range.

Test substance : The composition of the test material (Hallcomid M-8-10) was analytically confirmed six months prior to the start of the test and approximately 2 weeks after study termination. The test material contained 4.73% N,N-dimethylcaproamide, 53.9% N,N-dimethylcaprylamide (CAS No. 1118-92-9), 38.9% N,N-dimethylcapramide (CAS No. 14433-76-2), and 0.55% N,N-dimethyllauramide.

Reliability : (1) valid without restriction
The study was performed according to GLP and standard guidelines. There were no deviations that could affect the outcome.

Flag : Critical study for SIDS endpoint

30.09.2002 (17)

Type : Unscheduled DNA synthesis
System of testing : rat primary hepatocytes
Concentration : from 29.8 to 118.6 micrograms/ml
Cytotoxic conc. :
Metabolic activation : without
Result : negative
Method : other:OECD 402;EEC Directive 87/302; USEPA PB 84-233295 October 1983
Year : 1994
GLP : yes
Test substance : other TS
Result : The hepatocytes used in the test had a viability of 74.0% after isolation and 78.4% after attachment. After 18 hours, the average cell viability of control cultures was 72.6% (92.6% of cell viability at the beginning of the treatments). The cells had normal morphological appearance. The highest concentration used in the test (118.6 micrograms/ml) was toxic to 47.9% of cells; therefore, cells treated with this concentration could not be evaluated. Moderate toxicity (approximately 10-20%) was observed for other concentrations. The positive control was toxic to approximately 25% of the cells.

The number of heavily labeled nuclei (representing cells undergoing DNA replication) was in the normal range for hepatocytes. The net grains per nucleus (-1.15 +/- 0.3) and the average number of cells in repair (0) of the vehicle control also were within historical ranges (-1.67 +/- 1.19 for net grains/nucleus and 0.24 +/- 0.42 cells in repair).

Test material did not cause an increase in nuclear labeling or of the percentage of cells in repair at any concentration (with respect to control). The highest number of net grains per nucleus and average percentage of cells in repair was 0.03 +/- 0.40 at 49.4 micrograms/ml and 1.33% at 29.8 micrograms/ml (the lowest concentration tested), respectively. The positive control induced large increases in the number of net nuclear grains (7.79 +/- 1.22) and the percentage of cells in repair (82.67%).

Test condition : Cells used for the study were primary hepatocytes obtained from a single, young, adult male rat. The cells were obtained by perfusing the rat liver in situ with collagenase, followed by purification. Monolayer cultures were established on plastic coverslips and maintained at 37 degrees C in Williams E Medium supplemented with L-glutamine, gentamycin sulfate and heat-inactivated fetal calf serum (10%) under a humidified atmosphere containing approximately 5% CO2. During treatment, the serum concentration of the medium was reduced to 1% and gentamycin was omitted.

Solutions of test material in ethanol were prepared immediately prior to treatment. The final concentration of ethanol in the medium was 1% or less. A cytotoxicity test was performed to determine the dose range for the UDS assay. Test material (at 10 concentrations ranging from 1.78 to 909 micrograms/ml) or vehicle control was applied to the cells (750,000 cells/60 mm Petri dish) in duplicate. After 18-24 hours, cells were tested for viability using trypan blue. The highest dose to be used in the UDS assay was one that resulted in a sufficient number of survivors with intact morphologies.

To determine the cytotoxicity of the test material in the UDS test, the procedure described above was repeated on cells grown on dishes precoated with collagen. Positive and negative controls were tested. Two additional control dishes (no treatment) were seeded to determine cell viability, attachment rate and morphology 2 hours after cultures were established.

For the UDS test, a 25 -mm, round plastic coverslip precoated with collagen was placed into each well of a 6-well culture dish, and 3.75 x 10E5 viable cells were seeded per well. Three wells were established per test concentration (29.8, 39.6, 49.4, 59.5, 79.1, 98.8 and 118.6 micrograms/ml) and negative and positive (0.25 micrograms/ml 2-acetylaminofluorene) controls. All cultures were incubated for 90-150 min at 37 degrees C.

