

H. ENVIRONMENTAL ASSESSMENT

EN



1. Date

June 30, 1989

2. Name of Petitioner

GATTEFOSSÉ S.A.

3. Address of Petitioner

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France

91F- 0457

EA 1

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4. Description of the Proposed Action

The Food Additive Petition, in conjunction with which this Environmental Assessment (EA) was prepared, requests affirmation of Food Additive Status for a class of products which are mixtures of glycerides and polyglycides of fatty acids of vegetable origin, hereinafter collectively referred to as "Gattefossé Excipients". These products are intended for use as excipients in vitamin tablets, pills and liquid formulations.

Gattefossé Excipients are already in use as excipients in tablets, pills and liquid formulations for pharmaceutical products. For example, Labrafil 1944 CS has been used in oral formulations in France since 1956. It is a constituent of Sandimmune^R Oral Solution [cyclosporine] (Sandoz Pharmaceuticals) available in the United States. Most of the products referred to in the Food Additive Petition have been subjects of Drug Master Files submitted to the U.S. Food and Drug Administration.

Similar or related substances already approved for food use include the Multipurpose Food Additives (21 CFR §172, Subpart I), "ethoxylated mono- and diglycerides" (21 CFR §172.834) and "polyglycerol esters of fatty acids" (21 CFR §172.854), and the GRAS Food Substances, "mono- and diglycerides of edible fats or oils, or edible fat-forming acids" (21 CFR §182, Subpart E [Emulsifying Agents] §182.4505).

An FDA-sponsored telephone survey¹ was conducted to assess the potential U.S. consumption of glyceryl behenate as an excipient in vitamin/mineral supplements. The survey estimated that 40% of U.S. consumers over 16 years of age ingest at least one supplement per day and that the median intake is one supplement per day. A total of 200 million consumers in the U.S. could be postulated although this is likely to be an overestimate of the population over 16 years. Taking these estimates, calculations of the likely exposure of consumers to Gattefossé Excipients are given in Item 6.

It is likely that a proportion of the excipients, particularly the glyceryl fatty acid esters (glycerides) would be absorbed in the gut and metabolized by the physiological mechanisms which act on natural fats and oils.

Any of the constituents not absorbed and metabolized by individuals consuming vitamin or mineral supplements containing Gattefossé Excipients would be excreted and require disposal via sewage systems. In the United States, this would most likely be by local POTWs (Publicly Owned Treatment Works). The amounts of these materials utilized in any one area would not be large enough to have a significant impact on the waste streams being treated. Calculations detailing environmental exposure to the glyceride/polyglycide mixtures as a result of the proposed use are given in Items 6 and 7 of this EA.

5. Identification of Chemical Substances that are the Subject of the Proposed Action

5.1. Name of Food Additive Class

a. Chemical Name

Glycerides and polyglycides of fatty acids of vegetable origin
(see Table A-1 for listing of representative compounds).

b. Trade Names

The Gelucire group (various types)

The Labrafil group (several types)

Labrasol, Labrafac

(See Table A-1)

5.2. Chemical Identity

a. Structural Formulae

$R'-CO-O-CH_2-CH_2-[O-CH_2-CH_2]_p-O-CH_2-CH_2-O-CO-R''$ (polyglycides)

$[R^*-CO-O]_n - C_3H_5 - [OH]_{3-n}$ (glycerides)

$p = 0$ to 35

$n = 1$ to 3

R' and R^* = straight-chain fatty acids

R'' = either H or straight-chain fatty acids

b. Molecular Formulae

Not applicable since these products are mixtures

c. Molecular Weights

Range: 425 to 1160

(See Table A-1)

5.3. Organoleptic Properties

a. Appearance b. Odor c. Color

These properties are listed in Table A-1.

Color: Refer to Appendix A [Analytical Methods] 1).

(A.O.C.S. Official Method, Td 1a-64).

The Gelucires are waxy solids with a faint odor and creamy white in color (≤ 5 on the Gardner scale).

The **Labrafil**s are either waxy or doughy solids or liquids. They have either faint or characteristic odors and range from cream colored solids to yellow liquids. (Color ≤ 5 on the Gardner scale).

