NUCRO TECHNICS

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EXPERT STATEMENT:

SURROGATE TOXICOLOGICAL DATA

1-TETRACOSANOL (CASRN: 506-51-4)
AND
1-HEXACOSANOL (CASRN 506-52-5)

Study Sponsor

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GLOBALTOX JOB No.: 1747/1748

PROJECT NO.: 135761

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EXPERT STATEMENT: SURROGATE TOXICOLOGICAL DATA 1-TETRACOSANOL (CASRN: 506-51-4) AND 1-HEXACOSANOL (CASRN 506-52-5)

This review was conducted at Nucro-Technic over the period from April 28, 2004 to May 6, 2004.

NUCRO-TECHNICS

Kresimir Pucaj, D.V.M., M.Sc.
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May 12, 2004
Date

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SUMMARY

This project examined and reviewed 1-Docosanol toxicological data as surrogate data for 1-Tetracosanol and 1-Hexacosanol.

1-Docosanol (surrogate compound), as well as 1-Tetracosanol and 1-Hexacosanol (notifiable compounds), belong to a family of policosanols, aliphatic (non-ring) fatty alcohols. Policosanols are commonly found in the human diet in forms such as bees wax, apples, olive oil, grapes, etc., and are also available as ingredients in several marketed nutritional supplements. Policosanols (including 1-Docosanol, 1-Tetracosanol and 1-Hexacosanol) are found and extracted as nutritional supplements from several natural sources, including sugar cane, bees wax and rice bran wax. Furthermore, aliphatic alcohols when ingested (absorbed) are most likely converted to fatty acids, which are either metabolized in the liver by β-oxidation or incorporated into wax esters, sphingolipids, glycolipids etc., thus making this group of aliphatic alcohols unlikely to be of significant toxicity.

The toxicity of 1-Docosanol is well characterized, and its lack of toxicity is well documented in the scientific literature. 1-Docosanol is non-mutagenic and non-genotoxic in several *in vivo* and *in vitro* assays including: Ames *Salmonella typhimurium* Assay, Chromosome Aberration Assay in Chinese Hamster V79 Cells, Gene Mutation Assay in Chinese Hamster V79 Cells and in The Mouse Micronucleus Test. This compound was not toxic by acute oral ingestion (LD_{50} >10,000 mg/kg) in Sprague Dawley rats. No toxicity of this compound was found in subchronic toxicity studies in CD Rats and Beagle Dogs (1000 mg/kg/day for 26 weeks in rats, and 2000 mg/kg/day for 26 weeks in dogs). Embrionic developmental studies in New Zealand Albino Rabbits dosed at up to 2000 mg/kg revealed no effects related to the treatment. Fertility and reproduction studies in CD Rats (treated up to 1000 mg/kg) revealed no effects of the treatments on the fetuses, or reproductive organs.

In a 1-year double blinded study of efficacy, safety and tolerability of policosanol in human subjects (dosed at 10 mg daily), policosanol showed sustained efficacy, as well as a high degree of safety and tolerability.

Potential therapeutic investigations include a publication in which 1-Hexacosanol was injected intraperitonealy to mice at 1.0 mg/kg/day for 7 days, in order to study the regeneration of both sensory and motor axons in lesioned nerves, leading to improved functional recovery.

The extensive toxicology data available on 1-Docosanol indicates that this product is practically non-toxic. There are also some limited safety/toxicity data on 1-Hexacosanol and policosanols (which contain all 3 fatty alcohols) that also indicate no discernible toxicity of these related products. As the chemical structure of 1-Docosanol (C22:0) is similar to the longer chain length fatty alcohols 1-Tetracosanol (C24:0) and 1-Hexacosanol (C26:0), all three compounds are expected to exhibit similar physical/chemical properties and correlative toxicological behaviour.

In conclusion, all available data from published scientific literature indicate that long-chain fatty alcohols in general are of insignificant toxicity.