Cultures were washed with phosphate buffered saline (PBS) after the attachment period. Cell number and viability in the two controls was determined. The medium in the remaining wells was replaced with culture medium containing 1% fetal calf serum, test material and 10 microcuries/ml tritiated thymidine (16 curies/mmole). The cultures were then incubated for 18-24 hours. Afterward, the cultures were washed twice with PBS, and 1% sodium citrate was added for 5-10 minutes to swell the nuclei. The cells were then fixed by three changes of a 1:3 acetic acid:absolute ethanol solution for a total fixing time of at least 30 min. Wells were then washed 2-6 times with deionized, distilled water and coverslips were air dried. The coverslips were mounted cell-side-up on microscope slides. They were dipped in a NTB-2 photographic emulsion (either undiluted or diluted 1:1 with distilled water) in the dark and dried in air overnight. The slips were then stored in light-tight boxes containing a drying agent for 4-10 days at -20 degrees C. The photographic emulsion was then developed for 2-4 min at temperatures below 15 degrees C. The slips were rinsed with distilled water, fixed for 5-8 min and air dried. Slips were then stained with hematoxylin and eosin.

Grain counting was done by hand using a microscope (100x objective under oil immersion) interfaced to a TV color screen with a high resolution TV color camera. Each slip was examined by counting 50 cells per slip (moving along the x-axis first, then parallel to the axis, in the opposite direction). Only cells viable at the time of fixation were scored. Isolated nuclei, cells with abnormal morphology, and S-phase cells with dense grains were excluded. UDS was measured by counting nuclear grains and subtracting the average number of grains in 3 cytoplasmic areas of the same size as the corresponding nucleus. The resulting number was the net nuclear grain count (NG) of the cell. The number of cells in repair (nuclei with 5 or more net grains) also was determined.

The means and standard devotions were calculated from the means calculated individually for each of the 3 coverslips per concentration. The response was considered positive if the NG was +2 or more (population average) with 20% or more of the cells responding. A population average of between 0.5 and 2.0 NG was considered a marginal response. A positive dose-response in both the net number of nuclear grains and the percentage of cells in repair was required for a designation of positive if the

NG was less than 2.0. The percentage of cells in repair per dose group was compared to the negative control using a one-sided 2 x 2-chi square test corrected for continuity. The square root of the test statistic was compared to the upper 95% quantile of the normal standard distribution.

For the assay to be acceptable, viability of the hepatocytes and monolayer cell cultures had to be at least 50% and 75% (respectively), viability of control cultures had to be 60% or greater after 16-24 hours, the average number of NG in negative control ranged between -8 to +0.5 (i.e. no more than 10% of the controls should be in repair), the highest dose produced approximately 50% cytotoxicity or resulted in insolubility, and a minimum of 4-5 dose levels were analyzed. Repeat trials were to be conducted to achieve a total of five different concentrations (if necessary). An assay was invalid if the cytoplasmic background counts of controls exceeded 30 grains per nuclear-sized area.

Test substance : The composition of the test material (98.3 and 98.08%) was analytically confirmed on two separate occasions, 10 and 4 months before the study was started. The test material (Hallcomid M-8-10) contained 3.45% N,N-dimethylhexaneacidamide, 53.3% N,N-dimethyloctaneacidamide (CAS No. 1118-92-9), 39.5% N,N-dimethyldecaneacidamide (CAS No. 14433-76-2), and 1.4% N,N-dimethyldodecaneacidamide.

Reliability : (1) valid without restriction
The study was performed according to GLP and standard guidelines. There were no deviations that could affect the outcome.

30.09.2002 (6)

5.6 GENETIC TOXICITY 'IN VIVO'

5.7 CARCINOGENITY

5.8 TOXICITY TO REPRODUCTION

Type	:	other: examination of reproductive organs from 91-day Guideline study
Species	:	rat
Sex	:	male/female
Strain	:	Wistar
Route of admin.	:	oral feed
Exposure period	:	91 days
Frequency of treatment	:	continuously
Premating exposure period		
Male	:	
Female	:	
Duration of test	:	91 days (main study), 120 days (recovery)
Doses	:	400, 2000, 10000 ppm (27.4, 136.8, 787.6 mg/kg/day for males and 35.2, 178.5, 894.6 mg/kg/day for females)
Control group	:	yes, concurrent no treatment
NOAEL Parental	:	= 10000 ppm
Method	:	other:OECD 408; EPA Pesticide Assessment Guideline Subdivision F, Series 82-1; EEC Directive 87/302, Part B.
Year	:	1992
GLP	:	yes
Test substance	:	other TS
Remark	:	The study pathologist did not consider any of the effects noted to be related to administration of test material.
Result	:	Changes other than those observed in reproductive tissues are described

in Section 5.4, record 1. One high dose main study male had tubular dilation of the testes (+2) and round cell infiltration in the epididymides (+1). Sperm granuloma were found in the prostate or epdidymides of two additional high dose main study males (+2) and one control main study animal (+3). One low dose main study male exhibited tubular atrophy (+4), mineralization (+2) and aspermia of the epidiymides (severity was not scored). One high dose male in the recovery group had testicular atrophy (multifocal, unilateral, grade 4).

