1-CU990 - GRAS Notice

Ecomate™

December 2, 2009 | 1.0

Prepared for:

John Murphy

Foam Supplies

Written by:

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1. Claim of GRAS Status

1.1. Name and Address of Notifier

Foam Supplies, Inc.
4387 North Rider Trail
Earth City, Missouri 63045
Telephone: 314-344-3330
Facsimile: 314-344-3331

All communications on this matter are to be sent in care of Notifier's Representative Dr. Jeffrey Eberhard, Nerac, Inc., 1 Technology Drive, Tolland, Connecticut 06084, 860-872-7000, extension 1130.

1.2. Common or Usual Name of the Notified Substance

Ecomate™

1.3. Applicable Conditions of Use

Ecomate™ is intended for use as a blowing agent in rigid polyurethane foam insulation, not to exceed 5% by weight, when the polyurethane foam is used to insulate refrigeration units intended to hold food. The polyurethane foam insulation may not exceed a density of 6 pounds per cubic foot, and must be separated from the food holding compartment by a functional barrier (liner) comprised of high impact polystyrene or acrylonitrile-butadiene-styrene polymer sheet having a minimum thickness of 0.016 inches (16 mils).

1.4. Basis for GRAS Determination

The described use for Ecomate™ has been shown to be generally recognized as safe (GRAS) on the basis of scientific procedures, in accordance with 21 C.F.R. § 170.30, as discussed more fully in the accompanying summary of the basis for GRAS determination. This determination is supported by an expert panel review of the relevant toxicological data set forth below.

1.5. Statement of Availability of Data

The data and information that are the basis for the GRAS determination are available for Food and Drug Administration's review and copying, or will be sent to FDA upon request.

The foregoing and accompanying information considered, Foam Supplies, Inc. hereby notifies the Agency through its representative that its Ecomate™, as described below, is GRAS when used as a foam polymer blowing agent in insulation for refrigeration units used to hold or store food when Ecomate™ is used at levels not to exceed 5% (w/w) in the foam having a density not to exceed 6 pounds per cubic foot, and separated from the food storage compartment by a functional barrier of high impact polystyrene or acrylonitrile-butadiene-styrene polymer sheet having a minimum thickness of 0.016 inches (16 mils). Accordingly, Ecomate™ is exempt from premarket approval requirements of the Federal Food, Drug and Cosmetic Act.

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2. Detailed Information about the Identity of the Notified Substance

2.1. Name

2.1.1. Chemical Name

Methyl formate

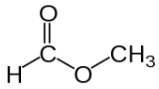
2.1.2. Other Names

Ecomate™
Methyl methanoate
Formic acid methyl ester

2.2. Chemical Description

2.2.1. Structural Formula

$C_2H_4O_2$



2.2.2. CAS Registry Number

107-31-3

2.2.3. Molecular Weight

60.05 g/mol [1]

2.3. Physical Description

Ecomate™ is a colorless liquid, or gas with a pleasant or agreeable odor at temperatures in excess of its boiling point, 31.7°C. [1] Its vapor pressure is 476 mm Hg at 20°C, and at 31.7°C Ecomate™ has a vapor density of 2.1 g/mL. [2] The water solubility of Ecomate™ is 300 g/L, and the octanol-water partition coefficient (Log $K_{o/w}$) is -0.21. [3]

2.4. Method of Manufacture

In the laboratory, Ecomate™ can be produced by the condensation reaction of methanol and formic acid, as follows:

$HCOOH + CH_3OH \rightarrow HCOOCH_3 + H_2O$

Industrial Ecomate™, however, is usually produced by the combination of methanol and carbon monoxide (carbonylation) in the presence of a strong base, such as sodium methoxide:

$CH_3OH + CO \rightarrow HCOOCH_3$ [4]

This process, practiced commercially by BASF among other companies gives >96% selectivity towards Ecomate™, although it can suffer from catalyst sensitivity to water which can commonly be present in the carbon monoxide feedstock, typically derived from synthesis gas. Very dry carbon monoxide is therefore an essential requirement. [5]

2.5. Specifications/Quantitative Composition

The quality control data for several recent lots are summarized in **Table 1**.

Table 1 - Quality Control Data for Ecomate™

Lot #	Delivery Date	Methyl Formate (%)	Methanol (%)	Formic Acid (ppm)
08705456P0	10/3/2008	97.4	2.59	<10
33794836W0	7/14/2008	97.4	2.56	>10
92486924U0	12/17/2008	97.3	2.61	<10
48081816K0	5/12/2008	97.3	2.71	10
87122724U0	8/19/2008	97.4	2.56	<10
85276624U0	10/29/2008	97.4	2.56	<10
Mean		**97.4**	**2.60**	

3. Information on Self-Limiting Levels of Use

In practice, the amount of blowing agent used in rigid polyurethane foam rarely exceeds 5% by weight, and the density rarely exceeds 6 pounds per cubic foot. The dimensions, mass and insulating ability of foams prepared with excess blowing agent limit their functionality for the intended condition of use, or become cost prohibitive.

4. Detailed Summary of the Basis for the Notifier's GRAS Determination

4.1. Data and Information Relied on to Establish Safety

Safety of Ecomate™ when used as intended will be established by demonstrating that a functional barrier separates Ecomate™ from potential food contact. Functional barrier calculations are based the amount of Ecomate™ used as a blowing agent in the rigid polymer foam insulation, as well as physical properties of the polymer sheet that serves as the barrier to separate the rigid foam insulation from the food storage compartment of the refrigeration unit. The functional barrier (liner or internal surface) defines the internal volume of the refrigeration unit where food is stored. Behind the internal surface of the refrigeration unit lies the rigid foam insulation made with Ecomate™. Thus, we will show that the thickness of the functional barrier (polymer sheet, liner) is such that the amount of migrating Ecomate™ is 0.

4.1.1. Diffusion Principles

Calculations based on the complete migration of the Ecomate™ when used as intended in rigid polymer foam insulation result in significant exaggeration of the estimate for potential human exposure. This exaggerated estimate is due, primarily, to lack of consideration of the effects of diffusion on the process of migration. The polymer sheet separating the foam insulation from the food storage compartment can serve as a functional barrier to diffusion of Ecomate™, as defined by FDA, under certain circumstances.

Piringer, *et al* have set forth a widely adopted approach to calculating the effects of diffusion on migration. [6] Assuming Fickian diffusion, the amount of migration of a substance from one phase to another in direct physical contact can be expressed as:

Equation 1 $M_t = 2C_{p0}(D_p t/\pi)^{1/2}$

where M_t is migration at time t, C_{p0} is the initial migrant concentration in the source phase (polymer), and D_p is polymer diffusion coefficient. [7] The general assumptions supporting this function are (1) the migrant concentration in the polymer does not change significantly with time, (2) the contacted substance is an infinite "sink" for the migrant with no appreciable resistance to mass transfer, and (3) the migrant is uniformly distributed in the source phase.

Using this equation (Equation 1), and setting the migration at time t to 0 (no migration), Piringer has derived an expression for the thickness of a barrier layer (functional barrier):

Equation 2 $b_t = [(16tD_p)/\pi]^{1/2}$

Where b_t is a function of only the diffusion coefficient, and represents the thickness resulting in no migration.

The diffusion coefficient for a polymer as a function of temperature and polymer molecular weight is given in an empirical relationship derived by Piringer: [8]

Equation 3 $D = 10^4 \exp(A_p - aM_r - bT^{-1})$

where D (D_p) is the diffusion coefficient, A_p accounts for the effect of the polymer on diffusivity, M_r is the migrating substance's molecular weight, T is the absolute temperature, and *a* and *b* (0.01 and 10450, respectively) are correlation coefficients for the effects on diffusion of the molecular weight and temperature, respectively. The values for *a* and *b* are independent of the polymer system.