Labrasol and **Labrafac Hydro WL 1219** are clear yellow liquids with faint odors. (Color ≤ 5 on the Gardner scale).

5.4. Physical and Chemical Properties

Specifications for ten **Gelucires**, eight **Labrafil**s, one **Labrasol**, and one **Labrafac** are given in Tables A-2 and A-3.

Analytical data on several batches for representative products are given, for some of the parameters described in this subsection, in Tables A-4 through A-17.

a. Solubilities

Refer to Table A-18 for solubilities of nine **Gelucires**, four **Labrafil**s, and one **Labrasol**. The analytical method used (European Pharmacopeia, II, 1971, page 5) is described in Appendix A, 2.

NOTE: *HLB* (hydrophilic:lipophilic balance) values are calculated using the Griffith formula:

$$HLB = 20[1-S/A]$$

where *S* = Saponification Index and *A* = Acid Value

b. Acid Value

≤ 2 mg KOH/g (Refer to Tables A-2 and A-3 and Appendix A, 3).
(French Pharmacopeia, 9th. Ed., II, 275a).

c. Sulfated Ash

≤ 0.1 % (Refer to Tables A-2 and A-3 and Appendix A, 4).
(French Pharmacopeia, 9th. Ed., II, 259).

d. Saponification Index

Units:- mg/KOH/g (Refer to Tables A-2 and A-3 and Appendix A, 5).
(French Pharmacopeia, 9th. Ed., II, 280a).

e. Melting Point

Units:- °C (Refer to Tables A-2 and A-3)
Drop Point Method (Refer to Appendix A, 6).
(European Pharmacopeia, 2nd. Ed., I, 1980, V.6.11.4).

f. Iodine Index

< 3 g I₂/100g, except for certain Labrafils which contain unsaturated fatty acids (Refer to Tables A-2 and A-3 and Appendix A, 7)
(Norme Française, NF T 60 203, December 1968)

g. Water Content

≤ 0.5 % (Refer to Tables A-2 and A-3 and Appendix A, 8).
(Norme Française, NF T 60 225, September, 1968).

h. Peroxide Index

Units:- meq O₂/kg (Refer to Tables A-2 and A-3 and Appendix A, 9).
(French Pharmacopeia, 9th. Ed., II, 279a).

i. Hydroxyl Index

Units:- mg KOH/g (Refer to Tables A-2 and A-3 and Appendix A, 10).
(French Pharmacopeia, 10th. Ed.,).

j. Free Glycerol and α-Monoglycerides

Units:- % (Refer to Tables A-2 and A-3 and Appendix A, 11).
(French Pharmacopeia, 10th. Ed.,).

k. Alkaline Substances

Units:- ppm NaOH (Refer to Tables A-2 and A-3 and 12).
(French Pharmacopeia, 9th. Ed., II, 322.13 or 10th. Ed.,).

l. Heavy Metals

< 10 ppm (Refer to Tables A-2 and A-3 and Appendix A, 13).
(French Pharmacopeia, 10th Ed., V.3.2.8).

m. Arsenic

< 2 ppm (Refer Tables A-2 and A-3 and to Appendix A, 14).
(French Pharmacopeia, 10th. Ed., V.3.2.2).

n. Infrared Spectrum

(Refer to Figures A-1 through A-14 and Appendix A, 15).
(French Pharmacopeia, 9th. Ed., II, 334a, V.16.18).

o. Polyethylene Glycols

The polyethylene glycols used in these products meet the specifications of the monograph in the French Pharmacopeia, 9th. Edition (Appendix B). The amounts of residual free polyethylene glycol in the products are shown in Tables A-2 and A-3.

p. Fatty Acid Composition

The fatty acid composition of ten Gelucires, eight Labrafils, one Labrasol, one Labrafac are shown in Tables A-19 and A-20. For the procedures: i) Fatty Acid Methyl Esters, Preparation, refer to Appendix A, 16 (Norme Française, NF T 60-233, May 1977) and ii) Fatty Acid Methyl Esters, Analysis by Gas Chromatography, refer to Appendix A, 17 (Norme Française, NF T 60-234, May 1977).

q. Refractive Index

(Refer to Table A-3 and Appendix A, 18 [Gattefossé Laboratory Method]).

r. Specific Gravity (Relative Density)

(Refer to Table A-3 and Appendix A, 19 [Gattefossé Laboratory Method])

s. Viscosity

(Refer to Table A-3 and Appendix A, 20 [Gattefossé Laboratory Method])

t. Impurities, By-products (limits)

Either none or traces of sodium hydroxide and orthophosphoric acid when these are added to the reaction vessel during manufacture.