Females did not exhibit any changes (with the exception of round cell infiltrations and alopecia in the skin around the mammary region of one high dose main study female and round cell infiltrations in the skin around the mammary region of one recovery control female).

Test condition : Test material was mixed with the feed (Altromin 1321 with 1% peanut oil) using a mixing granulator. Fresh diets were prepared weekly. A purity of 100% test material was assumed when preparing the diets. Feed mixtures containing test material at 400, 2000 and 10000 ppm were analyzed before the study and 3 times within the study period for concentration of the test material. The test material was extracted with ethylacetate in a Soxtec apparatus and the concentration analyzed by gas chromatography with NP detection. Results of a previous study (T 941022) were included to show that the material remained stable and homogeneously distributed in feed at concentrations of 100 and 20000 ppm over a period of 14 days.

Five to 6 week-old animals (Wistar BOR:WISW (SPF-Cpb) were acclimated for one week before treatment. Healthy animals were randomly allocated to 6 groups of 10 animals/sex. Four groups were given diet containing 0, 400, 2000 or 10000 ppm test material over a period of 91 days. Two additional groups of 10 animals/sex were given 0 or 10000 ppm test material for 91 days and then control diet for 28 days (recovery animals). Doses were chosen based on results of a 28-day range-finding study. Mean body weights (ranges) of males and females at the beginning of treatment were 130 g (116-145 g) and 120 g (103-135 g). Animals were housed individually during the study. Food and water were available ad libitum. Contaminant levels of the food were within accepted limits. Water quality complied with the Drinking Water Ordinance of Dec 5, 1990, Federal Law Gazette No. 66, p. 2612-2629.

Animals were inspected at least twice daily (once on weekends or holidays) for clinical signs or mortality. A detailed examination of the body surfaces, orifices, posture, general behavior, breathing and excretions was performed once weekly. Body weights were measured before treatment commenced, weekly until week 13, and at necropsy on day 91 (main groups). Body weights of recovery animals continued to be recorded weekly during the 28-day post treatment period, and at necropsy on day 120. Weekly feed and water consumption was determined for each rat. From these data the mean daily feed consumption per animal and kg body weight, cumulative feed consumption per animal and kg body weight, mean water consumption per animal and kg body weight and cumulative water consumption per animal and kg body weight were calculated. Cumulative food and water consumption for the main study and recovery period were calculated separately. Opthalmologic examinations (as described in Section 5.4, record 1) were performed on all control and high dose animals in the main study groups before treatment and at necropsy on day 91.

Blood samples were collected during week 4, 13 (main animals only) and 17 (recovery animals only) from tail veins (for determination of glucose in deprotinized whole blood) and from the retroorbital vein. Urine was collected over approximately 16 hour periods (overnight) a few days before taking blood (weeks 4 and 12 for the main groups and week 17 for the recovery groups). Drinking water was available during the collection period, but feed was withheld. Hematological, urinalysis and clinical chemistry

parameters examined are described in Section 5.4, record 1.

Any animals that died during the study were dissected as soon as possible after death and the organs/ tissues were subjected to a detailed gross pathological assessment. Animals in the main study were euthanized on day 91 (males) and 92 (females). Those in the recovery study were euthanized on day 120. The brain, heart, testes, liver, lung, spleen and kidneys were excised and weighed. Over 40 different organs (Section 5.4, record 1), including the epididymus, mammary gland, ovaries, ovarian tubes, prostate gland, seminal vesicles, testes, uterus, and vagina (in the appropriate sexes) from control and high dose animals (both main study and recovery animals) were fixed and examined histologically. Gross changes in reproductive organs in other animals also were recorded.