4.1.2. Polymer Specific Constant

The polymer sheet serving as the functional barrier, or the material defining the internal volume of the refrigeration unit, and separating the rigid foam insulation from the food storage volume, is typically constructed of high impact polystyrene (HIPS) or acrylonitrile-butadiene-styrene (ABS) polymer. A worst case scenario for modeling the barrier properties of the functional barrier involves the use of ABS, a less dense polymer, and overall lower barrier to migration. According to Piringer *et al* [8], an A_p value of 0 for non-polyolefinic polymers should be employed in diffusion calculations.

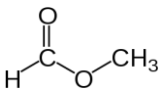
4.1.3. Time and Temperature

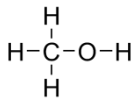
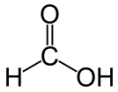
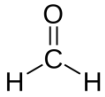
While we note that the refrigeration unit *per se* will typically be housed in a room temperature environment (25°C), the barrier layer will be exposed to refrigerated temperatures, generally <5°C. As a worst case scenario, and to provide a uniform frame of reference, subsequent calculations will use temperatures associated with Condition of Use A, "High Temperature Heat Sterilized." According to FDA guidance on the topic, under this Condition of Use, migration testing, and therefore diffusion calculations, should be conducted at 121°C for 2 hours followed by 238 hours at 40°C. This is intended to model thermal treatment and extended storage conditions for polymers used with food at temperatures above their glass transition temperatures. [9]

4.1.4. Functional Barrier Layer Thickness

The potential migrants resulting from the use of Ecomate™ are shown in **Table 2**. They are comprised of the active ingredient and a number of potential impurities and synthetic precursors or byproducts.

Table 2 - Potential Migrants

Migrant	Structure	M_r (g/mol)
Methyl formate		60.05

Methanol		32.04
Formic acid		46.03
Formaldehyde		30.03

Since diffusion is a function of molecular weight, M_r, the worst case scenario is presented by the lowest molecular weight migrant formaldehyde (30.03 g/mol).

Substituting M_r, A_p, a, b into Equation 3, we have:

Equation 4: $D = 10^4 \exp\{0 - [(0.01)(30.03)] - [(10450)T^{-1}]\}$

On this basis, we can calculate a diffusion coefficient for each temperature associated with Condition of Use A (121°C and 40°C). It should be noted that the modeled diffusion coefficients, 2.2×10^{-8} and 2.3×10^{-11} respectively (see Appendix 7.1 for calculations), comport very closely with experimentally derived coefficients for ABS polymer (10^{-7} to 10^{-11} depending on time and temperature). [10]

Substituting the resulting diffusion coefficients, along with the corresponding Condition of Use A times (2 hr and 238 hr) into Equation 2, we can calculate minimum barrier thicknesses associated with each time/temperature regime. Since the time/temperature regimes are sequential, the resulting minimum barrier thicknesses at each time/temperature regime are additive, and for this set of conditions, we have a minimum barrier thickness of 15.3 mils, or 0.0153 inches. The details of the calculations are found in Appendix 7.1.

4.2. Intake Estimate

Intake of Ecomate™ and its potential impurities methanol, formic acid and formaldehyde is estimated to be 0 mg/kg bw. This estimated intake is a result of the fact that a functional barrier of at least 0.0153 inches thickness comprised of ABS or HIPS polymer exists between the Ecomate™ source (rigid polymer foam insulation) and the contacted food.

In the event that the functional barrier fails, the exposure to Ecomate™, methanol, formic acid and formaldehyde is still expected to be safe on the basis of 100% migration calculations.

4.2.1. Methodology

The diffusion based methodology by which intake was estimated is based on principles of diffusion, and is discussed in Section 4.1 above.

As an alternative estimate of exposure, in the event that the functional barrier fails, exposure can be estimated on the basis of 100% migration calculations. The 100% migration calculations use a typical rigid polyurethane foam density of 3 lb/ft^3, a blowing agent use rate of 5%, and the worst case single use food contact ratio of 10 g/in^2.

Equation 5 3 lb/ft^3 x 454 g/lb x (1 ft)^3/(30.5 cm)^3 = 0.048 g/cm^3

Equation 6 **(**5 x 10^{-2} g Ecomate™/g foam) x (0.01 inch thick foam) x

(0.048 g foam/cm^3 foam) x (2.54 cm/in)^3 x (1 in^2 foam/10 g food)

= 3.93 x 10^{-5} g Ecomate™/g food = 39 ppm

Experimental data for CFC blowing agents indicate that 96% of the blowing agent remains dispersed in the polyurethane foam throughout the service life of the refrigerator, so only 4% of the blowing agent is available for migration, or 1.6 ppm (1600 ppb).[1] [11] Assuming similar behavior of Ecomate™ and given lot analysis data that indicate that 97.4% of this amount is methyl formate, 2.60% is methanol, and less than 0.1% is attributable to other impurities. The amounts of individual components of Ecomate™ available for migration to food are given in **Table 3**.

Table 3 - 100% Migration Calculation of Ecomate™ Components

Substance	Relative amount in Ecomate™ (%)	Available for migration (ppb in food)
Methyl formate	97.4%	1558
Methanol	2.60%	42
Formic acid	0.1%	1.6
Formaldehyde	0.1%	1.6

4.2.2. Quantitative Exposure Assessment

On the basis of the functional barrier argument, the dietary concentration of methyl formate, methanol, formic acid and formaldehyde resulting from the use of Ecomate™ as intended as a blowing agent in rigid foam insulation for refrigeration units is 0 mg/kg food, 0 kg/kg bw, and 0 mg/person/day.

[1] The mean loss as calculated from data reported in Table 1 of the report is 3.7%.

Out of an abundance of caution, we present here the maximum potential dietary concentration of Ecomate™ components that may result from the total failure of the barrier layer separating the rigid foam insulation from the food-holding compartment of the refrigeration unit, and complete migration of all available Ecomate™ components to food stored in the refrigerated food-holding compartment.

In converting the concentration of a substance in food to a dietary concentration, FDA typically uses the concept of consumption factor, or the fraction of the daily diet expected to contact specific packaging material. Absent specific information, FDA recommends use of a consumption factor of 5%. [9] In this case 5% represents the fraction of the daily diet stored in a refrigeration unit fabricated using Ecomate™ containing rigid polymer foam insulation. Absent empirical data substantiating an actual consumption factor, we use 5% as a default value for calculating dietary exposure to the components of Ecomate™.

Some might argue that use of the default 5% consumption factor might not be conservative or exaggerative enough under this set of circumstances to provide an exposure estimate that is protective of human health. We argue that there are other conservatisms built in to this calculation that offset any perceived problems with the use of the 5% consumption factor. Specifically:

- Relative amounts of components in Ecomate™ - We assume that the unaccounted for balance of components of Ecomate™ (formic acid and formaldehyde) is entirely attributable to each component, ignoring the fact that in actuality that as much as 0.1% is made up of the combination of formic acid, formaldehyde, and (in all probability) water.
- Single Use Scenario – We use the single use food contact ratio of 10 g food per square inch of food contact material (Equation 6). In all probability, that food contact ratio is much higher, representative of the fact that the same food is not stored in the refrigerator for its entire service life.
- Catastrophic failure – We assume that all available Ecomate constituents™ migrate in a single catastrophic event representing the total failure of the barrier layer. In all likelihood, any failure will be incremental with migration of the Ecomate™ components occurring over the entire service life of the refrigerator.
- Food Packaging – In typical usage, the food stored in the food-holding compartment of the refrigeration unit will be packaged. This packaging will offer an additional barrier to migration commensurate with its material of construction and thickness. For the purposes of this calculation, we assume no such packaging is used.