Any impurities which may be present are tested for by measurement of the pH of a 10 per cent emulsion of the product in water, according to the procedure described in the French Pharmacopeia, 9th. Edition, II, 324a (Appendix A, 21).

5.5. Residues

There are no residues from the manufacturing process.

The Gelucires, Labrafils, Labrafac Hydro WL 1219, and Labrasol are non-corrosive and have no effect on the packaging material used.

These products are packaged in drums constructed of paperboard (cardboard, kraft paper), and aluminum and lined with polyethylene (welded closure). The drums are supplied either by ROCHETTE CENPA or BERNHARD, usually in 12 liter (10 kg) or 22 liter (20 kg) sizes. Occasionally, a product (e.g. Gelucire 50/12) may be supplied in larger quantities such as 30 liters (25 kg) or 223 liters (180 kg).

The packaging material is tested in the quality control laboratory prior to use. It will in no way adulterate the products.

6. Introduction of Substances into the Environment

Glycerides and polyglycides of fatty acids of vegetable origin (Gattefossé Excipients), as described in this Food Additive Petition, are manufactured in Saint Priest, France. The manufacturing process does not result in the emission of any air pollutants of concern (i.e., those listed in 40 CFR §52.21 (c)(23)(i)). Vapor phase materials emitted from chemical reactions during manufacture of Gattefossé Excipients are condensed by passing them through chilled water contained in receptacles designed for the purpose. In fact, the only noncondensable gas, discharged as a result of the synthetic process, is nitrogen. The reactions take place in vessels filled with nitrogen. Further nitrogen is used to purge filters and atomizers used in the processes.

None of the water pollutants for which a National Pollutant Discharge Elimination System (NPDES) permit would be required in the United States is emitted in the manufacture of Gattefossé Excipients (40 CFR §122, Appendix D). The only liquid substance emitted is water which has been used in equipment cleaning. The rinse water will contain small amounts of starting materials (polyethylene glycols, glycerol, fats, oils, and fatty acids) and products (mixtures of polyglycides and glycerides of fatty acids of vegetable origin).

The manufacturer states that no harm to the environment results from the manufacture of Gattefossé Excipients.

The manufacturing process is carried out in conformance with all French Laws covering environmental pollution. The relevant French legislation applicable to the chemical industry in France is as follows:

Regarding Air Pollution:

Law of August 2, 1961, relating to enforcement of control of atmospheric pollution and odors;
Decree of May 13, 1974, relating to the control of emissions of pollutants and certain usages of thermal energy;
Council Directive No. 84-360 dated June 28, 1984, relating to enforcement of control of atmospheric pollution derived from industrial plants.

Regarding Water Pollution:

Circular dated June 6, 1953, relating to the discharge of waste water.

Regarding Protection of Workers:

Workers Code, Subsection 4, Enforcement of Fire Prevention, Articles R. 233-38 through 233-40;

Workers Code, Subsection 7, Sanitation, Articles R. 232-12 through 232-14.

The increase in manufacture of Gattefossé Excipients over current production levels, which would occur if the Food Additive Petition were approved, would not result in emissions that exceed requirements under the French laws cited above.

The environmental exposure has been estimated in order to provide two types of information:

- a) the environmental impact of formulating with Gattefossé Excipients, and
- b) the environmental impact of the use of vitamin or mineral supplements containing Gattefossé Excipients.