Test substance : The test material (Hallcomid M-8-10) contained 4.59% N,N-dimethyl-hexaneacidamide, 53.4% N,N-dimethyl-octaneacidamide (CAS No. 1118-92-9), 39.6% N,N-dimethyl-decaneacidamide (CAS No. 14433-76-2) and 0.58% N,N-dimethyl-dodecaneacidamide. The purity was 98.17%.

Reliability : (2) valid with restrictions
A reliability of 2 was assigned because the study did not assess the effect of test material on reproduction.

30.09.2002 (31)

5.9 DEVELOPMENTAL TOXICITY/TERATOGENICITY

Species : rat
Sex : female
Strain : Wistar
Route of admin. : gavage
Exposure period : Days 6 through 15 of gestation
Frequency of treatment : daily
Duration of test : up to Day 21 of gestation
Doses : 50, 150, 450 mg/kg/day
Control group : yes, concurrent vehicle
NOAEL Maternalt. : = 50 mg/kg bw
NOAEL Teratogen : = 150 mg/kg bw
Method : other: OECD Guideline 414; USEPA Pesticide Assessment Guideline, Subdivision F, Series 83-3, November 1984
Year : 1991
GLP : yes
Test substance : other TS
Remark : Study personnel did not consider the abnormal skeletal findings in fetuses from dams treated with the high dose to be indicative of a specific teratogenic effect of the test article because they are commonly found in Wistar rats and correlated with reduced fetal weight.
Result : Maternal: There were no adverse effects in dams treated with 50 mg/kg/day test material. Reduced food consumption (-6.1%) was noted in rats treated with 150 mg/kg/day. There were no other adverse findings at this dose. Treatment with 450 mg/kg/day was associated with adverse clinical signs (particularly from gestation days 8 to 14) such as ruffled fur, ventral recumbancy, dyspnea, and apathy. Five of the rats treated with this dose were in a comatose state on gestation days 10, 11, and/or 12. Animals treated with 450 mg/kg had reduced food consumption (-24.1 and -18.0% between gestation days 6-11 or 11-16, respectively) during the dosing period. Animals treated with 450 mg/kg/day did not gain weight from days 6 to 9 of gestation. Thereafter, slight reductions in weight gain occurred, so that body weight gains were significantly different from control on gestation days 18 and 19. Body weight gain corrected for uterus weight also was slightly lower in high dose animals than controls (4.9% in treated vs. 7.8% in control). At terminal necropsy, blood was noted in the uterus of

one control animal and 2 animals treated with 150 mg/kg. Abdominal hair loss was found in one high dose animal. None of these changes were attributed to treatment.

Treatment with 50 or 150 mg/kg/day test material had no effect on any reproductive parameter. There was no effect of treatment on the mean number of corpora lutea (ranged from 13.0 to 13.4 in treated vs. 13.6 in control) and implantations (ranged from 11.2 to 12.4 in treated vs. 12.2 in controls), and pre-implantation loss (ranged from 1.1 to 2.5 in treated vs. 2.4 in control). Rats treated with 450 mg/kg/day had increased post-implantation loss (9.4% vs. 5.6% in controls). All resorptions in treated animals were embryonic. All animals littered.

Fetal: The total number of fetuses born from animals treated with 0, 50, 150 or 450 mg/kg/day test material were 287, 287, 260 and 281, respectively. The mean number of live fetuses per dam ranged from 10.4 to 11.5 in treated vs. 11.5 in controls (no significant difference). All fetuses were born alive. Offspring of animals dosed with 0, 50 or 150 mg/kg/day had sex ratios of nearly 50:50. The sex ratio of offspring from high dose animals (55.9 male:44.1 female) was significantly different from control (46.3 male:53.7 female). Study personnel did not consider this to be related to test material. The mean fetal body weight of offspring of high dose animals was reduced by 8.5% with respect to controls. The increased body weight of female fetuses from mid-dose animals (6.7%) was considered to be incidental by study personnel.

The external examination revealed caudal malposition of the right or both hind legs in one fetus from the low-dose group and mid-dose group, respectively. One fetus from each of the mid and high dose groups was denoted as a runt (< 2.5 g). Pelvic dilation of the right kidney was noted in 1/137 fetuses in the vehicle control group and 1/134 fetuses in the high dose group. Study personnel considered these changes to be incidental.