PROJECT DESCRIPTION

I.	**Project No.:**	135761
II.	**Project Title:**	Expert Statement: Surrogate Toxicological Data for 1-Tetracosanol (CASRN 506-51-4) and 1-Hexacosanol (CASRN 506-52-5)
III.	**Project Purpose:**	To review the toxicological data provided for Behenyl alcohol (C22:0), a long-chain fatty alcohol, and assess the appropriateness of conducting toxicological testing for 1-Tetracosanol (C24:0) and 1-Hexacosanol (C26:0) based upon the known toxic potential of 1-docosanol (behenyl alcohol).
IV.	**Management of Study:**	
	Study Director:	Kresimir Pucaj, D.V.M., M.Sc.
V.	**Sponsor:**	
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VI. Test Articles:

Identity:	1-Tetracosanol; and 1-Hexacosanol
Common Name(s):	Lignoceryl alcohol; and Ceryl alcohol
Chemical Formula:	$C_{24}H_{50}O$; and $C_{26}H_{54}O$
Molecular Weight:	354.7 g/mole; and 382.7 g/mole
Color/Form:	Off-white solid at room temperature. Light brown liquid when melted.
Odor:	Sweet, pungent odor
Chemical Composition:	1-Tetracosanol; and 1-Hexacosanol, respectively
CAS No.:	506-51-4 (1-Tetracosanol), 506-52-5 (1-Hexacosanol)
Storage Conditions:	Room temperature (15 – 30°C)

VII. Surrogate Test Article:

Identity:	1-Docosanol
Common Name(s):	Behenyl alcohol
Chemical Formula:	$C_{22}H_{46}O$
Molecular Mass:	326.6 g/mole
Color/Form:	Off-white solid at room temperature
Odor:	Sweet, pungent odor
Chemical Composition:	1-Docosanol
CAS No.:	661-19-8
Storage Conditions:	Ambient temperature

EXPERT STATEMENT: REVIEW OF 1-DOCOSANOL BEHENYL ALCOHOL TOXICOLOGICAL DATA AS SURROGATE DATA FOR 1-TETRACOSANOL AND 1-HEXACOSANOL

1-Docosanol, known commonly as behenyl alcohol, is a saturated 22-carbon, linear chain, aliphatic fatty alcohol that occurs endogenously within the human body and is found in a variety of organic materials including foods common to the human diet. The chemical structure of 1-Docosanol is similar to the longer chain length fatty alcohols: 1-Tetracosanol (C24:0) and 1-Hexacosanol (C26:0), and therefore is expected to exhibit similar physical/chemical properties and toxicological behaviour.

The toxicity of 1-Docosanol is well characterized and is documented in the scientific literature. These include an acute oral toxicity study in adult male and female Sprague-Dawley rats; genotoxicity studies using the Ames *Salmonella typhimurium* bacterial reverse mutation assay, chromosome aberration assays in Chinese hamster V79 cells, and the micronucleus assay in male and female NMRI mice. Sub-chronic studies in male and female CD strain rats, and male and female purebred beagle dogs, reproduction studies in adult female New Zealand white rabbits, and adult male and female Sprague-Dawley rats, exist to characterize the toxicological parameters for 1-Docosanol.

There are also some data available on the efficacy and safety toxicology of policosanols (a family of aliphatic alcohols) which contain usually up to 8 fatty alcohols including 1-hexacosanol, 1-tetracosanol and 1-docosanol.

This expert statement is based on a detailed review of the above-referenced literature provided in Appendices 2-4.

Summary of 1-Docosanol (Behenyl Alcohol) Toxicity (Surrogate Compound)

I. Mutagenicity Studies

1. *Salmonella typhimurium Reverse Mutation Assay* (Ref # 2)

   The mutagenic potential of Behenyl Alcohol was evaluated using the S. typhimurium strains TA1535, TA1537, TA1538, TA98 and TA100, with and without metabolic activation.

   Behenyl alcohol was dissolved in ethanol and tested at concentrations of 10.0, 100.0, 333.3, 666.6 and 1000.0 µg/plate.

The selection of doses was based on the results of a previously conducted range-finding study. Assays were performed in two independent experiments, using identical procedures, both with and without metabolic activation. Each concentration, including the controls, was tested in triplicate.

Both assays demonstrated a lack of mutagenic activity by behenyl alcohol. No significant or reproducible increases in the number of revertants were found in any combination of strain and behenyl alcohol treatment group, relative to the solvent control and/or negative control. In addition, no concentration-dependent enhancement of the revertant number occurred, and no differences were observed between behenyl alcohol treatments with or without metabolic activation.

2. *Gene Mutation Assay in Chinese Hamster V79 Cells* (Ref # 2)

The potential for behenyl alcohol to induce gene mutations, *in vitro*, at the HGPRT locus was evaluated in Chinese hamster V79 cells, with and without metabolic activation.