On these bases, we calculate the maximum potential dietary exposure to Ecomate™ components, given the usual assumptions of a 60 kg body mass and 3 kg/day food consumption. [9] The results are given in **Table 4**.

Table 4 - Dietary Exposure to Ecomate by Alternate Scenario

Substance	Available for	Dietary	Dietary

	migration (ppb in food)	Concentration (ppb)	Concentration (mg/kg bw/day)
Methyl formate	1558	78	3.9
Methanol	42	2.1	0.11
Formic acid	1.6	0.08	0.004
Formaldehyde	1.6	0.08	0.004

We note that according to EPA [12], and based on Til's drinking water study [13], the reference dose for formaldehyde carcinogenicity is 0.2 mg/kg bw/day, yet the dose from this source is more than an order of magnitude lower than the reference dose, acknowledging that no single source can contribute the entire reference dose.

4.3. ADME of Title Substance

Ecomate™ undergoes hydrolytic metabolism to methanol and formic acid, and because of its volatility, inhalation is the primary route of exposure. Hydrolysis can occur non-enzymatically, or by esterases present is plasma, liver and other tissues. Besides ester cleavage, Ecomate™ oxidation with Cytochrome P450 enzymes has also been shown, resulting in the production of formaldehyde and formic acid. The hydrolytic cleavage mechanism predominates with 85% - 97% of the Ecomate™ converted to methanol and formic acid. [14] Urinary formic acid correlates with occupational inhalation exposure to Ecomate™, however there is some variability introduced by chronic versus acute exposure. [15] In fact, a non-linear relationship between Ecomate™ exposure and urinary formic acid has been determined, while there is a linear relationship between Ecomate™ exposure and urinary methanol. Low exposure produces only marginal increase in urinary formic acid excretion, but when exposure is elevated, urinary formic acid excretion is elevated because of saturation in the mechanism of reabsorption. [16]

Methanol is extensively (~75%) metabolized in humans in the liver by alcohol dehydrogenase to formic acid, which is then metabolized by aldehyde dehydrogenase to formaldehyde. In the presence of folate, formic acid is converted to CO_2 and water. Methanol is readily absorbed by inhalation and in the gastrointestinal tract, and is excreted in urine. [17]

4.4. Toxicological Studies

4.4.1. Toxicity Data on Title Substance

Table 5 - Summary of Animal Toxicity Data for Methyl Formate

Type	Specie	Dose	Duration	Response	Reference
Acute oral	Sprague-Dawley rats (60M, 60F)	464, 681, 1000, 1470, 2150 mg/kg	Bolus	LD_{50}=1500 mg/kg; 10/10 of 2150 and 4/10 of 1470 dose groups died within 1 hour of dosing	[3]
Acute Inhalation	Sprague-Dawley rats (4M, 4F)	20 mg/L	4-exposure, 7-day post-exposure	LC_{50}>21 mg/L	[18]
Acute Dermal	Rats	4000 mg/kg	14 day	LC_{50}>4000 mg/kg	[18]
Acute Dermal	Rabbits	5000 mg/kg	14 day	LC_{50}>5000 mg/kg	[18]
Genotoxicity, Ames assay	*Salmonella typhimurium* TA 1535, TA 100, TA 1537, TA 98	20-5000 µg/plate	Protocol	Negative, with and without metabolic activation	[1]

Table 6 - Summary of Human Toxicity Data for Methyl Formate

Type	Specie	Dose	Duration	Response	Reference
Inhalation	Human	100 up to 400 ppm	Unspecified	No impairment of neurobehavioral responses; may produce a subjective feeling of fatigue	[18]
Inhalation	Human	100 ppm	8 hours	No impairment of neurobehavioral	[19]

				responses; may produce a subjective feeling of fatigue	
Inhalation	Human	Unspecified	Unknown	Nasal and conjunctival irritation	[18]
Inhalation	Human	30% solution	Unspecified	Euphoria or depression may occur	[20]

4.4.1.1. Genotoxicity

Standard Ames assay was conducted with *Salmonella typhimurium* strains TA 1535, TA 100, TA 1537, TA 98 with and without metabolic activation by rat liver S9 fraction. Plates were dosed in the range of 20 to 5000 µg/plate. Results were uniformly negative. [1]

4.4.1.2. Acute Toxicity

Acute oral toxicity was determined by the supplier BASF, giving an LD_{50} of 1500 mg/kg. Five Sprague-Dawley rats of each gender were used at each of five dose levels (464, 681, 1000, 1470, 2150 mg/kg). All high dose animals died, 2/5 males and 2/5 females died in the 1470 mg/kg dose group. Surviving rats gained weight, and did not appear to have delayed effects. All deaths occurred within one hour of dosing. The time course of death, clinical observations, and post-mortem findings are consistent with solvent-narcotic activity resulting from the bolus dose of Ecomate™ overwhelming the hydrolytic capability of the test animals being the cause of death. [18]

Acute inhalation toxicity was determined by the supplier BASF, giving an LC_{50} of >21 mg/L. Three 10 week old animals of each sex were exposed to the test material for four hours in a whole body exposure chamber in a study conducted under GLP guidelines. Rats were observed daily for clinical signs during the exposure and for seven days thereafter. They showed few clinical signs during the exposure, and recovered rapidly after the test material was withdrawn. During exposure, observations indicated lacrimation, reduced activity, and closed eyes. For two hours post exposure, observations were limited to a few secretory signs, and no ano-genital staining. There were no deaths, and all animals gained weight during the seven day post exposure period. [18]

Acute dermal toxicity at screening levels was studied by BASF and Hoechst Celanese (sponsor, BioDynamics performing). No further information is available about the rats study; however in the rabbit study, no animals died, and the following clinical signs were observed: slight apathy, staggering, spastic gait, irregular breathing. [18]

4.4.1.3. Chronic Toxicity

No repeat dose data for Ecomate™ were discovered after a thorough search of the peer reviewed literature using proprietary and publicly available databases such as Nerac's Advanced Research Environment[2], and the National Library of Medicine's PubMed database services.

4.4.1.4. Carcinogenicity

No repeat dose data for Ecomate™ were discovered after a thorough search of the peer reviewed literature using proprietary and publicly available databases such as Nerac's Advanced Research Environment, and the National Library of Medicine's PubMed database services.