The incidence of fetuses (and litters) with skeletal abnormalities from rats treated with 0, 50, 150 or 450 mg/kg/day were 5/150 (4), 4/150 (4), 3/137 (3) and 12/147 (9). The incidence at the high dose was significantly different from control. The abnormalities were predominantly wavy ribs and dumbbell shaped thoracic vertebral bodies. The incidences of variations that showed significant* differences between control (0 mg/kg) and treated animals (50 mg/kg, 150 mg/kg and 450 mg/kg), respectively were:

Non-ossified Cervical Vertebra 3: 7 (28%), 4 (16%), 10 (40%), 16 (64%)*;
Incompletely ossified Sternebra 1:1 (4%), 0, 0, 8 (32%)*;
Incompletely ossified Sternebra 2: 13 (52%), 9 (36%), 13 (52%), 22 (88%)*;
Incompletely ossified Sternebra 3: 3 (12%),1 (4%), 3 (12%), 8 (32%)*;
Left hindlimb, Non-ossified, Metatarsala 1: 13 (52%), 8 (32%), 10 (40%), 20 (80%)*; and
Right hindlimb, Non-ossified, Metatarsala 1:15 (56%), 8 (32%), 10 (40%), 20 (80%)*

The mean concentrations of test material found in the dosage preparation were 99.4 to 103.8% of nominal. The homogeneity ranged from -4% to 5% of the mean concentration.

Test condition : Female Wistar (Hanlbm:WIST, SPF) rats were acclimated for 11 days before being mated with sexually mature males (1:1). Rats were a minimum of 11 weeks old at pairing, and weighed 179-226 g. The day that spermatozoa were found in the vaginal smear or a vaginal plug was observed was designated day 0 of gestation. Feed and tap water were supplied ad libitum. Mated female rats were randomly assigned to 4 groups of 25 animals each.

Groups of mated rats were given 50, 150 or 450 mg/kg/day test material

homogenized in bi-distilled water containing 0.5% Cremophor (vehicle) once daily from gestation days 6 through 15. The doses were chosen based on results of a range-finding study. Dosing solutions of test material in the vehicle were prepared daily. Samples were taken immediately after preparation and 2 hours later for confirmation of concentration, homogeneity and stability. A standard dose volume of 10 ml/kg body weight was adjusted daily to body weight. Control animals were dosed with bi-distilled water containing 0.5% Cremophor.

Animals were checked twice daily for mortality or signs of toxicity. Food consumption was recorded from days 0-6, 6-11, 11-16 and 16-21 of gestation. Body weights were recorded daily from days 0 to 21 of gestation. Animals were euthanized on day 21 of gestation and the fetuses were removed by Caesarean section. A gross examination of all internal organs, with particular emphasis on the uterus, uterine contents, position of fetuses in the uterus and number of corpora lutea and implantation sites was performed. Pre-implantation and post-implantation loss, embryonic deaths and fetal resorptions were calculated. The uteri (and contents) of all females with live fetuses were weighed at necropsy to obtain corrected body weights. The fetuses were sexed, weighed (individually) and examined for gross external abnormalities. The numbers of live and dead fetuses were recorded. One half of the live fetuses were fixed in a mixture of ethyl alcohol, formol and acetic acid, sectioned and examined for visceral defects. The remaining fetuses were placed in a solution of potassium hydroxide for clearing, stained with alizarin red S and examined for skeletal defects. All fetal tissues were preserved for future analyses (if necessary). Fetuses with abnormalities were photographed.

Body weight, food consumption, reproductive and skeletal data were analyzed with a univariate one-way analysis of variance (ANOVA). Normally distributed data were then analyzed with a Dunnett's t-test to determine if differences occurred between treated animals and controls. The Steel rank test was used to analyze data that did not follow a normal distribution. The Fisher's exact test (2 x 2) was applied if the variables could be dichotimized without loss of information.

Test substance : The test material (Hallcomid M-8-10) was a commercial product containing 3.45% N,N-dimethyl hexanacidamide, 53.31% N,N-dimethyl octanacidamide (CAS No. 1118-92-9), 39.48% N, N-dimethyl decanacidamide (CAS No. 14433-76-2), and 1.43% N,N-dimethyl dodecanacidamide. The stability of the material was guaranteed up to approximately 3 months after completion of the study.

Conclusion : The concentration of test material in the dosage preparation was stable for at least 2 hours. Treatment of dams with 450 mg/kg/day test material during days 6 to 15 of gestation was associated with reduced maternal weight gain and food consumption, increased post-implantation loss, reduced mean fetal body weight and an increase in the incidence of fetuses with common abnormal skeletal findings and retardations in skeletal development. Treatment with 50 or 150 mg/kg was not associated with fetal toxicity.

