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FOOD ADDITIVE SAFETY

Dr. Linda Kahl
Office of Premarket Approval, HFS-200
Center for Food Safety and Applied Nutrition
Food and Drug Administration
200 C Street, SW
Washington, DC 20204

Dear Dr. Kahl:

We wish to notify you that T&R Chemicals, Inc. has determined glycerol ester of gum rosin is "generally recognized as safe" ("GRAS"), through scientific procedures, for use as an ingredient in oil-based citrus flavorings for beverages. Accordingly, glycerol ester of gum rosin is exempt from the premarket approval requirements of the Federal Food, Drug and Cosmetic Act.

We are hereby submitting the attached document, relied upon by T&R Chemicals, Inc. to make its GRAS determination. As directed by the agency, the information is formatted in accordance with proposal 21 CFR 170.36(c) (62 Fed. Reg. 18937 (April 17, 1997)).

The data and information that serve as the basis for this GRAS notification will be sent to FDA upon request or are available for the FDA's review and copying at reasonable times at the office of Claire Kruger, Ph.D., Principal, ENVIRON Corporation, 4350 North Fairfax Drive, Suite 300, Arlington, VA. 22203, telephone: (703) 516-2309, facsimile: (703) 516-2393.

Sincerely,

Claire L. Kruger, Ph.D., D.A.B.T.
Principal

cc: V. H. Frankos
R. S. Slesinski
C. de la Canal

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GENERALLY RECOGNIZED AS SAFE (GRAS) NOTIFICATION FOR GLYCEROL ESTER OF GUM ROSIN

Prepared for

T&R Chemicals Inc.
Clint, TX

Prepared by

ENVIRON International Corporation
Arlington, VA

June 24, 2002

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I. GRAS NOTIFICATION FOR GLYCEROL ESTER OF GUM ROSIN

A. Name and Address of Notifier

T&R Chemicals, Inc.
P.O. Box 330
700 Celum Road
Clint, TX 79836

Contact: Mr. Cesar de la Canal
Telephone: 915-851-2761
Facsimile: 915-851-2961

B. Common or Usual Name of GRAS Substance

Glycerol ester of gum rosin is the common name for the chemical mixture that is the subject of this GRAS Notification. The trade name for this product is "Resina 8/RE" and it is manufactured in Mexico by Resinas Sintéticas. Other common names for this chemical include: glycerol-modified gum rosin, rosin glycerol ester, glycerol abietate, glyceryl triabietate, or ester gum. These names are also used synonymously for related rosin glycerol esters, e.g., glycerol esters of wood and tall oil rosin.

Glycerol ester of gum rosin is made from processed gum rosin obtained from pine trees that is then esterified with food-grade glycerol. Gum rosin is one of three rosins produced commercially. The three types of rosins—gum, wood, and tall oil—are defined by the part of the pine tree from which they are obtained and the method by which they are produced commercially. Because they are obtained from the same source (i.e., the pine tree), gum, wood, and tall oil rosins are similar in composition and in physical/chemical properties.

C. Intended Use

Glycerol ester of gum rosin (Resina 8/RE manufactured by Resinas Sintéticas) is intended for use as an additive in oil-based citrus flavorings for beverages. Addition of gum rosin has the intended technical effect to produce an increase the density of citrus oils (e.g., lemon oil, orange oils) and to act as an emulsifier, which results in improved stability and imparts a desirable degree of cloudiness when they are dispersed in the finished beverage (Bailey 1998). Glycerol ester of gum rosin will be used in citrus beverages at a maximum level of addition of 100 ppm.

D. Basis for GRAS Determination

The GRAS determination for glycerol ester of gum rosin is based upon scientific procedures in accordance with section 201(s) (21 U.S.C. §321(s)) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C.§301 et. seq.) ("the Act"), as described under Title 21 of the Code or Federal Regulations (21 CFR §170.30(b)), which states:

- General recognition of safety may be based on the view of experts qualified by scientific training and experience to evaluate the safety of substances directly or indirectly added to food. The basis of such views may be either (1) scientific procedures or (2) in the case of a substance used in food prior to January 1, 1958, through experience based on common use in food.
- General recognition of safety based upon scientific procedures shall require the same quantity and quality of scientific evidence as is required to obtain approval of a food additive regulation for the ingredient. General recognition of safety through scientific procedures shall ordinarily be based upon published studies that may be corroborated by unpublished studies and other data and information.

1. Safety of Glycerol Ester of Gum Rosin for its Proposed Use

A scientific procedures GRAS determination requires that first, information about the substance establish that the intended use of the substance is safe. The FDA has defined "safe" under 21 CFR §170.3(i) as a reasonable certainty in the minds of competent scientists that the substance is not harmful under its intended conditions of use. This same regulation specifies that three factors must be considered in determining safety. These three factors are:

1.) The probable consumption of the substance and of any substance formed in or on food because of its use (i.e., Estimated Daily Intake ("EDI"));
2.) The cumulative effect of the substance in the diet, taking into account any chemically- or pharmacologically-related substance or substances in such diet; and,
3.) Safety factors, which, in the opinion of experts qualified by scientific training and experience to evaluate the safety of food and food ingredients, are generally recognized as appropriate.