Environmental Impact of Excipient Manufacture and Use in Formulation

As stated above, the manufacturing process does not involve the release of pollutants either in vapor phase or in water discharge. The water used to rinse the manufacturing equipment contains only small amounts of starting materials and products. These comprise polyethylene glycols, glycerol, oils, and fatty acids and their derivatives. The fatty materials are of vegetable origin.

The products are routinely consigned in polyethylene-lined paperboard and aluminum drums and, if the Food Additive Petition were approved, would be shipped to the United States for formulation into pills, tablets, or liquid formulations of vitamin and/or mineral supplements. It is assumed that the wastage of Gattefossé Excipients in the formulation process will be minimal and therefore will not have any significant additional environmental impact. Any such material would be carried in the waste water and disposed of largely at POTWs. Formulators would be required to have permits for any waste water discharged at their plants in conformance with EPA guidelines. It is further assumed that the Gattefossé Excipients will largely substitute for, rather than augment, the usage of other excipients used in vitamin and mineral supplements, such as magnesium stearate and lactose.

Environmental Impact of Use of Vitamin/Mineral Supplements Containing Gattefossé Excipients

The population of the United States is approximately 240 million. As stated above, from the survey reported by Stewart *et al.*¹ about 40% of the adult population (aged over 16 years) consume an average of one vitamin/mineral supplement daily. Taking a figure of 200 million adults over 16 years (probably an overestimate) and a maximum content of 480 mg of Gattefossé Excipient per tablet, the daily consumption of these excipients would be:

$$200 \text{ M} \times 40/100 \times 480 \text{ mg}$$

$$= 80 \text{ M} \times 480 \text{ mg}$$

$$= 38,400 \text{ kg}$$

In a year $38,400 \text{ kg} \times 365 \text{ days}$ or $14,016,000 \text{ kg}$ of the material will be consumed. Assuming that none of the excipient material is metabolized on ingestion, the entire $14,016,000 \text{ kg}$ will enter the waste stream each year. Based on information available to the FDA that 71% of all U.S. sewage is treated in POTWs, 71% of $14,016,000 \text{ kg}$ or $9,951,000 \text{ kg}$ will enter POTWs per year. This is equal to $21,893,000 \text{ lbs}$. There is information showing that inflow to POTWs is 78.1×10^{12} pounds per year. Therefore, the average concentration of the excipient material in POTW

inflow would be approximately 0.28 ppm. Assuming an average POTW removes 90% of the entering pollutants, approximately 0.028 ppm of the excipient material would be present in the POTW outflow to the environment.

The calculation above assumed none of the excipient material would be metabolized by the body. However, it is likely that a major proportion of the glyceride moiety of these excipients would be hydrolysed and absorbed in the gut. Thereafter, their metabolic fate would be the same as that for other natural or modified fatty materials, derived from cooking oils, butter, margarine, or mayonnaise, etc..

Polyethylene glycol monostearate [polyoxyethylene (4) stearate] and polyethylene glycol esters of other fatty acids (e.g. oleic acid) are hydrolyzed in the bowel. The fatty acid is absorbed and metabolized and, at least, the shorter polyoxyethylene residues are absorbed but excreted unchanged in the urine². However, Culver *et al* (1951)²⁴ recovered only 2.3-3.1% of the polyoxyethylene (40) moiety from the urine of humans fed the corresponding stearate whereas 90.2-96.6% was found in the feces.

7. Fate of Emitted Substances in the Environment

Gelucires, Labrafils, Labrafacs and Labrasol (referred to collectively as "Gattefossé Excipients") are products are manufactured by Gattefossé Etablissements, Saint-Priest, France, and are the subject of this Food Additive Class Petition. The projected use of Gattefossé Excipients, proposed at this time, is as components of the excipient mixture in vitamin/mineral pills, tablets, or liquid formulations.

Gattefossé Excipients are mixtures of vegetable-origin fatty acid esters of glycerol (mono-, di-, and triglycerides) and of polyethylene glycols (mono- and diglycides).

As discussed above in Item 6, no pollutants will be released during the production of Gattefossé Excipients. The additional amounts of fatty material introduced into the environment through the use and disposal of Gattefossé Excipients will not make a significant contribution to the total of natural and modified fats and oils consumed and disposed of in the United States. For example, in 1977 about 11.7 billion pounds of domestic fat and oil production went into food products with a *per capita* consumption of 54.4 pounds³.