4.4.1.5. Human Toxicity

The human toxicity of methyl formate has been studied in an occupational context for exposure by inhalation. At exposure as high as 400 ppm, no impairment of neurobehavioral responses is observed; however, exposure may produce a subjective feeling of fatigue. Some euphoria or depression, and nasal or mucosal irritation may occur at elevated concentrations. [18], [19], [20]

4.4.2. Toxicity Data on Substances Similar to the Title Substance

Table 7 - Summary of Animal Toxicity Data for Methanol

Type	Specie	Dose	Duration	Response	Reference
Acute Oral	Rat	6 g/kg bw	Daily bolus - 7 days	Free radicals yield increase in malondialdehyde and carbonyl groups in liver proteins	[21]
Acute Intraperitoneal	Monkey (*Macaca nemestrina*)	2-4 g/kg bw	Single bolus	Metabolic acidosis, decreased blood pH, distress, coma, death;	[22]

[2] Combined search of the following databases: Biobase, Biological Abstracts, CAB Abstracts, Embase, International Pharmaceutical Abstracts, Life Sciences Collection, Medline, Medline Preprints, Analytical Abstracts, Agricola, Chemical Business News, Engineering Index, Technology Collection, Food Science and Technology Abstracts

				LD_{50} = 3-4 g/kg bw	
Acute Oral	Monkey (*Macaca mulatta*)	Various	Single oral	CNS depression, coma, death, LD_{50} = 3 g/kg bw	[22]
Acute Oral, Intraperitoneal	Fischer, Long-Evans Rats	2-3 g/kg bw	Single bolus	Hypothermia	[22]
Acute Oral	Mouse, 40 strains	Various	Single oral	72 h oral LD_{50} range 7.3 – 10.0 g/kg bw	[22]
Acute Oral	Female minipig YU	1, 2.5 and 5.0 g/kg bw	Single oral	CNS depression, tremors, ataxia, recumbency	[22]
Acute Intraperitoneal	Rats	3 g/kg bw	Single intraperitoneal	Changes in levels of dopamine, norepinephrine, serotonin and 5-hydroxyindole acetic acid resulting from the direct effect of methanol *per se* on the monoaminergic neuronal membranes	[22]
Chronic Inhalation	Fischer 344 Rats (20/sex/dose)	13, 130, 1300 mg/m^3	Inhalation, 12 months	130 mg/m^3 NOEL	[22]
Chronic Inhalation	Monkey (*Macaca fascicularis*)	13, 130, 1300 mg/m^3	Inhalation, 29 months	Reversible hyperplasia of reactive astroglias (only)	[22]
Genotoxicity, Ames assay	*Salmonella typhimurium* TA 1535, TA	Not given	Protocol	Negative, with and without metabolic	[22]

	100, TA 1537, TA 98, TA 1538			activation	
Genotoxicity, Sister Chromatid Exchange	Chinese hamster ovary	0.1% (v/v), 8 day	Protocol	Negative	[22]
Genotoxocity, Forward mutation	L5178Y mouse lymphoma cells	7.9 mg/mL	Protocol	Negative without activation, positive with S9 activation	[22]

Table 8 - Summary of Human Toxicity Data for Methanol

Type	Dose	Duration	Response	Reference
Chronic Inhalation	235-1140 mg/m^3 for 1 to 8 hours/day	3 years	Acute dizziness, headache, nausea, eye irritation, upset stomach	[22]
Ingestion	1 g/kg	10 hours	Formate blood level above 0.5 g/L indicated poisoning	[17]
Occupational Inhalation	160-1000 ppm	Up to 8 hours	No symptoms reported. Estimated Tolerance Values determined as 1000 ppm for 1 hour, 500 ppm for 8 hours, 200 ppm for 24 hours based on five 8 hour work days.	[17]
Occupational	Methanol vapors	Occupational	Permanent	[17]

Inhalation	for more than 20 hours or blood formate levels >322 mg/dL		visual damage	
Inhalation	249 mg/m^3	75 minutes	3 fold increase in blood and urine methanol but no change in plasma formate levels	[22]
Inhalation	Methanol inhalation abuse producing methanol level > 24 mg/dL; an anion gap > 17 mEq/L. The mean formic acid level was 71 µg/mL	Unspecified	Reversible acidosis	[23]

Table 9 - Summary of Animal Toxicity Data for Formates

Type	Specie	Dose	Duration	Response	Reference
Acute Oral	Rat	3000 mg/kg bw (sodium formate)	Single dose	LD_{50}>3000 mg/kg bw	[18]
Acute Oral	C57BL Mouse, with and without folic acid supplemented diet (FAD)	Up to 4700 mg/kg bw (sodium formate)	Single dose	LD_{50}=4700 mg/kg bw for FAD, 3700 mg/kg bw for non-FAD	[18]
Chronic Oral	Wistar rat	1% sodium formate in drinking water	18 months	No adverse effects	[18]

Chronic Oral	Canine	5 g/day dietary sodium formate	18 months	No adverse effects	[18]
Genotoxicity, Ames assay	*Salmonella typhimurium* TA 98, TA 100, TA 1535, TA 1537, TA1538	Up to 5000 µg/plate sodium formate	Protocol	Negative, with and without activation	[18]
Genotoxicity, Chromosomal aberration	Chinese hamster ovary	270, 360, 450, 540, 630 µg/mL sodium formate	Protocol	Negative, with and without activation	[18]
Genotoxocity, Forward mutation	L5178Y mouse lymphoma cells	4857-8714 mg/L with activation, 3571-10,000 mg/L without activation	Protocol	Positive, with and without activation	[18]

Table 10 - Summary of Human Toxicity Data for Formates

Type	Source	Dose	Duration	Response	Reference
Ingestion	Sodium Formate	10 g by mouth	Bolus	No ill effects	[24]
Ingestion	Sodium Formate	3 to 4 g/day	Not specified	Diuretic effect may occur	[25]
Ingestion	Formate from methanol abuse by ingestion	Abuse dose not specified but postmortem blood formate concentration	Not Specified	Death	[26]

		> 0.50 g/L			
Ingestion	Calcium Formate	1.3 g/ day	3 days	No evidence of toxicity or elevation of serum formate from baseline levels	[27]
Inhalation	Formate from methanol abuse by inhalation	Methanol inhalation abuse producing methanol > 24 mg/dL; anion gap > 17 mEq/L; mean formic acid 71 µg/mL	Not specified	Reversible metabolic acidosis	[23]

Table 11 - Summary of Animal Toxicity Data for Formaldehyde

Type	Specie	Dose	Duration	Response	Reference
Acute Oral	Rat	Includes 100 mg/kg bw	Single oral	LD_{50}=100 mg/kg bw	[28]
Acute Oral	Albino rat	Includes 2020 mg/kg bw	Single oral	LD_{50}=2020 mg/kg bw	[17]
Acute Oral	Mouse	Includes 42 mg/kg bw	Single oral	LD_{50}=42 mg/kg bw	[28]
Acute Oral	Guinea pig	Includes 260 mg/kg bw	Single oral	LD_{50}=260 mg/kg bw	[28]
Acute Intravenous	Rat	Includes 87 mg/kg bw	Single IV	LD_{50}=87 mg/kg bw	[28]
Acute Intraperitoneal	Mouse	Includes 16 mg/kg bw	Single IP	LD_{50}=16 mg/kg bw	[17]

Acute Subcutaneous	Canine	Includes 550 mg/kg bw	Single SC	LD_{50}=500 mg/kg bw	[17]
Chronic Dermal	Oslo hairless mice	200 µL 1 or 10% aqueous solution	60 weeks	Lower dose, no changes; higher dose, epidermal hyperplasia	[29]
Chronic Oral	Wistar rats (70/sex/dose)	0, 1.2, 15, 82 mg/kg bw	24 months	NOAEL = 15 mg/kg bw	[13]
Chronic Oral	Wistar rats	0, 0.02, 0.1, 0.5%	24 months	NOAEL 0.02% (10 mg/kg bw)	[30]
Genotoxicity, Ames assay	*Salmonella typhimurium* TA 100	Not specified	Protocol	Weak positive in absence and presence of rat liver S9 activation	[31]
Genotoxicity, Sister chromatid exchange	Human lymphocytes	Not specified	Protocol	1.5 to 3-fold increase over control	[32]
Genotoxicity, Forward mutation	Human lymphocytes, *Salmonella typhimurium*	0 – 150 µM, 0 – 2 mM, respectively	2 hr	Positive in lymphocytes, positive at >170 µM in *Salmonella typhimurium*	[33]