After consideration of these factors, an Acceptable Daily Intake ("ADI") and an EDI are typically established for the substance. The ADI represents the maximum amount of the substance that can be safely consumed by humans on a daily basis for a lifetime. An ADI is usually established by application of a safety factor of at least 100 to the highest no-observed-effect level ("NOEL") identified in the most sensitive animal species studied. Under 21 CFR §170.22, the FDA states that, except where evidence is submitted that justifies use of a different safety factor, a safety factor in applying animal experimentation data to man of 100 to 1 is to be used; that is, tolerance for the use of a human food ingredient will not exceed 1/100th of the maximum amount demonstrated to be without harm to experimental animals. Next, an EDI for the substance is derived based on the probable human consumption of the substance and of any substance formed in or on food because of its use. This EDI is typically derived in accordance with the FDA guidance, *Recommendations for Chemistry Data for Indirect Food Additive Petitions* (FDA 1995). Finally, the ADI for the substance is compared against its EDI. As long as the EDI is less than (or approximates) its ADI, the substance can be considered safe for its intended use (FDA 1993).

2. ADI of Glycerol Ester of Gum Rosin

The determination of glycerol ester of gum rosin as GRAS for use in citrus-flavored beverages is based in part on the demonstration that the glycerol esters of gum and wood rosin are equivalent toxicologically and chemically. This equivalence is demonstrated by the following:

1.) FDA's determination in other regulatory actions that the glycerol esters of wood and gum rosin are comparable toxicologically and chemically. For example, in their final evaluation of food additive petitions related to the use of rosin ester in chewing gum base, the FDA stated, "Toxicologically, the above mentioned rosin derivatives [glycerol or pentaerythritol esters] from "gum" or "wood" sources are practically similar."

2.) The comparability of rosin source materials. Gum and wood rosins, which are both obtained from the pine tree, are similar in composition. Both gum and wood rosins consist of two fractions: one fraction is composed of free organic acids called resin acids and the other is termed a neutral fraction; the proportions of these two fractions may vary with rosin source (species and

geographic location of pine tree) and with the processing conditions employed in manufacturing.

3.) Comparable analytical profiles, including infrared spectrophotometry (IR) and gas chromatography (GC) conducted by Resinas Sintéticas. These profiles show that samples of Resina 8/RE and ester gum 8BG (the glycerol ester of wood rosin produced by Hercules, Inc.), are comparable chemically.

The safety of glycerol ester of gum rosin for use as an ingredient in citrus beverages at a maximum concentration of 100 ppm is established by comparing the acceptable daily intake ("ADI") of glycerol ester of gum rosin with its estimated daily intake ("EDI"). By definition, a food substance is considered safe for its intended use if the EDI of the substance is less than, or approximates, its ADI.

The ADI for glycerol ester of gum rosin can be developed using the toxicity data for glycerol ester of wood rosin and confirmed by the available toxicity data for gum rosin and glycerol ester of gum rosin. In light of the demonstrated equivalence of glycerol ester of gum and wood rosins, the ADI for glycerol ester of gum rosin can reasonably be based on pharmacokinetic and toxicity data for glycerol ester of wood rosin. Food-grade glycerol ester of wood rosin is metabolically stable in the gastrointestinal tract. In repeat-dose toxicity studies, rosin and the glycerol esters of rosin, regardless of whether it was gum or wood, produced no systemic toxicity in experimental animals. Reported effects were principally limited to reduced body weight gain, which may have been secondary to problems with the palatability of a diet containing high levels of the test material. Esterification appeared to reduce the toxicity of the basic rosin. In *in vitro* assays for genotoxic activity, glycerol ester of wood rosin was negative in assays with both bacterial and mammalian cells.

JECFA (1996b, 1997) concluded that the available toxicity data and studies demonstrating the low degree of bioavailability of glycerol ester of wood rosin were adequate to establish an ADI for this compound of 0 to 25 mg/kg. The JECFA ADI is based on a 13-week toxicity study in rats with food-grade glycerol ester of wood rosin (Blair 1991, 1992, cited in JECFA 1996a). This study identified a NOAEL of 2,500 mg/kg/day (comparable to a dietary level of approximately 5%). Application of a safety factor of 100 to this NOAEL yields an ADI of 25 mg/kg. For a 60-kg individual, the JECFA ADI of 25 mg/kg is equivalent to an intake of 1,500 mg/day. In light of the chemical and

toxicological equivalence of the glycerol esters of gum and wood rosin, the JECFA ADI was selected for use in the current safety assessment of glycerol ester of gum rosin.

The results of the 13-week study of glycerol ester of wood rosin (which form the basis of the JECFA ADI) are consistent with the available toxicity data for glycerol ester of gum rosin. As reported by the NACGM/EACGI (1996), no effects were observed in rats fed glycerol ester of gum rosin at dietary levels up to 1% (equivalent to a dose of approx. 500 mg/kg/day), the highest level tested.

3. Estimated Daily Intake (EDI) of Glycerol Ester of Gum Rosin from Proposed Uses

a). ENVIRON Intake Estimate

ENVIRON conducted a dietary analysis to estimate consumption of glycerol ester of gum rosin associated with its intended uses to adjust density of citrus oils and as a clouding agent in citrus beverages. ENVIRON estimated intake of citrus beverages using data from the 1994-96 USDA Continuing Survey of Food Intake by Individuals (94-96 CSFII) (ARS 1998). ENVIRON assumed a maximum use level of 100 ppm of glycerol ester of gum rosin in citrus beverages consistent with current limits for glycerol ester of wood rosin in citrus beverages. This estimate of intake is exaggerated for two reasons. First, it assumes that all citrus-based beverages, including soft drinks, sport drinks and artificial fruit drinks, would contain glycerol ester of gum rosin. Second, ENVIRON assumed that glycerol ester of gum rosin would be used in all of these beverages at its maximum use level of 100 ppm.