As regards dispersal of Gattefossé Excipients, the maximum estimated daily consumption of these products (see Item 6) would not exceed 38,400 kg, equivalent to approximately 14×10^6 kg per year or approximately 31×10^6 pounds per year.

In Item 6, it was shown that the maximum average concentration of the excipients in POTW inflow nationwide would be 0.28 ppm with the outflow to the environment amounting to one-tenth of that amount or 0.028 ppm. Such an extremely low concentration leaving POTWs should remove any requirement for additional fate analysis. The amounts calculated, low as they are, still constitute an overestimation of the actual amounts emitted because factors such as human metabolism and biodegradation have been ignored. No environmental effects are expected from these effluents.

It is assumed the remaining 29% would be disposed of largely via septic tank sewage systems. The distribution volume of such systems is not known so that the concentration of Gattefossé Excipients in non-POTW sewage cannot be estimated, but this quantity of material would be widely distributed in minute amounts, unlikely to cause adverse environmental effects.

Some of the polyethylene glycol residues may be removed by biodegrading bacteria in the sewage (Watson and Jones [1977]⁴ cited in the Toxic Substances Source Book, Series 2, Section 19, Water Pollution, Item 78-04800).



8. Environmental Effects of Released Substances

As discussed in Item 6, no pollutants will be released during the production of Gattefossé Excipients. It is also assumed that little waste containing these excipients will be introduced into the environment as a result of their use in formulating vitamin and/or mineral supplements. The only possible environmental impact will be as a result of consumption of vitamin/mineral preparations and excretion and subsequent disposal via POTWs and other sewage treatment systems, as described in Item 7. The amounts calculated for these releases show them to be extremely small.

In addition to the lack of environmental effect from the projected use and disposal levels, the excipients themselves have been shown to be innocuous in a variety of feeding studies.

Toxicity Studies Performed on Gattefossé Excipients and Other Glycerides

8.1. Animal Studies Sponsored by Gattefossé

8.1.1 Acute Oral Toxicity in the Rat

Tests of acute toxicity by oral dosage in the rat were performed by IFREB Laboratories in Lyons, France.

A single oral dose of each of the Gattefossé Excipient products (Gelucires, Labrafils or Labrasol) was administered to ten rats (5 males, 5 females), per product, at a level of 20 g/kg body weight or 20 ml/kg body weight in the case of the products which are liquid at ambient temperatures. Animals were observed for 14 days following dosage for mortality and other signs of toxicity.

With the exception of Gelucire 50/02, discussed below, none of the excipients administered caused any mortality leading to the conclusion that the materials may be considered Non-Toxic at these dosages under the experimental conditions used.

Gelucire 50/02 was administered to ten rats at a level of 20 ml/kg of body weight. Since the material has a density of 0.9 g/ml, this dose is equivalent to 18 g/kg. The rats were observed for 14 days. One male rat died on the seventh day. The experiment was repeated, using a dose of 20 ml/kg of body weight on another 10 rats and a dose of 15 ml/kg of body weight (equivalent to 13.5 g/kg) on a further ten rats. Again one male rat receiving the 20 ml/kg dose died on the seventh day of observation. None of the rats receiving the 15 ml dose died during the 14 day observation period. Under these experimental conditions, the LD₅₀ for Gelucire 50/02 in the rat by oral administration is greater than 20 ml/kg (18 g/kg).