Table 12 - Summary of Human Toxicity Data for Formaldehyde

Type	Dose	Duration	Response	Reference
Acute Inhalation	17 mg/m^3	30 minute	Lacrimation, changes in lungs, thorax,	[34]

			respiration	
Occupational Inhalation	300 µg/m^3	Occupational	Changes in olfaction, behavioral aggression	[35]
Occupational Inhalation	1 – 10 ppm	Occupational	Eye irritation with lacrymation at 4 ppm	[36]
Occupational Inhalation	3 ppm	2 hr	ENT irritation, headache, discomfort, cough	[37]
Acute Oral	643-646 mg/kg bw	Single oral	Respiratory obstruction, gastritis, ulceration or bleeding from stomach, nausea, vomiting	[38]
Acute Oral	1 mL/kg bw	Single oral	Coma, alteration in gastric secretion	[39]
Occupational Inhalation	0.1 ppm, 0.5 ppm, 2 – 3 ppm	Occupational	Upper respiratory and ENT irritation, cough, wheezing	[40]
Repeat Dose Carcinogenesis	Occupational and environmental	Chronic	IARC human carcinogen (nasopharyngeal), strong evidence of causal association with leukemia	[41]

4.4.2.1. Genotoxicity

Methanol has been studied in 3 genotoxicity assays, Ames, sister chromatid exchange, and forward mutation, using various strains of *Salmonella typhimurium*, Chinese hamster ovary and mouse lymphoma cells respectively. With the exception of mouse lymphoma cells activated with rat liver S9 fraction, all assays were negative. An increase in the mutation frequency in S9 activated L5178Y mouse lymphoma cells was observed, possibly because this assay detects chromosome damage as well as gene mutation. [22]

Formate (as sodium formate) was studied in 3 genotoxicity assays, Ames, sister chromatid exchange, and forward mutation, using various strains of *Salmonella typhimurium*, Chinese hamster ovary and mouse lymphoma cells respectively. With the exception of forward mutation assay, all assays were negative. The forward mutation assay results are considered suspicious because no colony sizing data were given. [18] The current OECD 476 (adopted 21 July 1977) guideline requires colony sizing to confirm the positive result. Likewise, the 1994 Mammalian Cell Gene Mutation Assays Working Group Report states that "ability to recover small colonies must be convincingly demonstrated when using the L5178Y TK mouse lymphoma assay". [42] In addition, the 1997 report by Coombs *et al* also emphasizes the importance of colony sizing to the acceptability of mouse lymphoma results. [43]

Formaldehyde has been studied in 3 genotoxicity assays, Ames, sister chromatid exchange, and forward mutation, using various strains of *Salmonella typhimurium*, and human lymphocytes. In all cases, the assays were positive. [31], [32], [33]

4.4.2.2. Acute Toxicity

Acute toxicity of methanol was studied in the mouse, rat, minipig, and monkey (*Macaca nemestrina*), dosed orally and/or intraperitoneally. The LD_{50}'s among the various species and administration routes was in the 3 – 10 g/kg bw range. Other high dose responses included hyperthermia, CNS effects, metabolic acidosis and changes in levels of dopamine, norepinephrine, serotonin and 5-hydroxyindole acetic acid resulting from the direct effect of methanol *per se* on the monoaminergic neuronal membranes. [22]

Acute toxicity of formates (as sodium formate) was studied orally in mouse and rats. The LD_{50}'s ranged from 3 – 5 g/kg bw. [18] NTP studied inhalation of formic acid in mice and rats in 2 and 13 weeks studies. Effects were limited to local degeneration of respiratory and olfactory epithelia, and no evidence for systemic toxicity was observed. [44]

Acute toxicity of formaldehyde has been widely studied in mouse, rat, guinea pigs and canines with oral, intravenous, intraperitoneal and subcutaneous administration. The LD_{50}'s varied widely by species and route of administration from 16 mg/kg bw (mouse IP) to 2 g/kg bw (rat, oral). [17], [28]

4.4.2.3. Chronic Toxicity

The chronic toxicity of methanol was studied in Fisher 344 rats (20 animals per gender/dose), dosed at 13, 130, 1300 mg/m^3 by inhalation for approximately one year. The NOEL was 130 mg/m^3, and high dose effects were limited to a slight decrease in weight gain in both sexes. [22]

Chronic toxicity of sodium formate was studied in rats and dogs (drinking water and feed, respectively) for 18 months. Although the study was ongoing at the time the data were reported and no pathological or histopathological results were available, no effects were observed at any dose level in either specie. [18]

The chronic toxicity of formaldehyde administered dermally (200 µL of 1% or 10% aqueous solution) was studied in mice for 60 weeks. In the low dose group, no adverse effects were observed, while in the high dose group, epidermal hyperplasia was observed. [29]

4.4.2.4. Carcinogenicity

Carcinogenicity of methanol was studies in *Macaca fascicularis* monkeys by inhalation at 13, 130, 1300 mg/m^3 for 29 months. The only observed effect was a reversible hyperplasia of reactive astroglias, which comports with the CNS activity observed in acute studies. [22]

Carcinogenicity of sodium formate was studied in rats and dogs (drinking water and feed, respectively) for 18 months. Although the study was ongoing at the time the data were reported and no pathological or histopathological results were available, no effects were observed at any dose level in either specie. [18]

Carcinogenicity of formaldehyde by oral administration (drinking water) was studied by Til and Tobe. [13], [30] In the Til study, used by EPA to establish the formaldehyde reference dose of 0.2 mg/kg bw/day, the mean formaldehyde doses administered were 0, 1.2, 15 or 82 mg/kg bw/day for males, and 0, 1.8, 21 or 109 mg/kg bw/day for females. There were no adverse effects on general health, survival, or hematological or clinical chemistry parameters. Body weight and food intake were decreased in the high-dose group. Liquid intake was decreased by 40% in the high-dose group in both sexes in comparison with the controls. There was a slight temporary increase in the density of urine, whereas there was a tendency towards lower urine production in the high-dose group. The relative kidney weights were increased in the high-dose females. Gross examination at autopsy revealed a raised and thickened limiting ridge of the forestomach in most high-dose rats. In addition, several rats in the high-dose group showed irregular mucosal thickenings in the fore- and/or glandular stomach. Treatment-related histopathological gastric changes seen in most of the animals of the high-dose group included papillary epithelial hyperplasia frequently accompanied by hyperkeratosis and focal ulceration in the forestomach and focal chronic atrophic gastritis, occasionally accompanied by ulceration and/or glandular hyperplasia in the glandular stomach. A higher incidence and/or degree of renal papillary necrosis occurred in the high-dose rats. From this study it appeared that the 'no-observed-adverse-effect level' of formaldehyde was 15 and 21 mg/kg body weight/day for male and female rats, respectively. Oral administration of formaldehyde at doses of 82 and 109 mg/kg bw/day to male and female rats, respectively, caused severe damage to the gastric

mucosa but did not result in gastric tumors or tumors at other sites. The study did not provide any evidence of carcinogenicity of formaldehyde after oral administration.