Using these maximum exposure (i.e., "worst case") assumptions, ENVIRON estimates that the intake of glycerol ester of gum rosin would be 43.3 mg/day for the typical user and 75.0 mg/day for the 90th percentile or heavy user (Table 1).

TABLE 1 Estimated Intake of Glycerol Ester of Gum Rosin Associated with its Intended Use in Citrus Beverages		
Age Group	Intake Estimate for Mean User (mg/day)	Intake Estimate for 90th Percentile User (mg/day)
Total Population	43.3	75.0
Females	38.8	62.3
Males	47.5	94.0

b). FDA Intake Estimate for Glycerol Ester of Wood Rosin

In the early 1970s, the FDA conducted its own dietary analysis to estimate consumption of glycerol ester of wood rosin associated with its proposed use as a density adjuster for citrus oils in beverages.[1] The FDA estimated that the maximum daily intake of soft drinks was 1.5 liters and assumed that the consumption of citrus-flavored beverages would not exceed 65% of all soft drink consumption. On this basis, the Agency concluded that a maximum use level of 100 ppm of glycerol ester of wood rosin in citrus-flavored soft drinks would result in an average expected use level in all soft drinks of 65 ppm. The Agency noted in their 1971 evaluation that the average expected use level in all soft drinks of 65 ppm is likely to be highly exaggerated based upon their communications with the Soft Drink Bottlers Association that only 10 to 15% of all beverages sold at that time employed glycerol ester of wood rosin, glycerol ester of tall oil rosin, or brominated vegetable oil (BVO) to adjust the density of citrus oil.

Using FDA's soft drink consumption estimate of 1.5 liters per day, an average use level of wood rosin ester of 65 ppm, and assuming a density approximately equal to water, the intake of glycerol ester of wood rosin is calculated as follows:

[1] Memorandum to Dr. Leo Friedman, Director, Division of Toxicology, through Dr. H. Blumenthal, Chief, Petitions Review Board, Division of Toxicology, Re Glycerol ester of wood rosin as a density adjuster for citrus oils, CFR 121.1084, FAP 85, November 23, 1970; and Additional evaluation of FAP 85. Glycerol ester of wood rosin (GEWR). Fritzsche, Mr. Schaefer, DRPC, January 14, 1971 (Copies provided in Attachment 3).

$$\frac{65}{10^6} x 1.5\ L/day\ x 10^6\ mg/L\ =\ 97.5\ mg/day$$

This EDI of 97.5 mg/day derived using the FDA intake assumptions is consistent with ENVIRON's more rigorous intake analysis based on the most current beverage consumption data available (Attachment 1). The fact that FDA's analysis yields an intake estimate that somewhat exceeds the 90th percentile value derived by ENVIRON of 75 mg/day is consistent with the Agency's position that their analysis resulted in an exaggerated estimate of intake. The difference in the ENVIRON and FDA values is likely due to the generous assumptions by FDA of consumption of glycerol ester in 1.5 liters of beverage/day and the assumption of use of 65 ppm in all soft drinks.

4. General Recognition of Safety of Glycerol Ester of Gum Rosin

The determination of glycerol ester of gum rosin as GRAS for use in citrus-flavored beverages is based in part on the demonstration that the glycerol esters of gum and wood rosin are equivalent toxicologically and chemically. The glycerol ester of wood rosin is already approved by the FDA as a direct additive to adjust the density of citrus oils in the preparation of beverages (21 CFR § 172.735). Glycerol ester of gum rosin has the same intended use and the same intended use level of 100 ppm as the current use limit set by the FDA for glycerol ester of wood rosin in the finished citrus beverage. This same limit will also apply to glycerol ester of gum rosin when used as an ingredient in beverages based on the maximum level to achieve the intended technical effect (36 Fed. Reg. 17360, August 28, 1971). The conclusion of safety is also based upon the long history of use of glycerol ester of gum rosin in chewing gum 21 CFR §172.615.

Safety was established by estimating potential consumer exposure to glycerol ester of gum rosin employing several conservative assumptions regarding the use of this material in citrus beverages. Publicly available animal toxicity studies on glycerol ester of gum rosin and related compounds were then utilized to establish an ADI for glycerol ester of gum rosin in humans. This consumer exposure estimate, or EDI, resulting from the use of glycerol ester of gum rosin as an ingredient in beverages was then compared to the ADI for glycerol ester of

gum rosin. As long as the EDI is less than (or approximates) the ADI, glycerol ester of gum rosin can be considered safe for its intended use. Finally, because this safety evaluation satisfies the common knowledge requirement of a GRAS determination, this intended use can also be determined to be GRAS.

The EDIs for the average and 90th percentile consumer at the maximum intended use level of glycerol ester of gum rosin in citrus beverages were determined to be 43.3 and 75 mg/day, respectively (Attachment 1). Both of these EDIs are below the ADI of 1,500 mg/day (Section I.D.2.(3)). On this basis, the intended use of glycerol ester of gum rosin in citrus beverages can be considered safe at concentrations of up to 100 ppm.

Determination of the safety and GRAS status of glycerol ester of gum rosin as an ingredient in citrus beverages at use levels up to 100 ppm has been made through the deliberations of Vasilios H. Frankos, Ph.D., Principal, ENVIRON International Corporation, Claire Kruger Ph.D., DABT, Principal, ENVIRON International Corporation, and Ronald S. Slesinski Ph.D., DABT, Senior Science Manager, ENVIRON International Corporation. These individuals are qualified by scientific training and experience to evaluate the safety of foods and food ingredients. These experts have carefully reviewed and evaluated the publicly available information summarized in this document, especially regarding the toxicity of glycerol ester of gum rosin, as well as consideration of the potential human exposure to this compound, and have concluded:

> No evidence exists in the available information on glycerol ester of gum rosin that demonstrates, or suggests reasonable grounds to suspect, a hazard to the public health when glycerol ester of gum rosin is used at levels that are now current or that might reasonably be expected from its proposed use.