8.1.2 Chronic Toxicity Study in Mice

A chronic toxicity study on Labrafil M 2130 CS was performed on white mice by Professor J. Bost of the Veterinary School in Lyon, France. Incorporation of this Labrafil into the diet of mice over a period of 18 months covering five generations resulted in no mortality nor was there any effect on fecundity.

glycol monostearate, and 8.2 percent succinic anhydride and succinated polyols. Levels as low as 2.5 percent succistearin in the diet of rats decreased the absorption of dietary fatty acids within 4 weeks. This resulted in a decreased utilization of feed by the animals and at a level of 10 percent succistearin, the decreased fatty acid absorption resulting in a substantial caloric loss. These numbers suggested that this was a reflection of the high level of stearic acid in succistearin. The fact that the absorbability of stearic acid is low when the content of unsaturated fats in the diet is low supports this suggestion.¹³

The Select Committee was not aware of published reports concerning the allergenicity, carcinogenicity, mutagenicity, or teratogenicity of any of the glycerides discussed above.⁵ Oxystearins (no chemical identification or data on purity provided) were not acutely toxic to rats at doses up to 14.5 g/kg intraperitoneally, or up to 16 g/kg orally. In chronic feeding studies with weanling male and female albino rats at dietary levels as high as 15 percent (about 7.5 g/kg/day) oxystearins for 2 years, all animals grew well. For the most part, no chronic toxic effects were observed. However, Leydig cell adenoma of the testes was found in 5 of 23 rats receiving oxystearin at the 15 percent level, but the workers noted that it was only remotely possible that this occurrence was related to the oxystearin fed.¹¹

With one exception, no biological data were found on the sulfoacetyl derivatives, monosodium phosphate derivatives, or monoglyceride citrate. Two studies on phosphate derivatives were available. In one study of toxic and teratogenic effects on the developing chick embryo, the LC₅₀ of a commercial sample identified as phosphated mono- and diglycerides, administered by air cell injection after 96 hours of incubation, was estimated to be >3,000 mg/kg; at 0 hours, the LC₅₀ was estimated to be 1,000 mg/kg.¹⁴ There was no significant increase in embryo mortality after yolk injection under all conditions except at the highest dose (2,400 mg/kg) at 0 hours. Increased abnormalities occurred only on air cell injection at 0 hours with very high doses (2,000 to 2,500 mg/kg). No increase in incidence of abnormalities followed yolk injection. In the other study, a sample designated as "mono- and diglycerides monosodium phosphate derivatives, FDA 71-59," was found to exhibit no genetic activity in a series of *in vitro* microbial assays.¹⁵ Included were plate and suspension tests employing a strain of *Saccharomyces cerevisiae* and three strains of *Salmonella typhimurium*, either non-activated or activated with homogenates of mouse, rat, or monkey liver, lung, or testis. A concentration of 5 percent of the test compound was used.

From this review the Select Committee concluded that: "There is no evidence in the available information on mono- and diglycerides of fat-forming acids that demonstrates or suggests reasonable grounds to suspect a hazard to the public when they are used at levels that are now current or that might reasonably be expected in the future."¹⁵

Furthermore, the FAO/WHO Expert Committee on Food Additives (JECFA) has placed no limit on the acceptable daily intake of mono- and diglycerides.¹⁶

8.3. Literature Review of Toxicity of Polyethylene Glycol Fatty Acid Esters

The majority of safety data for this type of compound (synonym: polyoxyethylene fatty acid derivatives) have been generated for certain emulsifiers for food use, particularly in retarding the firming of bread. The Food Protection Committee of the Food and Nutrition Board, National Academy of Sciences reviewed all the available oral toxicity studies on the polyoxyethylene stearates (such as Myrj, Tween and Span emulsifiers) and published a report in 1953.¹⁷

The Registry of Toxic Effects of Chemical Substances (1985/86, Vol. 4, page 3693) contains the following entry:

64550. POLYETHYLENE GLYCOL MONOSTEARATE (Myrj 45)

Oral Toxicity: hamster LD₅₀ = 27 gm/kg; rat LD₅₀ = 64 gm/kg

No oral toxicity data was given for polyethylene glycol distearate in this publication.

Fitzhugh et al.¹⁸ reviewed subsequent animal safety data for polyoxyethylene stearates from 1953 through 1959 and concluded that these data indicate some degree of safety to animals but do not establish clearly the no-effect levels.

These researchers investigated chronic oral toxicities of four stearic acid emulsifiers, in rats, with diets prepared at the 0, 2, 5, 10, and 25% levels by weight and fed for 2 years.