In the Tobe study, concentrations of 0.50, 0.10, 0.02 and 0% were administered for 24 months. Significant decreases in body weight and food and water intake were observed in the 0.50% group of both sexes and all rats in this group died by 24 months. Various non-neoplastic lesions were observed in rats, mostly in the 0.50% group. In this group, erosions and/or ulcers were evident in both the forestomach and glandular stomach. In the forestomach, squamous cell hyperplasia with or without hyperkeratosis and downward growth of basal cells were observed. Glandular hyperplasia of the fundic mucosa was noted along the limiting ridge. A few of such changes of the upper GI tract were seen in the 0.10% group. No toxicological abnormalities were found in 0.02% group of both sexes. There were no significant differences in the incidences of any tumors among groups of both sexes. Based on these findings, the no observable effect level of formaldehyde was 0.02% in the drinking water (10 mg/kg body wt/day).

4.4.2.5. Human Toxicity

Occupational exposure to methanol has been fairly well characterized. Although individual responses of man to methyl alcohol may vary considerably, industrial exposures are not very hazardous if concentrations are maintained within the upper limit of 200 ppm by proper ventilation. [17]

Abusive inhalation of methanol in the range of 235-1140 mg/m^3 for 1 to 8 hours/day results in significantly elevated methanol and formic acid levels, but low risk for methanol complications of visual dysfunction and refractory acidosis. [23]

Accidental ingestion of methanol results in peak serum levels after 30 to 90 minutes, and distribution throughout the body with a volume of distribution of approximately 0.6 L/kg. Methanol is metabolized primarily in the liver by sequential oxidation to formaldehyde, formic acid, and carbon dioxide. Elevated formate levels in blood are concomitant with methanol ingestion. [45]

Ingestion of formate, as the sodium or calcium salt, in bolus doses as high as 10 g, yields no effects other than elevated serum formate and mild diuresis. [24]

HSDB reports that the estimated median lethal dose for formaldehyde is 523 mg/kg bw, based on the ingestion of a 37% solution. [46] A recent review by Zhang reports on the carcinogenicity of formaldehyde, and summarizes various occupational exposure limits. [41]

Figure 1 - Occupational Exposure Limits for Formaldehyde

Country	OEL (ppm)		
	TWA	STEL[e]	TLV
Australia	1	2	
Canada[a]			0.3
China[b]			0.4
Germany	0.3		
Japan	0.1		
Sweden	0.5		1
South Africa	1	2	
United Kingdom	2	2	
United States			
PEL[c]	0.75	2	
REL[d]	0.016	0.1	0.3

[a]Canadian OEL are similar to the TLV by ACGIH in many provinces but regulated differently within each province. [b]China only has the maximum allowable concentration (MAC), which is equivalent to TLV. As of 2007, MAC = 0.5 mg/m^3 (~ 0.4 ppm). [c]The federal standard is called "permissible exposure limit" (PEL) instead of "OEL". [d]Recommended exposure limits (RELs as TWA and STEL) were recommended by NIOSH, and TLV by ACGIH. [e]The procedure for obtaining STEL measurements for each country varies by jurisdiction, with most countries defining "short-term exposure limits" at 30-min periods, with the exception of the U.S., which has adopted 15-min periods.

The Agency for Toxic Substances and Disease Registry (ATSDR) has established a chronic inhalation minimal risk level (MRL) of 0.04 ppm based on respiratory effects in humans. The MRL is an estimate of the daily human exposure to a hazardous substance that is likely to be without appreciable risk of adverse non-cancer health effects over a specified duration of exposure. Repeated contact with liquid solutions of formaldehyde has resulted in skin irritation and allergic contact dermatitis in humans. In a recent analysis of a new generation of textiles and related safety issues for children's apparel made of textiles which incorporate formaldehyde, supporting studies that show no toxic effects in skin of immature rats exposed to formaldehyde at 20 µg/g. [47] Dhareshwar and Stella [48] argue that the release of formaldehyde from prodrugs is safe for humans. While toxicity induced by the release of formaldehyde upon bioconversion of prodrugs has been repeatedly mentioned in the literature, no convincing evidence for toxicity has been documented in experimental studies.

4.5. Information Unfavorable to GRAS Determination

Formaldehyde by inhalation has been classified a human carcinogen by IARC, and probable human carcinogen by EPA. [29], [12]

4.6. Basis for Concluding that the Notified Use of the Title Substance is GRAS

Foam Supplies, Inc. has concluded that the above described use of Ecomate™ has been shown to be GRAS for the intended use on the basis of scientific procedures, in accordance with 21

C.F.R. § 170.3. This conclusion is supported by the determinations of an independent panel of qualified experts,[3] which evaluated the safety of Ecomate™ and determined the general recognition of safety of the substance under its intended condition of use.

4.7. Conclusion

Considering the foregoing, we respectfully submit that all criteria for general recognition of safety based on scientific procedures are met and, thus, that Ecomate™ is generally recognized as safe for use at the specified levels in the above described scenarios as a blowing agent for rigid foam insulation.

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[3] The panel consisted of Dr. Jeffrey S. Eberhard, Dr. Richard Hendriks, KimLa'Ree Johnson, Dr. John Leavitt and Irene Zajac, all of Nerac's Analyst Services Group. Their respective statements of qualifications appear in Section 6, below.

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6. GRAS Panel Qualifications

6.1. Jeffrey Eberhard, Ph.D.

Analyst Jeffrey Eberhard, Ph.D., brings 14 years of industry experience to answering critical technical questions and creating solid business solutions for food, beverage, and pharmaceutical companies. Dr. Eberhard began his career with Morton International Specialty Chemicals (now a division of Dow Chemical), where he developed expertise in the application of analytical chemistry techniques to the support of assessments of the safety and efficacy of new chemical products. That led to a position with the contract research organization Covance Laboratories, as a director of regulated studies, supporting regulatory submissions to the FDA and its European counterparts. At Keller and Heckman, Dr. Eberhard advised lawyers, governmental organizations and trade associations in regulatory, legislative, and international affairs regarding chemical and life sciences. As managing scientist at Exponent, he advised industrial clients regarding regulatory and international affairs. A graduate of the United States Patent and Trademark Office's Patent Training Academy, Dr. Eberhard spent a year as a patent examiner in the areas of pharmaceutical sciences and medical devices. Dr. Eberhard, a native of Buffalo, N.Y. and a graduate of Canisius College, earned advanced degrees at the University of Cincinnati College of Medicine. His master's research focused on occupational exposure monitoring, and his doctoral research investigated metabolism and environmental fate of aromatic azo and amino compounds. Dr. Eberhard is knowledgeable in the areas intellectual property, food science and food packaging, pharmaceuticals, medical devices, polymers, plastics additives, environmental science, analytical chemistry, chromatography, mass

spectroscopy, atomic spectroscopy, and occupational and public health. He is a member of the American Chemical Society, the Association of Official Analytical Chemists, and Sigma Xi, the scientific research society. He has presented at conferences worldwide and has written for scientific journals.

6.1.1. Credentials

Ph.D., Environmental Health, University of Cincinnati College of Medicine,
Pre-Doctoral Fellow, National Institute of Environmental Health Sciences
M.S., Environmental Health, University of Cincinnati College of Medicine
B.S., Chemistry, Canisius College
Graduate, United States Patent and Trademark Office, Patent Examiner's Training Academy
Member, American Chemical Society
Member, Association of Official Analytical Chemists
Member, Sigma Xi

6.1.2. Publications

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6.2. Richard Hendriks, Ph.D.