Other qualified and competent scientists reviewing the same publicly available data would reach the same scientific conclusion. Therefore, glycerol ester of gum rosin, used to adjust the density of citrus oils in beverages and as a clouding agent in citrus beverages, is safe, and is GRAS, at a maximum level of addition of 100 ppm. Because glycerol ester of gum rosin is GRAS for its intended use, it is excluded from the definition of a food additive, and thus may

be marketed for this use without the promulgation of a specific food additive regulation by the FDA.

E. Availability of Information

The data and information that serve as the basis for this GRAS notification will be sent to the FDA upon request or are available for the FDA's review and copying at reasonable times at the office of Claire Kruger, Ph.D., Principal, ENVIRON International Corporation, 4350 North Fairfax Drive, Suite 300, Arlington, VA 22203; Telephone:703-516-2309; Facsimile: 703-516-2393.

II. DESCRIPTION OF THE SUBSTANCE

A. Identity

1. Common and Trade Names

Common names for glycerol ester of gum rosin include: glycerol-modified gum rosin, rosin glycerol ester, glycerol abietate, glyceryl triabietate, or ester gum. The trade name for the glycerol ester of gum rosin, manufactured in Mexico by Resinas Sintéticas, is "Resina 8/RE."

2. Chemical Composition and Identification

Glycerol ester of gum rosin is a chemical mixture that has been assigned a Chemical Abstracts Service ("CAS") Registry number of 8050-31-5. This same CAS number is also used for other chemically-related glycerol rosin esters, e.g., glycerol esters of wood and tall oil rosins.

B. Chemical Formula

Glycerol ester of gum rosin is a chemical mixture that can be represented by the generalized molecular structure shown in Figure 1.

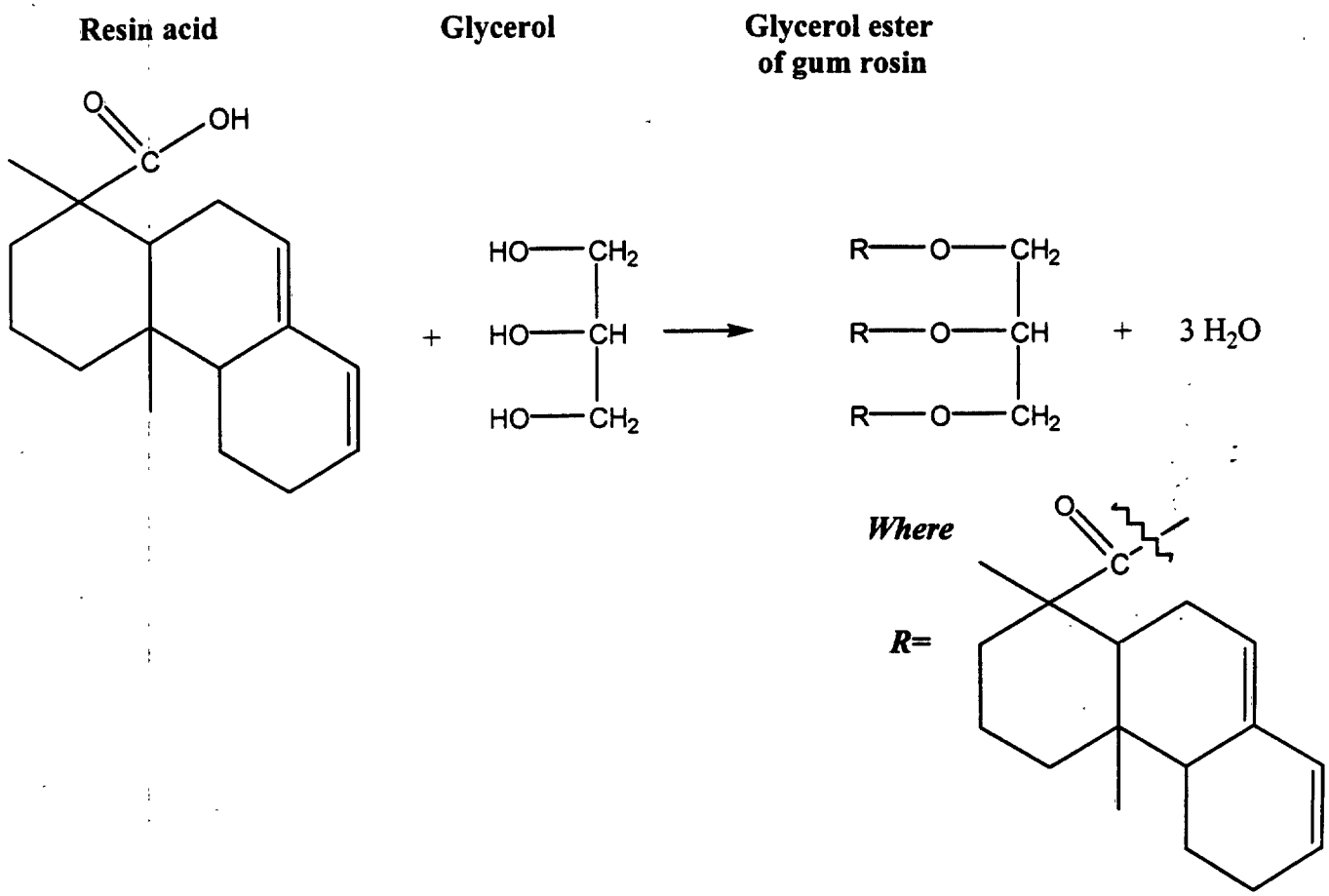
C. Manufacturing Process

Glycerol ester of gum rosin is made from processed gum rosin obtained from pine trees (*Pinus spp.*) that is then esterified with food-grade glycerol. Gum rosin, a natural product derived from the pine tree, consists of a complex mixture of soluble organic compounds. The following sections describe the process by which glycerol ester of gum rosin is manufactured.