Compounds tested were:

- Myrj 45 polyoxyethylene-8-stearate
- Myrj 52 polyoxyethylene-40-stearate
- Span 60 sorbitan monostearate
- Tween 60 polyoxyethylene-20 sorbitan monostearate

Myverol 18-00 (distilled monoglycerides made from hydrogenated lard) was fed as a comparative control.

Significant growth depression occurred in some groups at the 25% feeding level but none at 10% or below. Adverse effects were more pronounced in males than females. The authors concluded that the figures indicate decreased food efficiency beyond the level of 18.75% non-nutritious polyol in the total diet. Myrj 52 caused diarrhoea at all but the lowest feeding level. Myrj 45 and Span 60 showed decreased survival at the 10% and 25% dosages. No effect on survival was noted in any other group. Hematology parameters were normal.

No significant liver enlargement occurred in rats at lower dosages. Most animals on the highest emulsifier dosage (25%) had livers which were enlarged and more friable than normal. Enlargement of the cecum and common bile duct occurred infrequently.

The main concern in this and other studies¹⁹ was the incidence of nephropathology; specifically, renal stones, bladder stones and tumors. In the first part of the study of Fitzhugh et al.¹⁸, conducted in rats fed Myrj 45, bladder stones and tumors were found only at the 25% level.

Twenty five of 150 animals had bladder stones (calcium oxalate) and of these, eleven also had bladder tumors. There were no instances of bladder tumors in which stones were not present also. All but one rat with stones were male. The one female with a single stone had no tumor.

A second test of Myrj 45 was conducted on 950 rats to obtain a careful analysis of the spontaneous tumors arising over two years of feeding at 0, 2, 5, 10, and 25% of the article. As in the first part of this study, bladder stones (27 of 87 animals) and epithelial tumors (13 of these 27) were restricted to males at the highest dose levels. In females, the most common type of tumors found were mammary tumors.

Since bladder tumors were always accompanied by bladder stones, Fitzhugh *et al.* concluded that tumor formation was secondary to bladder stones, presumably from mechanical irritation. This same situation occurred with the chronic feeding of diethylene glycol to rats²⁰, in a study carried out by the same group. Fitzhugh *et al.*¹⁸ were unable to say whether the 0.1% of diethylene glycol in Myrj 45, reported by the Food Protection Committee, 1953,¹⁷ was responsible for the stone formation.

These authors stated that the observed effects, in their opinion, should not label Myrj 45 as a weak carcinogen, but rather, in view of the known lability of rodent tumor production under various influences, should be considered a by-product of some effect on metabolism. Examples of such influences in tumor production are increase in certain fats in the diet or decrease with caloric restriction.

A comprehensive literature survey and review was carried out by the Joint FAO/WHO Expert Committee on Food Additives (JECFA) in 1963.²¹ The findings of this committee are summarised in the following section. Literature prior to 1959 examined by this committee is largely the same as that reviewed by Fitzhugh *et al.*¹⁸

8.4. Toxicology Evaluation of Some Food Additives - Emulsifiers - Polyoxyethylene (8) and Polyoxyethylene (40) Stearates, JECFA Meeting, Geneva, June 25-July 4, 1973²¹.

The substances, polyoxyethylene (8) stearate and polyoxyethylene (40) stearate (stearic acid esters of the polyethylene glycols) were evaluated for acceptable daily intake. The acceptable daily intake (ADI) for man, expressed on a bodyweight basis, is the amount of food additive that can be taken daily in the diet, even over a lifetime, without risk. As a result of this evaluation, the ADI for these substances was established for man as 0-25 mg/kg bodyweight.

In addition to the extensive toxicology review, certain biochemical aspects were evaluated. The committee found that 60% of the stearate fraction was absorbed when polyoxyethylene (8) stearate was fed at a concentration of 25% in the diet. Excretion of this fraction was complete in 24 to 32 hours and there was no evidence of accumulation in the body. The feeding of polyoxyethylene (40) stearate did not increase oxalate formation (National Academy of Science, 1958²²). It may be noted here that calcium oxalate is the most common constituent of renal tract calculi.

The average coefficient of digestibility, in the rat, of the fatty acid moiety of polyoxyethylene (8) stearate was 80% and, for the fatty acid moiety of polyoxyethylene (40) stearate, the coefficient was 96% (Oser and Oser, 1957²³).