Analyst Richard Hendriks, Ph.D., partners with pharmaceutical companies to discover the most effective ways of expanding their business goals. This encompasses a range of solutions from innovations in biotechnology to analytical assessments of recent trends in disease treatments. Qualitative analyses of citation and patent literature is the foundation of such endeavors, and Dr. Hendriks has specialized in this area for almost 10 years with Nerac. During that time, he has gained significant industry and government insight. He has a Ph.D. in neuroscience from University of Melbourne, Australia, and a background in the area of neuronal electrophysiology. During his research career, Dr. Hendriks received several grants and fellowships from the National Institutes of Health and the National Science Foundation. He has been a principal investigator for various studies, including early collaborative research with Sandoz that focused on neuronal receptor pharmacology for a compound that was eventually commercialized as Tropisetron. His subsequent research moved to the subject of the central nervous system and included an investigation into the role of potassium channels in embryonic neuronal migration as part of an investigation into potential cures for deafness. Dr. Hendriks has authored dozens of published articles and abstracts on such topics as physiology and electrophysiology. Besides neuroscience and electrophysiology, Dr. Hendriks' areas of expertise include neurophysiology, pharmacology, receptors & ion channels, biophysics, developmental neuroscience, drug development, electrophysiology, bioengineering and neurotransmitters.

6.2.1. Credentials

Ph.D., Neuroscience, University of Melbourne, Australia

B.Sc. Hons, Medical Physiology, Flinders University of South Australia
B.Sc., Biophysics, Flinders University of South Australia (FUSA)

6.2.2. Grants and Fellowships

NIH, National Institute on Deafness and Communicative Disorders (NIDCD) T32 DC00025-12: from 8-1-94 to 8-1-96. “Communicative Disorders: Cellular and Neural Biology.” Role: Principal Investigator

NIH, National Institute on Deafness and Communicative Disorders (NIDCD) F32 DC00267-01: from 12-1-96 to 12-1-97. “Role of potassium channels in neuronal migration”. Role: Principal Investigator

NIH, National Institutes of Health, RO1 from 1-1-99 to 12-31-01. “Prenatal Protein Malnutritionand Hippocampal Plasticity.” Role: Research Associate

NIH, National Institutes of Health, R21, Technology Grant 1-1-2000 to 12-31-2001"Neurophysiology of the Developing Hippocampus” Role: Research Associate

NSF, National Science Foundation, RU1, . 6-15-99 –6-15-2002. “ Noradrenergic changes associated with hippocampal LTP in the freely moving male and female rat.” Role: Research Associate

NIH, National Institutes of Health, R15, AREA GRANT. 1-1-2000 to 12-31-2001"Neurophysiology of the Developing Hippocampus” Role: Research Associate

6.2.3. Publications

Hendriks, R. Bornstein, J.C. and Furness, J.B., “Evidence for two types of 5-hydroxytryptamine receptor on secretomotor neurons of the guinea-pig ileum,” Naunyn-Schmied. Arch. Pharmacol. 339: 409-414, 1989

Pompolo, S., Furness, J.B., Bornstein, J.C. Hendriks, R. and Trussell, D.C., “Dogiel type II neurons in the guinea-pig small intestine: ultrastructure in relation to other characteristics,” In Nerves in the Gastrointestinal Tract, Eds: M.V.Singer and H.Goebell, Martin Lister, Carnforth, U.K., pp 57-67, 1989

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Bornstein, J.C. Hendriks, R., Furness, J.B., and Trussell, D.C., “Ramifications of the axons of neurons with sustained post-spike hyperpolarizations and type II morphology in the myenteric plexus of the guinea-pig small intestine,” J. Comp. Neurol. 314 (3): 437-451, 1991

Hendriks, R., Coggan, J.S., Knoper, S.R., Purnyn, S.L., Xian, H., Anthony, T.L. and Kreulen, D.L., “Electrophysiology of cultured sympathetic neurons,” In: Innervation of the Gut:

Pathophysiological Implications, Eds. Tache, Y., Wingate, D.L. and Burks, T.F. CRC press. Boca Raton, USA. pp 137-149, 1992

Kunze, W.A.A., Bornstein, J.C., Furness, J.B., Hendriks, R., and Stephenson, D.S.H.. "Charybdotoxin and iberiotoxin but not apamin abolish the slow afterhyperpolarization in myenteric plexus neurons," Pfluger's Arch. 428: 300-306, 1994

Hendriks, R.; Kreulen, D. L., "Evidence for a sodium-dependent outward current in cultured stellate ganglion neurons of the guinea-pig," Biophysical Journal 66 (2) - 2 PP. A254, 1994

Bronzino, J.B., Kehoe, P., Hendriks, R., Vita, L., Golas, B., Vivona, C. and Morgane, P.J., "Hippocampal Neurochemical and Electrophysiological Measures from Freely Moving Rats." Exp. Neurol. 155: 150-155, 1999

Morest, D. Kent; Hendriks, Richard; Kaczmarek, Leonard K., "Role in neuronal cell migration for high-threshold potassium currents in the chicken hindbrain," Journal of Neuroscience Research 58 (6) 805-814, 1999

Morest, D.K.; Hendriks, R.; Kaczmarek, L.K , "Shaw-like potassium currents in the auditory rhombencephalon throughout embryogenesis," Journal of Neuroscience Research 58 (6) 791-804, 1999

Hendriks, R. Bornstein, J.C. and Furness, J.B. 1988. Two types of 5-HT receptor on submucosal secretomotor neurons revealed by the use of a 5-HT3 receptor antagonist (ICS 205-930). Australian Neuroscience Society (ANS) Meeting. Canberra, Australia. 1988. Neurosci. Lett. 30: S75.

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6.2.4. Presentations

Furness, J.B., Bornstein, J.C. Smith, T.K. and Hendriks, R. 1990. Physiological and morphological characterization of tertiary plexus neurons of the guinea-pig small intestine. Proc. Aust. Physiol. Pharmacol. Soc. (Sydney, Aust.) 21, 142P

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Hendriks, R., Kunze, W.A.A., Bornstein, J.C. and Furness, J.B. 1991. Charybdotoxin selectively blocks the prolonged post-spike afterhyperpolarizations in AH neurons of the guinea-pig small intestine. Proc. Aust. Physiol. Pharmacol. Soc. (Melbourne, Aust.) 22, 110P.

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Anthony, T.L., Hendriks, R., and Kreulen, D.L. Effect of Nw-nitro-L-arginine methyl ester (L-NAME) on stimulation evoked slow excitatory synaptic potentials in guinea-pig inferior mesenteric ganglion neurons. Am. Motility. Soc. Meeting. (Lake Tahoe, USA) 1992.

Hendriks, R., Karim, Gad-El.M.M. and Kreulen, D.L. 1993. Electrophysiological characteristics of stellate ganglion neurons of the guinea-pig. Am. Neurosci. Soc. 23rd Meeting (Washington DC, USA) Abstr. 23: 626.13.

Hendriks, R., and Kreulen, D.L. 1994. Evidence for a sodium dependent outward current in cultured stellate ganglion neurons of the guinea-pig. 38th Biophysical Society Meeting (New Orleans, USA). Abstr. 38: A254.

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Zheng, Z.L., Satterfield, B., Dey, R.D., Anthony, T.L., Hendriks, R., and Kreulen, D.L. 1995. Nitric oxide of primary sensory origin is a neuromodulator in sympathetic ganglia and blood vessels. Am. Neurosci. Soc. 25th Meeting Abstr. 25: 453.1 (San Diego CA, USA).

Hendriks, R., Hossain, W. Amin., Morest, D.K., Kaczmarek, L.K., Davidson, R.M., and E-M. Ostapoff. 1995. Development of Kv3.1-like currents in acoustico-vestibular neurons of the chicken embryo brain in vitro. Am. Neurosci. Soc. 25th Meeting Abstr. 25: 718.2 (San Diego CA, USA).