1. Production of Gum Rosin

Gum rosin is obtained by extracting oleoresin gum obtained from living pine trees followed by refining by washing, filtration and distillation to separate the rosin from other components in the oleoresin extract. After adding water to the oleoresin, the mixture is heated to 90°C to separate off the unusable portion followed by three washing and filtration steps of the remaining rosin mixture prior to direct

Figure 1
Glycerol Ester of Gum Rosin



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treatment to separate the turpentine and gum rosin components. The gum rosin then undergoes countercurrent steam distillation that further separates the material into light fractions, the desired distilled gum rosin, and heavyweight fractions. This final purification step distinguishes between gum and wood rosin glycerol esters intended for use in beverages in comparison to esters used in chewing gum base according to the specifications in the Food Chemicals Codex (1996). Glycerol ester of wood rosin is purified by countercurrent steam distillation for use in adjusting the density of citrus oils for beverages" while both glycerol esters of gum and wood rosin are purified only by steam stripping for use in chewing gum base. Glycerol ester of gum rosin produced by Resinas Sintéticas as the subject of this GRAS notification is purified by countercurrent steam distillation consistent with requirements for glycerol ester of wood rosin for beverage use (21 CFR §172.735).

2. Production of Glycerol Ester of Gum Rosin (Resina 8/RE)

The distilled gum rosin prepared in the preceding step is pumped into a batch-type reactor and esterified with food-grade U.S.P glycerin under an N_2 atmosphere. The reaction is conducted at 90°C and is allowed to proceed until the desired product specifications are met (Table 2). This ester is then purified by direct countercurrent steam distillation and analyzed for acid number, softening point R&B and color and it is then deodorized. The production process is conducted within an inert nitrogen atmosphere using stainless steel equipment and is confined to an area exclusively for food products.

D. Product Description

1. Physical Properties

Resina 8/RE is a glycerol ester of countercurrent distilled gum rosin with a clear yellow (light amber) appearance. Glycerol ester of gum rosin is soluble in aromatic and aliphatic hydrocarbons, terpenes, esters, ketones, citrus, and most other essential oils. It is insoluble in lower-weight alcohols and water (NAS 1996). The physical properties of Resina 8/RE glycerol ester of gum rosin are summarized in Table 2.

2. Chemical Properties

The main component of glycerol ester of gum rosin (glycerol abietate) is glyceryl triabietate but other products may be formed, mainly as a result of incomplete esterification. Gäfvert et al. (1994) identified five compounds after esterification of abietic acid with glycerol under experimental conditions. These were abietic acid (unreacted), glycerol triabietate, 1,2-glyceryl diabeitate, 1,3-glyceryl diabietate and glyceryl monoabietate (concentrations were not reported). The specifications glycerol ester of gum rosin, and typical properties of Resina 8/RE are presented in Table 2. The identification of glycerol ester of gum rosin is made by comparing its infrared (IR) absorption spectrum against the standard provided in Food Chemicals Codex (NAS 1996).

TABLE 2
Specifications and Typical Properties for Glycerol Ester of Gum Rosin

Specification or Test	Food Chemicals Codex (FCC) Specifications[1]	Resinas Sintéticas Specifications[2]	Typical Properties Based on Two Process Lots of Resina 8/RE
Iron	NS	<50 ppm	<50 ppm
Color	N or paler[3]	N or paler[3]	Complies
Color G'33 (50% Toluene)	NS	7 Max.	6
Acid number	3 - 9	9 Max.	5.9
Softening Point (Ring & Ball)	82 – 90°C	81 - 89°C	85°C
Drop Softening Point (°C)	NS	88 – 96°C	90
Odor	NS	No taste or odor	Good
Taste	NS	No taste or odor	Good
Cleanliness	NS	Pass (no exogenous material)	Pass
Peroxide index	NS	NS	1.1
Limonene solubility	NS	NS	Complete
Specific gravity at 25°C	NS	NS	1.071
Heavy metals	<10 mg/kg	NS	Not detected[4]
Lead	<2 mg/kg	NS	Not detected[4]

NS: not specified
[1]**Food Chemicals Codex (FCC) IV (NAS 1996) specifications for glycerol ester of gum rosin,**
[2]**Internal analysis specification and method.**
[3]**ASTM Standard A-459**
[4]**Based on periodic determinations for lead, arsenic, and cadmium**

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III. USE AND REGULATORY STATUS OF ROSINS

A. Background Information on Rosins

The three types of rosins—gum, wood, and tall oil—are defined by the part of the pine tree from which they are obtained and the method by which they are produced commercially. Gum rosin is obtained by the tapping of the living tree to collect oleoresin (gum) followed by distillation to yield a vitreous resin. Wood rosin is derived by solvent extraction of aged and ground pine stump wood. The trunk of the pine tree is used as the raw material in the production of tall oil rosin (Soltes and Zinkel 1989).