Reliability : (1) valid without restriction
The study was performed according to GLP and standard guidelines. There were no deviations that could affect the outcome.

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Species : rabbit
Sex : female
Strain : Chinchilla
Route of admin. : gavage
Exposure period : gestation days 6 through 18
Frequency of treatment : daily
Duration of test : to gestation day 28

Doses	:	100, 300, 1000 mg/kg/day
Control group	:	yes, concurrent vehicle
NOAEL Maternalt.	:	= 300 mg/kg bw
NOAEL Teratogen	:	= 1000 mg/kg bw
Method	:	other: OECD Guideline 414; USEPA Pesticide Assessment Guideline, Subdivision F, Series 83-3, November 1984
Year	:	1991
GLP	:	yes
Test substance	:	other TS
Remark	:	A preliminary range-finding study (RCC Project 274994, dated Jan. 28, 1991) conducted similarly to the main study (with the exception that skeletal examinations were not performed) showed reductions of food consumption and body weight gain in rabbits treated with 1000 mg/kg/day and total post-implantation loss in one dam treated with 300 mg/kg/day and another with 1000 mg/kg/day. There was no effect of treatment on fetal sex ratio or body weight. External and visceral examinations of treated animals were similar to controls. Based on these data 100, 300 and 1000 mg/kg/day were chosen for the main study described in this summary.
Result	:	Maternal: Five animals died during the study (3 treated with 100 mg/kg/day, 1 with 300 mg/kg/day and 1 with 1000 mg/kg/day). The cause of death of 2 of the rabbits treated with 100 mg/kg/day was intubation error. The cause of death for the other animals was unknown.

The high dose female that died exhibited slight dyspnea and ventral recumbancy prior to death on day 12 of gestation. Dyspnea also was noted on day 9 of gestation in an additional high dose animal that survived to termination. Study personnel considered these findings to be incidental and not related to the test material. No abnormal clinical signs were noted in controls or animals treated with 100 or 300 mg/kg/day test material.

There were no differences in food consumption or body weights between controls and animals treated with 100 or 300 mg/kg/day test material. Animals treated with 1000 mg/kg ingested less food than controls (-21.1%) during the dosing period and more food during the last few days of the recovery period (+36.4% from days 24-28). High dose animals also had reduced body weight gains between gestation days 6 through 19 (103 g vs. 218 g in controls) and increased weight gain from days 19-28 (198 g vs. 76 g in controls). The body weight gain corrected for uterus weight was similar in all groups.

There was no effect of treatment on the mean number of corpora lutea (ranged from 10.4 to 11.3 in treated vs. 11.2 in control) and implantations (ranged from 10.3 to 10.8 in treated vs. 11 in controls), and pre- (ranged from 0.1 to 0.4 in treated vs. 0.2 in control) and post-implantation (ranged from 0.4 to 0.8 in treated vs. 1.1 in control) losses. Two animals treated with 300 mg/kg had total resorption. Study personnel considered this to be incidental, since none of the females treated with the higher dose had total post-implantation loss.

Pathology of animals that died during the study or survived to termination was considered normal. The authors considered the isolated findings (mainly discolored foci, nodules or crateriform retractions in the mucosa of the fundus, forestomach or stomach) to be incidental because they are common findings in rabbits of the same age and strain.

Fetal: The total number of fetuses (and litters) born from animals treated with 0, 100, 300 or 1000 mg/kg/day test material were 158 (16), 145 (14), 120 (12) and 147 (15), respectively. The mean number of live fetuses per dam ranged from 9.8 to 10.4 in treated vs. 9.9 in controls (no significant difference). All fetuses were born alive. There were no significant differences in mean fetal body weights (on both a litter and individual basis) or sex ratios between treated animals and controls.

At external examination, no abnormal findings were noted in fetuses from animals treated with 100 or 1000 mg/kg/day test material. Two runts (body weight < 19.0g) were found in the control and mid-dose groups, respectively. Visceral examination revealed dilation of the aorta (with an arch of the aorta missing) in one female fetus from the low-dose group. One mid-dose male fetus had hemidiaphragm and female had an oval foramen in the diaphragm. One high dose female fetus had hydronephrosis of both kidneys. The study personnel concluded that these finding were incidental and were not related to administration of test material.