Behenyl alcohol was dissolved in ethanol, and V79 cells were exposed to behenyl alcohol concentrations of 2.0, 7.5, 15.0 and 20.0 μg/mL for 4 h cells were then monitored for the loss of functional HGPRT enzyme. The final concentration of ethanol in the culture medium did not exceed 1% v/v. The selection of doses was based on the results of a previously conducted range-finding experiment. Each concentration was tested with and without metabolic activation and the cells were subcultured twice per week. The assay was performed in two independent experiments, using identical procedures, both with and without metabolic activation. Concurrent negative and solvent controls were included, and positive controls consisted of ethylmethaesulfonate (EMS) and 7,12-dimethylbenz(a)anthracene (DMBA). All incubations were conducted at 37°C in a humidified atmosphere with 4.5% CO_2. Methylene blue (10%) was used for staining in 0.01% KOH solution. Stained colonies consisting of 50 cells were counted with a preparation microscope.

Mutation frequency was determined by seeding known numbers of cells in medium containing thioguanine (11 μg/mL) to detect mutant cells, and in medium without thioguanine to determine the total number of surviving cells.

No relevant increase in mutant colony numbers were found in both independent experiments at any concentration of behenyl alcohol tested, with or without metabolic activation.

3. *Chromosome Aberration Assay in Chinese Hamster V79 cells* (Ref # 2)

The potential for behenyl alcohol to induce structural chromosome aberrations in

Chinese hamster V79 cells was evaluated *in vitro*, with and without metabolic activation.

Behenyl alcohol was dissolved in ethanol and V79 cells were exposed to behenyl alcohol, both with and without metabolic activation. The liver microsomal fractions were obtained from 8 to 12-week-old male Wistar rats. In each experimental group, 2 cultures were used. Preparations of chromosomes were completed 7, 18, and 24 h after behenyl alcohol treatment had commenced. Cultures prepared at 7 and 24 h were treated with 20 µg/mL behenyl alcohol, while cultures prepared at 18 h were treated with 0.6, 10.0, and 20.0 µg/mL behenyl alcohol. Assays were initiated by seeding approximately 5.0×10^4 to 1.0×10^5 cells per Quadriperm dish in minimal essential medium (MEM). After 48 h (for cells harvested at 7 and 24 h) and 55 h (for cells harvested at 18 h), the medium was replaced with serum-free medium containing behenyl alcohol at the appropriate dose, with and without metabolic activation. All cultures were exposed to behenyl alcohol for 4 h. Following the treatment interval, the medium was replaced with normal medium after rinsing twice with saline. Colcemid (0.2 µg/mL), a metaphase-arresting substance, was added to the cultures for the last 2 h (for cells harvested at 7 h) or for the last 2.5 h (for cells harvested at 18 and 28 h) of incubation. The cells were then treated on the slides in the chambers with a hypotonic solution for 20 min at 37°C. After incubation, the cells were fixed, stained with Giemsa, and examined microscopically. One hundred metaphases per slide were scored for cytogenic damage.

The concentrations used in this study were based on the results from a pre-experiment, which used the plating efficiency assay as an indicator for toxicity response. Positive controls consisted of EMS (without metabolic activation) and cyclophosphamide (with metabolic activation).

Treatment with the highest concentration of 20 µg/mL behenyl alcohol did not reduce the plating efficiency of the V79 cells or the mitotic index in the study. No relevant increases in the number of cells with structural aberrations after treatment with behenyl alcohol at any fixative interval, either with or without metabolic activation, were observed.

4. *Micronucleus Assay* (Ref # 2)

The potential for behenyl alcohol to induce micronuclei in polychromatic erythrocytes (PCE) in the bone marrow of NMRI mice was evaluated *in vivo*. Animals at least 10 weeks old were housed individually under standard laboratory conditions.

Prior to treatment with behenyl alcohol, mice were fasted for 18 h, but continued to receive water *ad libitum*. Twelve mice (6 males and 6 females) were administered a

single oral dose of 0 (vehicle only), 50, 150, or 500 mg behenyl alcohol/kg body weight suspended in polyethylene glycol. These doses were based on the results from a previously conducted experiment in which 500 mg/kg body weight was estimated to be the maximum attainable dose. The volume administered was 10 mL/kg body weight. Cyclophosphamide (CPA) was used as the positive control at 40 mg/kg body weight.