Because all of the rosin starting materials are obtained from the same source (i.e., the pine tree), gum, wood, and tall oil rosins are similar in composition. All three oil rosins consist of free organic acids called resin acids and a neutral fraction; the proportions of these two fractions may vary with the source (e.g., species and geographical location of pine tree) and with the processing conditions (Soltes and Zinkel 1989).

B. Historical Use and Exposure to Rosin

Rosins and oleoresins have an extremely long history of documented use and human exposure. Retsina, a traditional Greek wine flavored by adding pine resin (oleoresin) during fermentation, has been made for more than 3,000 years (Herbst 1995; Redding, 1833). Human consumption of gum rosin can be traced back to Neolithic times (approx. 7,400 years) from analysis of pottery that contained traces of a resinated wine product similar to Retsina wine (McGovern et al. 1997). Gum rosin was originally added to wine in ancient Rome as a preservative to prevent conversion into vinegar as described by Pliny the Elder in the 1st century A.D. (McGovern et al. 1997). Current consumption of wine in Greece was approximately 30 L per wine consumer/year of which 30% has been estimated to represent consumption of Retsina (Messini, 1997; Greek Ministry of Agriculture, 1999b; Greek Ministry of Foreign Affairs, 1999b). Greek law limits the amount of resin in one liter of Retsina to 10 grams of resin per liter (10,000 ppm), although Mihali Xiradakis, a Greek wine authority, determined that the actual use in today's Retsina is averages approximately 1 g/L. Therefore, using the amount of wine consumed represented by Retsina, and the lower than permitted estimate of resin content, the resulting annual human consumption of oleoresin in Greece of approximately 9.0 g/consumer/year.

The oleoresin added to Retsina wine is the unrefined material containing both the rosin and volatile turpentine fractions, and is the starting material from which the rosin derivatives discussed in this report are produced. The distinct flavor imparted by the pine resin derives from the volatile turpentine fraction. The standard of identity for Retsina wine as a "grape table wine fermented or flavored with resin" is established in the U.S. by the Bureau of Alcohol, Tobacco and Firearms (BATF) under 47 CFR §4.21(i).

Glycerol ester of gum rosin was the first rosin ester used for protective coatings and this remains an important commercial use today. Glycerol ester of gum rosin is used in rosin-based printing inks and in adhesive "tackifiers," such as for manufacture of adhesive bandages. Glycerol esters of rosin have also been used in slow-release pharmaceutical preparations to increase digestive transit time (Shao et al. 1993; Pathak and Dorle 1987).

In the United States, rosin use dates back to native and colonial American times (Drew 1989). Uses of rosin included manufacture of rosin soaps, leather dressings, shoe polishes, and in pharmaceuticals such as ointments, astringents, a diuretic and laxative, plasters, veterinary internal remedies and disinfecting compounds (Lawrence 1989). Esters of rosin, including ester gums, are considered one of the most important groups of modified rosins (Wherry 1989). Specific food-related uses of glycerol ester of rosin are described below.

1. Chewing Gum

Glycerol ester of gum (as well as wood and tall oil) rosin is approved for use in chewing gum base (21 CFR §172.615). According to the National Association of Chewing Gum Manufacturers and European Association of the Chewing Gum Industry (NACGM/EACGI 1996), the amount of rosin ester in a chewing gum base may approach 50 percent. The rosin ester contents of two typical bubble gum bases are 13 and 44 percent, and the rosin ester content of a typical stick gum base is 27 percent (Wherry 1989).

Potential intake of glycerol ester of gum rosin associated with its approved use in chewing gum was estimated using data from a Market Facts Consumer Mail Panel survey of chewing gum intake conducted in 1995 (Market Facts 1995) that showed that gum users (based on the total surveyed population) chewed a mean amount of 6.5 grams/day (approximately two sticks of gum). For a heavy (90th percentile) user of gum, the amount of gum chewed was 13.5 grams (approximately 4.5 sticks of gum). Based on these use estimates, potential ingested intakes for glycerol ester of gum rosin in chewing gum were estimated to

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be 325 mg/day for the mean consumer of chewing gum and 675 mg/day for the 90th percentile consumer if chewing gum was swallowed after chewing and 0.16 mg/day for the average consumer of chewing gum and 0.34 mg/day for the 90th percentile consumer if the gum was not swallowed (assuming approximately 0.05% of the rosin ester was extracted from the chewing gum by saliva as reported by NACGM/EACGI in 1996 from results of studies with human volunteers).

2. Other Uses

Other food-related uses of rosin esters include coatings on fruits, can linings and in flexible films such as cellophane and paper. Rosin esters are also used in fragrances (perfumes) to retard rapid evaporation and in cosmetics such as mascara, other eye make-up and depilatories (Wherry 1989).

C. Current FDA Regulatory Status of Rosin Glycerol Esters

Currently, glycerol ester of gum rosin has two approved uses in foods, as a direct food additive in chewing gum base and as an indirect food additive. Glycerol ester of wood rosin is also approved for these two uses, and in addition, glycerol ester of wood rosin is approved for use as a direct food additive as an agent in citrus-based beverages.

1. Approval for Use in Chewing Gum (21 CFR §172.615)

Both glycerol ester of gum rosin and wood rosin are approved as plasticizing agents in chewing gum base (30 Fed. Reg. 747, January 23, 1965; 21 CFR §172.615). As stated previously, glycerol esters of gum or wood rosin are widely used in chewing gums, and especially in bubble gum, whose gum base may contain up to 44 percent (by weight) of rosin ester.