Studies in human subjects showed that polyoxyethylene (40) stearate, given by mouth, was poorly absorbed. Only 2.3-3.1 % of the polyoxyethylene (40) moiety was recovered from the urine while 90.2-96.6 % was found in the feces (Culver *et al.*, 1951).²⁴

The committee made the following comments on the animal toxicology findings. "Deleterious effects observed in the early experiments on hamsters have been shown due to management rather than toxicity. The biological effects of polyoxyethylene (8) stearate have been extensively investigated in more recent short-term and long-term studies which form an adequate basis for evaluation. It is considered that this ester is not carcinogenic and that the bladder tumors at the 20% and 25% levels of feeding are attributable to the presence of bladder stones which do not occur at lower levels of intake, even though these are still greatly in excess of any level likely to be used in food. the validity of using levels of feeding above 10% in the assessment of the toxicological hazard of a food additive is questionable."

"Although the studies with polyoxyethylene (40) stearate are not as extensive as those with polyoxyethylene (8) stearate, they are sufficiently complete to permit evaluation. The main difference between these two esters is the greater absorption of the polyoxyethylene (8) moiety and the formation of bladder stones at very high dosage levels (20% or more of the diet). The polyoxyethylene (40) moiety was not well absorbed and sometimes had a laxative effect at dosage levels of 5% or more; such an effect is not relevant to the ingestion of lower dosage levels and had no toxicological significance in this context."

The committee evaluated the Level causing no toxicological effect in the rat to be 50,000 ppm (5%) of the diet; equivalent to 2500 mg/kg bodyweight.

As regards observations in man, the committee cited the following studies. Polyoxyethylene (8) stearate was administered to 12 human subjects as 1% of an X-ray opaque meal and the effects on gastric emptying and intestinal motility were studied. No significant differences from control studies were found (Oler and Craemer, 1955²⁵).

Ten patients convalescing from hepatitis were given 3-6 g of polyoxyethylene (8) stearate for periods of five to 66 days without any demonstrable ill effects (Kruesi and van Itallie, 1956²⁵). Polyoxyethylene (40) stearate as 1% of an X-ray opaque meal had no untoward effects in 12 human subjects and had no effect on gastric or intestinal motility.²⁵



9. Use of Resources and Energy

Use of Gattefossé Excipients in the manufacture of vitamin/mineral tablets, pills, and liquid formulations will replace other excipient materials requiring similar inputs of energy and natural resources for their production, transport, use and disposal. Thus, there will be little or no net change from the current situation regarding energy and natural resource utilization.

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10. Mitigation Measures

Since no adverse environmental impacts have been identified associated with the proposed use of Gattefossé Excipients, no mitigation measures will need to be taken.



11. Alternatives to the Proposed Action

No potential adverse environmental impacts have been identified which would result from the use of Gattefossé Excipients as a components of excipients in vitamin/mineral pills, tablets, or liquid formulations. In fact, the substitution of these products for some excipients currently in use may actually be beneficial.

Two excipients widely used in the formulation of vitamin tablets are lactose and magnesium stearate. Lactose is known to cause problems for some individuals who are genetically deficient in the enzyme lactase, which splits lactose into glucose and galactose. The condition of lactase deficiency affects about 75% of adults in all ethnic groups except those of Northwest European origin. Ingestion of lactose by affected individuals causes digestive problems which may be severe.

Magnesium stearate is also commonly used as an excipient. In some cases, the magnesium has been shown to have an adverse effect on the active ingredient in the formulation.

A digestible, non-reactive, excipient would thus provide advantages over both lactose and magnesium stearate. Insofar as Gattefossé Excipients were substituted for these other substances, this could be considered a net benefit.

12. List of Preparers

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13. Certification

The undersigned official certifies that the information presented is true, accurate, and complete to the best of the knowledge of the firm or agency responsible for preparation of the environmental assessment.

Date June 30, 1989

Signature of responsible official Gene B. Sargis

Title Senior Vice President
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Endnotes - Section H

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