Hendriks, R., Morest, D.K., and Kaczmarek, L.K. 1996. Development of Kv3.1 - mediated potassium currents in cultured acoustico - vestibular neurons of the chicken. Association for Research in Otolaryngology (ARO): 19th Meeting, (St. Petersburg Beach, Florida).

Hendriks, R., Kaczmarek, L.K., and Morest, D.K. 1997. The influence of growth factors on the developmental expression of high threshold outward currents in cultured acoustico-vestibular neurons of the chicken. Association for Research in Otolaryngology (ARO): 20th Meeting, (St. Petersburg Beach, Florida).

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Roy, K.; Kehoe, P.; Hendriks, R.; Fortin, D. F. ; Bronzino, J. D. 1999. Increased norepinephrine levels are associated with the induction of LTP in the dentate gyrus of the freely moving rat. 25 (1-2); 881.

6.3. KimLa'Ree Johnson

Analyst KimLa'Ree Johnson partners with chemists, engineers and lawyers to provide solutions to assist with decision makers for product development. She provides technical support to 65 national and international companies and has trained analysts to facilitate advanced research and analytics. Prior to joining Nerac, Ms. Johnson formulated coatings; used chromatography, spectroscopy and thermal analysis to provide customer support; and evaluated end-use applications for new resins. She also led cast film extrusion trials; conducted onsite product scale-ups followed by post-trial evaluations and presentations; analyzed adhesive films, raw materials and competitor tape products; and procured raw materials and substrates for new tape products. Ms. Johnson, has expertise in the areas of polymer chemistry, adhesives and coatings, roofing, flooring and tapes, and material characterization and evaluation.

6.3.1. Credentials

B.S., Chemistry, Wilson College
Member, American Chemical Society (ACS)

6.4. John Leavitt, Ph.D.

Analyst John Leavitt, Ph.D., provides solutions to critical problems in various life science industries to help companies pursue novel business strategies. Dr. Leavitt applies his expertise in the biotech fields of diagnosis and treatment of human diseases, genetics, and cell and molecular biology to help companies make informed decisions. Dr. Leavitt's academic career as a molecular and cell biologist started as a graduate student in the Department of Biochemistry at the University of Pittsburgh School of Medicine, then as a postdoctoral fellow at Johns Hopkins University in cancer research. In addition, he was a senior fellow at the National Institutes of Health and a career civil servant with CBER, a part of the FDA located on the NIH campus involved with regulation of vaccines and biologic drugs. Later, as a senior scientist at the Linus Pauling Institute in Palo Alto, Calif., Dr. Leavitt cloned and characterized several important human gene families linked to development of cancer. After six years at the Pauling Institute, he became Scientific Director at the California Institute for Medical Research, and then Director of Research at Adeza Biomedical. During his academic career, Dr. Leavitt was responsible for the isolation of four fundamental human genes and the development of two powerful gene promoters for genetic engineering of cells and tissues. His research was supported with grants and contracts from the National Cancer Institute, American Cancer Society, the U.S. Air Force, and private foundations. Dr. Leavitt has published over 60 research

papers. He also has three patents, one of which Stanford University successfully licensed to the biotech industry.

6.4.1. Credentials

Senior Fellow, National Institutes of Health (FDA)
Postdoctoral Fellow, Johns Hopkins University
Ph.D., Biochemistry, University of Pittsburgh School of Medicine
B.S., Chemistry, Bethany College

6.4.2. Special Appointments

Peer Review NIH Funding Study Sections
Army Breast Cancer Funding Study Section
Consultant for the Channing, Weinberg Venture Fund
Visiting Scientist, Laser Lab, U.S. Air Force Academy

6.4.3. Publications

Leavitt & Kakunaga, "Expression of a variant form of actin and additional polypeptide changes following chemical-induced in vitro neoplastic transformation of human fibroblasts," J. Biol. Chem., 255:1650-61 (1980)

Vandekerckhove, Leavitt, et al, "Coexpression of a mutant beta-actin and the two normal beta- and gamma-cytoplasmic actins in a stably transformed human cell line," Cell, 22:893-9 (1980)

Leavitt et al, "Variations in expression of mutant beta actin accompanying incremental increases in human fibroblast tumorigenicity," Cell, 28:259-68 (1982)

Leavitt et al, "Molecular cloning and characterization of mutant and wild-type human beta-actin genes," Molec. Cell. Biology, 4:1961-9 (1984)

Ng, Leavitt, et al, "Evolution of the functional human beta-actin gene and its multi-pseudogene family: conservation of noncoding regions and chromosomal dispersion of pseudogenes," Molec. Cell. Biology, 5:2720-32 (1985)

Leavitt et al, "Expression of transfected mutant beta-actin genes: transitions toward the stable tumorigenic state," Molec. Cell. Biology, 7:2467-76 (1987)

Lin, Leavitt et al, "Molecular cloning and characterization of plastin, a human leukocyte protein expressed in transformed human fibroblasts," Molec. Cell Biology, 8:4689-68 (1987)

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Gunning, Leavitt et al, "A human beta-actin expression vector system directs high-level accumulation of antisense transcripts," Proceedings Natl Acad Sci, USA 84:4831-5 (1987) Communicated by Linus Pauling

Aebersold, Leavitt, et al, "Internal amino acid sequence analysis of proteins separated by one- or two-dimensional gel electrophoresis after in situ protease digestion on nitrocellulose," Proceedings Natl Acad Sci, USA 84:6970-4 (1987)

6.5. Irene Zajac

Irene Zajac works with pharmaceutical companies and other scientific clients in patent and literature research including clinical trials summaries, white papers in the pharmaceutical arena, and patent portfolio analytics. Ms. Zajac's 25 years of industry experience includes enzyme inhibitor assay development at both the National Institute of Environmental Health Sciences and at Glaxo in North Carolina. While with the Virginia-based Biotech company Argonex Inc., she was part of an immunology group that worked toward a vaccine for ovarian cancer. Outside the lab, Ms. Zajac was a clinical research associate for PRA International in Virginia and trained pharmaceutical research staff on various scientific software applications at Massachusetts-based Spotfire and Connecticut-based Pfizer. Ms. Zajac holds an M.S. in biochemistry from the University of North Carolina and a bachelor's in chemistry from Bucknell University. She is a member of the American Chemical Society and the Society of Competitive Intelligence Professionals.

6.5.1. Credentials

M.S., Biochemistry, University of North Carolina at Chapel Hill
B.A., Chemistry, Bucknell University
Member, American Chemical Society
Member, Society of Competitive Intelligence Professionals

7. Appendices

7.1. Barrier Layer Calculation

	$D=10^4\exp(A_p-aM_r-bT^{-1})$				D		diffusion coefficient (cm^2/sec)			
	D_{p1t1}	2.24314E-08	cm^2/sec		A_p	0	diffusivity constant for type of polymer			
	D_{p2t2}	2.34408E-11	cm^2/sec		a	0.01	constant			
					M_r	30.03	molecular weight (D)			
	$b_t=[(16tD_p)/\pi]^{1/2}$				b	10450	constant			
	b_{t1}	11.29134458	mils		T_1	121	°C			
	b_{t2}	3.98177937	mils		T_2	40	°C			
					t_1	2	hr			
					t_2	238	hr			
Polymer type		ABS					**enter value**			
COU		A								
Description		Refrigerator liner								
b_t=	15.3		mils							