2. Approval for Use as an Indirect Food Additive (21 CFR §178.3870)

Glycerol ester of gum rosin, purified by steam stripping to have an acid number of 3 to 9, a drop-softening point of 79 to 88°C, and a color grade of N or paler, is approved for use as an indirect food additive. It "...may safely be used in the manufacture of articles or components of articles intended for use in producing, manufacturing, packing, processing, preparing, treating, packaging, transporting, or holding food..." (21 CFR §178.3870).

3. Approval of Glycerol Ester of Wood Rosin as a Direct Food Additive (21 CFR §172.735)

Glycerol ester of wood rosin has been approved by the FDA since 1963 as a food additive for use as a direct agent to adjust the density of citrus oils used in the preparation of beverages (28 Fed. Reg. 13488, December 13, 1963). In 1973, the regulation was amended to limit the concentration in the finished beverage to 100 ppm (38 Fed. Reg., January 10, 1973). The FDA established the limit of 100 ppm based on the Agency's original (1963) safety analysis that included a maximum use level of 100 ppm in the finished beverage and the determination that such a limit ensured a 100-fold margin of safety.[2]

Specifications for glycerol ester of wood rosin in beverages are the same as those for both gum and wood glycerol rosin esters used in chewing gum (i.e., an acid number of 3 to 9, a drop-softening point of 88 to 96°C, and a color of N or paler as determined in accordance with Official Naval Stores Standards of the United States). The additive must also be purified by countercurrent steam distillation for use in foods (21 CFR §172.735).

IV. ANALYTICAL METHODOLOGY

Where the assurance of safe use of a substance depends on a limitation on the amount of a substance that a food can contain, an analytical method is generally needed that can quantify the substance in food for the purposes of ensuring that the limit is met. Quantifying the levels of a substance in food requires a practical method that can be readily performed in a properly equipped laboratory by appropriately trained personnel.

The FDA has not specified an analytical method for determining the quantity of glycerol ester of wood rosin in beverages as part of its approval of this substance as a direct food additive (21 CFR §172.735). In reviewing the petition for use of the substance in citrus beverages, the FDA, Division of Foods, stated:

> Analytical method. A method for the determination of the amount of additive in beverages is not available. However, the proposed use of the additive is "self-limiting," and we do not think a method is required at this time.[3]

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[2] Memorandum to Dr. Leo Friedman, Director, Division of Toxicology, through Dr. H. Blumenthal, Chief, Petitions Review Board, Division of Toxicology, Re Glycerol ester of wood rosin as a density adjuster for citrus oils, CFR 121.1084, FAP 85, November 23, 1970 (Attachment 3).

[3] Memorandum to O/C, FA, from M.P. Morris, Division of Food, re: Final evaluation of FAP #85, Use of glyceryl abietate in citrus oils for beverages. February 5, 1963 (Attachment 3).

In a subsequent briefing memorandum from the Food Additive Petitions Control Branch, the Agency similarly stated:

> Division of Food concurs that the additive accomplishes its intended effect, which is to adjust the densities of citrus oils. Because its use is essentially self limiting, no analytical method is required.[4]

Because no analytical method was deemed necessary by the FDA for the approval of the glycerol ester of wood rosin, no analytical method is needed for the glycerol ester of gum rosin, where the intended use is identical to that of the glycerol ester of wood rosin.

V. EQUIVALENCE OF THE GLYCEROL ESTERS OF GUM AND WOOD ROSIN

Equivalence of glycerol esters of wood and gum rosin is demonstrated by: (1) FDA's determination in other regulatory actions that the glycerol esters of gum and wood rosin are comparable chemically and toxicologically; (2) the comparability of source materials; and (3) analytical profiles that show the two materials to be comparable chemically. The glycerol ester of wood rosin is currently approved by the FDA as a food additive for use in adjusting the density of citrus oils in the preparation of beverages at levels of up to 100 ppm in the finished beverage. This approved use for the glycerol ester of wood rosin is identical to the intended use of glycerol ester of gum rosin. In support of the determination of glycerol ester of gum rosin as GRAS for use in citrus-flavored beverages, this chapter establishes the equivalence of the glycerol esters of gum and wood rosin. This equivalence is demonstrated by: (1) FDA's determination in other regulatory actions that the glycerol esters of gum and wood rosin are comparable chemically and toxicologically; (2) the comparability of source materials; and (3) analytical profiles that show the two materials to be comparable chemically.

A. Equivalence as Determined by the FDA

In the early 1960s, the FDA approved a food additive petition (FAP No. 85) submitted by H. Kohnstamm & Co., Inc., to permit the use of glyceryl abietate in beverages (28 Fed. Reg. 4509, May 4, 1963). In response to a comment received by the Hercules, Inc. Powder Company, the FDA revised the proposed regulation to define the approved additive as the glycerol ester of wood rosin (28 Fed. Reg. 13488, December 13, 1963; FAP No. 85, correspondence from H. Kohnstamm & Co., Inc. to Hearing Clerk,

[4] Memorandum to Commissioner of Food and Drugs, Division of Food , re: Food Additive Petition No. 85, April 18, 1963 (Attachment 3).

DHEW, June 3, 1963). However, in subsequent regulatory actions, the FDA has concluded that modified gum and wood rosins are essentially the same, chemically and toxicologically. This position was articulated in communication contained in FAP 5A-1606 concerning the use of rosin esters in chewing gum base.