At 24, 48, or 72 h after dosing, animals were killed and bone marrow cells were collected for micronuclei analysis. Only 5 rats/sex/dose group were evaluated in the event that remaining animals of each treatment group died spontaneously, or due to gavage error. Animals were killed by cervical dislocation. The femora were removed, the epiphyses were cut off, and the marrow was flushed out with fetal calf serum. The cell suspension was centrifuged at 1500 rpm for 5 min and the supernantant was discarded. A small drop of resuspended cell pellet was spread on a slide. The smear was air-dried and stained with May-Grünwald. Coverslips were mounted with EUKITT. Slides were scored for micronuclei, and the polychromatic-normochromatic (NCE) cell ratio was determined. For each animal, 1000 PCEs were scored for micronuclei. There was no increase in the percentage micronucleated PCE, or in the PCE: NCE ratio, of mice at any preparation interval after treatment up to 500 mg behenyl alcohol, as compared to the corresponding negative controls.

II. Toxicology Studies

1. Acute Oral Toxicity in Rats (Ref # 4)

For this experiment 5 male and 5 female Sprague-Dawley Rats were tested at both 8,250.0 and 10,000 mg/kg BW. Behenyl alcohol was administered once orally by gavage. Animals were observed for 14 days after the dosing. During the observation period, no mortalities or other symptoms of toxicity were observed, and there were no gross pathological findings observed at necropsy. Thus, the acute oral LD_{50} in rats of behenyl alcohol is estimated to be in excess of 10,000 mg/kg (Ref. #4).

2. Subchronic Toxicity Studies in Rats and Dogs (Ref # 2)

Male and female CD Rats and Beagle Dogs were dosed orally with behenyl alcohol, 7 days per week for 26 weeks.

Four groups of rats (20 per sex per group) were administered the test substance at dose levels of 0, 10, 100 and 1000 mg/kg/day. Four groups of dogs (4 per sex per group) were administered the test substance at dose levels of 0, 20, 200 and 2000 mg/kg/day.

Elements of observation included: daily clinical observations, body weights weekly, food consumption weekly; ophthalmoscopy was performed pre-study and during weeks 12 and 25. Standard clinical pathology was completed pre-study, and during weeks 14 and 26.

Gross necropsy including organ weights, was performed on all animals at the end of the study. Histopathology was performed on the following organs: adrenals, brain, eyes and optic nerve, femur (rats only), heart, kidney, liver, lungs, seminal vesicles (rats only), spinal cord, stomach, thyroid and uterus.

Treatment of rats and dogs with behenyl alcohol had no effects on body weight gain, haematology, food conversion efficacy, organ weight, haematology, blood chemistry, ophthalmological findings, and on macropathological and histopathological findings.

A single finding, in dogs only, was limited to observation of pale feces in animals treated with 2000.0 mg/kg/day. This finding is believed to be related to unabsorbed behenyl alcohol.

III. Reproductive Toxicology Studies

1. *Embryonic Development Study* (Ref # 3)

Eighty-eight sexually mature female New Zealand Albino Rabbits with synchronized oestrous cycle were administered the test substance at 0, 125, 500 and 2000 mg/kg (22 rabbits per group).

Females were mated with males of established fertility. All animals were dosed daily from Day 6 to Day 19 of gestation, inclusive.

Reproductive endpoints

Females were killed on Day 29 of gestation by an intravenous injection of pentobarbitone sodium, and their uterine contents were examined. In addition, each animal was macroscopically examined for evidence of disease or adverse reaction to behenyl alcohol. The number of corpora lutea in each ovary were recorded and the reproductive tract, including the ovaries, was dissected out. For each animal, the number of pre and post-implantation sites, early and late resorption sites, viable fetuses and the distribution of fetuses in each uterine horn, were examined. The uterus of any female presumed to be non-pregnant was stained using a 10% aq (v/v) ammonium sulfide solution, and examined for implantation sites by an established method.

Each fetus was weighed and given a detailed external examination. The fetuses were killed by a subcutaneous injection of pentobarbitone sodium, and uniquely identified within the litter with respect to their uterine position. Placental weights were recorded and examined macroscopically for any abnormalities. The neck, thoracic, and abdominal cavities from each fetus were dissected and the contents examined microscopically under low power. One-third of the fetuses were decapitated and the heads fixed in Bouin's fluid for subsequent examination using a modification of the Wilson free-hand serial sectioning technique. All fetuses were subsequently eviscerated, fixed in methylated spirit, and processed and stained with Alizarin Red for skeletal examination.