No abnormal findings were detected in the heads or brains of the fetuses. The absolute number (and number of litters effect) of skeletal abnormalities in fetuses from animals treated with 0, 100, 300 or 1000 mg/kg/day were 1(1), 2(2), 3(3) and 1(1), respectively (no significant difference). The findings were similar among groups and included thoracic vertebral bodies and/or arches (hemicentric, missing or fused), sternebrae abnormally ossified and/or fused, rib(s) bifurcated or fused and caudal vertebrae hemicentric or bipartate. Differences in the number of common skeletal variants were noted between treated and control animals. Expressed on a litter basis (vs. control), there was an increased incidence of sternebra 2 in mid-dose animals (33% vs. 0%), and decreased incidence of flying rib in low-dose animals (14% vs. 50%). The individual incidences of skeletal variations that showed significant differences (*greater than and ** less than) between control (0 mg/kg) and treated animals (150 mg/kg, 300 mg/kg and 1000 mg/kg), respectively were:

Incompletely ossified Sternebra 2: 0, 2 (1%), 5 (4%)*, 0
Non-ossifed Sternebra 5: 35 (22%), 17 (12%)**, 14 (12%)**, 14 (10%)**;
Non-ossified Rib 13 (l): 100 (63%), 90 (62%), 60 (50%)**, 82 (56%);
Non-ossified Rib 13 (r): 111 (70%), 89 (61%), 65 (54%)**, 82 (56%)**;
Shortened Rib 13 (r): 12 (8%), 14 (10%), 20 (17%)*, 15 (10%);
Flying Rib 13 (l): 14 (9%), 3 (2%)**, 7 (6%), 3 (2%)
Left forelimb Incompletely ossified
Digit 1, proximal phalanx (l): 26 (16%), 27 (19%), 33 (28%)*, 51 (35%)**;
Digit 2, medial phalanx (l): 99 (63%), 102 (70%), 74 (62%), 114 (78%)*;
Metacarpala 5 (l): 2 (1%), 8 (6%)*, 6 (5%), 12 (8%)*;
Digit 5, proximal phalanx (l): 21 (13%), 41 (28%)*, 17 (14%), 49 (33%)*;
Digit 5, medial phalanx (l): 52 (33%), 41 (28%), 27 (23%)**, 21 (14%)**
Left forelimb Non-ossified
Digit 4 medial phalanx (l): 4 (3%), 7 (5%), 2 (2%), 13 (9%)*;
Digit 4 medial phalanx (l): 105 (66%), 104 (72%), 93 (78%)*, 126 (86%)*
Right forelimb Incompletely ossified
Digit 1, proximal phalanx (r): 24 (15%), 30 (21%), 29 (24%)*, 48 (33%)*;
Digit 2, medial phalanx (r): 97 (61%), 99 (68%), 76 (63%), 106 (72%)*;
Metacarpala 5 (r): 3 (2%), 8 (6%), 7 (6%), 12 (8%)*;
Digit 5, proximal phalanx (r): 26 (16%), 50 (34%)*, 21 (18%), 55 (37%)*;
Digit 5, medial phalanx (r): 58 (37%), 35 (24%)**, 34 (28%), 23 (16%)**
Right forelimb Non-ossified
Metacarpala 1 (r): 18 (11%), 9 (6%), 15 (13%), 8 (5%)**;
Digit 1, proximal phalanx (r): 10 (6%), 11 (8%), 16(13%)*, 16 (11%);
Digit 4, medial phalanx (r): 2 (1%), 6 (4%), 3 (3%), 12 (8%)*;
Digit 5, medial phalanx (r): 100 (63), 110 (76)*, 86 (72%), 124 (84%)*
Left hindlimb Incompletely ossified
Toe 1, medial phalanx (l): 71 (45%), 70 (48%), 49 (41%), 81 (55%)*;
Toe 2, medial phalanx (l) 58 (37%), 51 (35%); 32 (27%)**; 69 (47%)*;
Toe 4, medial phalanx (l): 109 (69%), 92 (63%), 83 (69%), 78 (53%)**
Left hindlimb Non- ossified
Toe 4, medial phalanx (l): 47 (30%), 52 (36%), 37 (31%), 68 (46%)*
Right hindlimb Incompletely ossified
Toe 2, medial phalanx (r): 51 (32%), 47 (32%), 37 (31%), 62 (42%)*;

Toe 4, medial phalanx (r): 111 (70%), 93 (64%), 81 (68%), 80 (54%)**
Right hindlimb Non- ossified
Toe 4, medial phalanx (r): 43 (27%), 50 (34%), 38 (32%), 65 (44%)*
(l) = left, (r) = right

Since there appeared to be no clear cut, dose-dependent differences in the incidences of variants between treated and control animals, study personnel did not consider them to be related to administration of test material.