All female rabbits survived to their scheduled sacrifice. There were no remarkable clinical observations, with the exception of pale feces observed in the majority of females treated daily with 2000 mg behenyl alcohol/ kg body weight. Female body weight gains and food and water consumption from all dose groups were comparable to those of control rabbits throughout the duration of the study. No compound-related macroscopic findings were observed in any females at terminal necropsy. No intergroup differences suggestive of statistical significance were observed in the number of corpora lutea, pre- and post-implantation sites, early and late resorptions, or viable fetuses. Fetal and placental weights were unaffected by behenyl alcohol administration up to 2000 mg/kg material body weight. Fetal sex-ratios were comparable between each treatment groups and the control group. A total of 3 females, treated with 0, 125, and 500 mg behenyl alcohol/kg body weight, respectively, were observed with a total litter loss at necropsy. The uterus of each of these females revealed early resorptions.

Upon macroscopic, visceral, and skeletal examinations of the fetuses, no variations were observed that were not comparable to historical control values previously reported for the laboratory. There were no reported effects related to behenyl alcohol treatment (Ref. #3).

2. *Fertility and Reproduction Study* (Ref # 3)

Eight-eight CD male rats and 88 CD female rats were administered the test substance at dosages of 0, 10, 100, or 1000 mg behenyl alcohol/kg body weight/day (Groups 1, 2, 3, and 4, respectively). Each treatment group consisted of 44 rats (22 males and 22 females). Animals received the test material or vehicle control formulations by gavage. Males were treated with behenyl alcohol daily for 71 days prior to mating, during mating, and until termination. Females were treated with the test substance for 15 days prior to mating, during mating, and up to Day 17 of gestation.

Females were killed on Day 20 of gestation by carbon dioxide inhalation and their uterine contents examined. In addition, each female was macroscopically examined

for evidence of disease or adverse reaction to behenyl alcohol. The number of corpora lutea in each ovary was counted. The reproductive tract, including the ovaries, was then dissected out. For each female, the numbers of pre and post-implantation sites, early and late resorption sites, viable fetuses and the distribution of fetuses in each uterine horn, were examined. The uterus of any female presumed to be non-pregnant was stained using 10% aq (v/v) ammonium sulfide solution and examined for implantation sites.

Each fetus was weighed, subjected to a detailed external examination, and uniquely identified within the litter with respect to the uterine position. Placental weights were recorded and examined macroscopically for any abnormalities. The neck, thoracic, and abdominal cavities were removed from half of the fetuses, the contents of the thoracic and abdominal cavities were examined, and the sex was recorded. These fetuses were eviscerated, fixed in methylated spirit, processed and stained with Alizarin Red, and subjected to a skeletal examination. The remaining fetuses were placed in Bouin's fixative and internally examined using a modification of the Wilson free-hand serial sectioning technique.

Males were killed, *via* carbon dioxide inhalation, following necropsy of the females, and macroscopically examined externally and internally. Reproductive organs were weighed. The left vas deferens was ligated to obtain a 5 µL sample from the cauda epididymis. The sample was then diluted (1/200) in medium M199 + BSA factor V 0.5% w/v, pre-warmed to 37°C, and mixed to assess for motility according to the following grades: no sperm motile; few sperm motile; most sperm motile, slow moving; or most sperm motile, fast moving. The number of spermatozoa was assessed using a Fuchs-Rosenthal hemocytometer by further diluting the sample (1/20) in 4% v/v neutral buffered formaldehyde.

All female rats survived to their scheduled sacrifice. One male treated with 1000 mg behenyl alcohol/kg body weight/day and demonstrating abdominal distension, pallor, ptosis, irregular respiration, and a decrease in body weight was killed during Week 6. Examination of this male revealed watery blood, enlargement of the liver with the lobular pattern accentuated, enlarged pale spleen, and reduced gastrointestinal tract content. This was the only death that occurred in the study, and none of these indications were observed in any other study animal, or in any previously conducted subchronic toxicity assays. This death was not considered attributable to behenyl alcohol treatment. No other remarkable clinical observations were seen in any of the treated animals. Body weight gains, as well as food and water consumption for both male and female rats of all dose groups, were comparable to those of control rats throughout the duration of the study. No compound-related differences in female estrous cycles, or mating performance and fertility, were observed in any of the treatment groups when compared to the control group. Macroscopic findings at terminal necropsy revealed no findings attributable to behenyl alcohol. No

differences were observed in the number of corpora lutea, pre and post-implantation sites, early and late resorptions, and viable fetuses. Fetal and placental weights were not affected by material treatment with behenyl alcohol. Fetal sex ratios were comparable between each treatment groups and the control group.

Upon macroscopic, internal, and skeletal examination of the fetuses, no variations were observed that were not comparable to historical control values. There were no observed effects related to behenyl alcohol treatment.

No significant macroscopic findings were reported in males treated with behenyl alcohol. Absolute and relative body weights of reproductive organs were similar between each treatment group and the control group. Evaluation of sperm number and motility revealed no findings attributable to behenyl alcohol treatment (Ref. #3).

Justification for Utilizing Behenyl Alcohol (1-Docosanol) Toxicological Data as Surrogate Data for 1-Tetracosanol and 1-Hexacosanol

1-Docosanol (surrogate compound), 1-Tetracosanol and 1-Hexacosanol belong to the family of aliphatic (non-ring) fatty alcohols. All three compounds belong to a group of policosanol fatty alcohols which are found (and extracted) from several natural sources, including sugar cane, bees wax and rice bran wax. Sources of all three compounds in the human diet include bees wax, apples, olive oil, grapes, etc., and are also available as ingredients in several marketed nutritional supplements. Furthermore, aliphatic alcohols when ingested (absorbed) are most likely converted to fatty acids, which are either metabolized in the liver by β-oxidation or incorporated into wax esters, sphingolipids, glycolipids etc., thus making a group of aliphatic alcohols unlikely to be of significant toxicity.

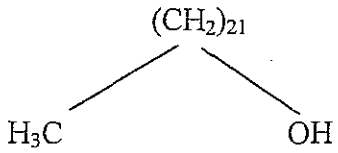
There are several published studies in both animals and humans in which policosanols were found to have had a beneficial effect on cholesterol metabolism with a reduction in circulating triglycerides. Policosanols were also studied in hypertensive patients with type II hypercholesterolemia, and in patients with non-insulin dependant diabetes mellitus and hypercholesterolemia (Ref. #6, 7, 8, 9).

In a 1-year double-blind study of the efficacy, safety and tolerability of policosanol (containing all 3 compounds, 1-tetracosanol, 1-hexacosanol and 1-docosanol) administration at 5 mg twice a day, policosanol showed sustained efficacy, as well as good safety and tolerability (Ref. #10).

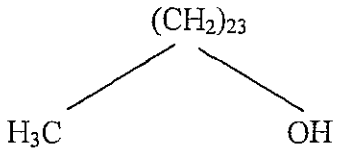
In addition, to the above potential therapeutic applications, a study in which 1-hexacosanol was injected intraperitonealy to mice at 1.0 mg/kg/day for 7 days, in order to evaluate the regeneration of both sensory and motor axons in lesioned nerve, reported improved functional recovery. No adverse toxic effects were observed in this study (Ref. #11).

Structurally a three alcohols have similar molecular formula, as illustrated, below:

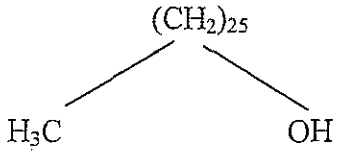
1) 1-Docosanol ($C_{22}H_{46}O$)



2) 1-Tetracosanol ($C_{24}H_{50}O$)



3) 1-Hexacosanol ($C_{26}H_{54}O$)



As a result of the similar molecular structure and formula of all three alcohols, it is anticipated that their chemical and biochemical behaviours will be similar, and consequently, all three alcohols are expected to exhibit similar toxicological properties.

Conclusion

All available data from the published peer-reviewed literature indicate that long chain fatty alcohols in general are of insignificant toxicity. There are extensive toxicology data on 1-Docosanol indicating that this product is practically non-toxic. There are also limited safety/toxicity data on 1-hexacosanol and policosanols (which contain all 3 fatty alcohols) that also indicate no discernible toxicity of these products either *in vitro* or *in vivo* in animals or humans.

The chemical structure of 1-Docosanol (C22:0) is similar to the longer chain length fatty alcohols: 1-Tetracosanol (C24:0) and 1-Hexacosanol (C26:0), and therefore is expected to exhibit similar physical/chemical properties and toxicological behaviour to these members of the common group of policosanol alcohols.

References Used in Review of Surrogate Data

1) Material Safety Data Sheet, Nacol® 22-98 (Behenyl alcohol). Sasol North America Inc., 09/04/01

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