The mean concentrations of test material found in the dosage preparation were 95.3 to 101.0% of nominal. The homogeneity ranged from -5% to 3% of the mean concentration.

Test condition : Female Chinchilla rabbits (Chbb: CH hybrids, SPF) were acclimated for at least 7 days before being mated with sexually mature males (1:1). Female rabbits were 4-6 months old at pairing, and weighed 2810-4825 g. The day of mating was designated as day 0. Feed and tap water were supplied ad libitum. Mated female rats were randomly assigned to 4 groups of 16 animals each. An additional mated rat was added to the 100 mg/kg/day group to replace one female that died on gestation day 7 due to an intubation error.

Groups of mated rats were given 100, 300 or 1000 mg/kg/day test material homogenized in bi-distilled water containing 0.5% Cremophor (vehicle) once daily from gestation days 6 through 18. The doses were chosen based on results of a range-finding study (see remark). Dosing solutions of test material in the vehicle were prepared daily. Samples were taken immediately after preparation and 2 hours later for confirmation of concentration, homogeneity and stability. A standard dose volume of 4 ml/kg body weight was adjusted daily to body weight. Control animals were dosed with bi-distilled water containing 0.5% Cremophor.

Animals were checked at least twice daily for mortality or signs of toxicity. Food consumption was recorded from days 0-6, 6-11, 11-15, 15-19, 19-24 and 24-28 of gestation. Body weights were recorded daily from days 0 to 28 of gestation. Animals were euthanized on day 28 of gestation and the fetuses were removed by Caesarean section. A gross examination of all internal organs, with particular emphasis on the uterus, uterine contents, position of fetuses in the uterus and number of corpora lutea and implantation sites was performed. Pre-implantation and post-implantation loss, embryonic deaths and fetal resorptions were calculated. If no implantation sites were evident, the uterus was placed in an aqueous solution of ammonium sulfide to accentuate possible hemorrhagic areas of implantation sites. The uteri (and contents) of all females with live fetuses were weighed at necropsy to obtain corrected body weights. The fetuses were sexed, weighed (individually) and examined for gross external abnormalities. The numbers of live and dead fetuses were recorded. Craniums were examined for the degree of ossification, fixed in a solution of tricholoroacetic acid and formaldehyde, serially sectioned, and examined. The trunks were placed in a solution of potassium hydroxide for clearing, stained with alizarin red S and examined for skeletal defects. All fetal tissues were preserved for future analyses (if necessary). Fetuses with abnormalities were photographed.

Body weight, food consumption, reproductive and skeletal data were analyzed with a univariate one-way analysis of variance (ANOVA). Normally distributed data were then analyzed with a Dunnett's t-test to determine if differences occurred between treated animals and controls. The Steel rank test was used to analyze data that did not follow a normal distribution. The Fisher's exact test (2 x 2) was applied if the variables could be dichotimized without loss of information.

Test substance : The test material (Hallcomid M-8-10) was a commercial product containing

3.45% N,N-dimethyl hexanacidamide, 53.31% N,N-dimethyl octanacidamide (CAS No. 1118-92-9), 39.48% N, N-dimethyl decanacidamide (CAS No. 14433-76-2), and 1.43% N,N-dimethyl dodecanacidamide. The stability of the material was guaranteed up to approximately 2 months after completion of the study.

Conclusion : The study personnel concluded that maternal toxicity was noted at 1000 mg/kg/day and that reproductive/fetal toxicity was not found at doses up to and including 1000 mg/kg/day.

Reliability : (1) valid without restriction
The study was performed according to GLP and standard guidelines. There were no deviations that could affect the outcome.

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5.10 OTHER RELEVANT INFORMATION

5.11 EXPERIENCE WITH HUMAN EXPOSURE

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7.1 END POINT SUMMARY

7.2 HAZARD SUMMARY

7.3 RISK ASSESSMENT