In 1964, the American Turpentine Farmers Association Cooperative petitioned the FDA to expand the approved uses of esters of wood rosin as plasticizing materials (softeners) in chewing gum bases to include the same esters of gum rosin (FAP No. 5A-1606; correspondence from the ATFAC to FDA, October 19, 1964[5]). The petitioner supported its request on the following basis: (1) the recognized use of esters of gum rosin as a food additive in chewing gum over the past several decades; (2) their history of safe use; and (3) the lack of difference in chemical and physical properties of gum rosin esters and wood rosin esters.

In their final evaluation of the petition, the FDA stated, "Toxicologically, the above mentioned rosin derivatives [glycerol or pentaerythritol esters] from "gum" or "wood" sources are practically similar (FAP No. 269 and 336). The basis of safety rests on our prior evaluation of rosin derivatives as components of chewing gum base." The Agency concluded that the esters of gum rosin are safe and acceptable and that "The basis of safety rests on prior evaluation and identical toxicity similarity between the "gum" and "wood" derived rosin derivatives requested in this petition" (FAP No. 5A-1606; FDA memorandum, December 22, 1964. The amended regulation included the following approved plasticizing materials in chewing gum base: glycerol ester of partially hydrogenated gum or wood rosin, glycerol ester of gum or wood rosin, pentaerythritol ester of partially hydrogenated gum or wood rosin, and pentaerythritol ester of gum or wood rosin (30 Fed. Reg. 747, January 23, 1965).

In another regulatory action, the FDA also based a determination of the safety of an unapproved rosin derivative in chewing gum base on the similarities in physical and chemical properties when used in the same manner and amount as the approved rosin. In FAP No. 9A-2402, the petitioner proposed to include glycerol ester of a tall oil rosin as an alternative to those derived from gum or wood rosin. In their review of the petition, the FDA observed the following:

> Since the proposed glycerol ester of tall oil rosin is essentially identical in IR spectra, with glycerol ester of wood rosin and this leads SC-470 to suggest that both esters would have essentially similar chemical and physical properties, we would, in context with the toxicity data that we

[5] The regulation approving the use of rosin esters in chewing gum was originally contained in 21 CFR §121.1059; the citation was changed in 1977 to 21 CFR §172.615.

have in FAP nos. 269 and 336, concur that both esters would have essentially similar toxicological behavior as well.[6]

Thus, in both FAP Nos. 5A-1606 and 9A-2402, the FDA has concluded that the glycerol esters of gum, wood and tall oil rosin are essentially similar with respect to physical, chemical and toxicological properties.

It is also noteworthy that not all countries recognize a distinction between the glycerol esters of gum and wood rosin. For example, the Mexican General Directorate of Health (copy provided in Attachment 2) approves the use of "glycerol ester, ester gum or glycerol ester of wood rosin" as an ingredient in chewing gum base and non-alcoholic beverages. This agency has no specific regulations that address the glycerol esters of gum or wood rosin separately.

B. Equivalence Based on Source Rosin[7]

As noted previously (Section II.A), rosin is a natural product derived from the pine tree, consisting of a complex mixture of soluble organic compounds. Rosins are produced commercially by one of three methods: (1) tapping of the living tree to collect oleoresin (gum) followed by distillation of the turpentine to yield a vitreous resin called gum rosin; (2) solvent extraction of aged and ground pine stump wood (wood rosin); and (3) extraction of tall oil rosin as a byproduct of the kraft pulping process by which paper is made. The trunk of the pine tree is used as the raw material in the latter process (Soltes and Zinkel 1989).

Gum and wood rosins, which are both obtained from the pine tree, are similar in composition. Both gum and wood rosins consist of free organic acids called resin acids and a neutral fraction; the proportions of these two fractions may vary with the source (species and geographic location of pine tree) and with the processing conditions. In general, both refined wood and gum rosins (the lighter color grades) are composed of approximately 90% resin acids and a 10% neutral fraction (Soltes and Zinkel 1989).

1. Resin Acids

The typical resin acid composition of gum and wood rosins from various countries summarized in Table 3 shows that the composition of typical Mexican gum rosin and U.S. wood rosin are very similar. Comparison of the percent composition of resin acids in gum rosins from three different locations (the U.S.,

[6] FAP No. 9A-2402; Memorandum from Drs. D.K. Misra and J. McLaughlin, Division of Pharmacology and Toxicology, Petitions Review Branch to Petitions Control Branch, May 19, 1969 (Attachment 3).
[7] "Source rosin" is used to denote the unreacted material used to derive glycerol ester of gum (or wood) rosin.

Mexico, and China) suggests that much of the difference between source rosins is attributable to the source of the pine tree itself, and not necessarily whether the rosin comes from the oleoresin of the living tree (gum rosin) or from the stump wood (wood rosin). Gas chromatography results of typical gum and wood rosins using packed column gas chromatographic analysis (Zinkel and Russell 1989) show generally similar peak patterns, attesting to the similarity of these two rosins.

The resin acids found in gum and wood rosins are C_{20} monocarboxylic diterpene resin acids. These resin acids are grouped into one of four classes: abietane, pimarane, isopimarane and labdane. The basic structures of these resin acid classes are shown in Figure 2. Resins acids of the abietane, pimarane and isopimarane series are similar in structure, differing only in the number and arrangement of double bonds or the configuration of the three carbons at the C-13 location (Soltes and Zinkel 1989). In addition, the various resin acids within a group are structurally closely related. For example, see Figure 3 that shows the chemical structures of common resin acids of the abietane group, which comprises approximately 70% of both gum and wood rosins. Wood and gum rosins of comparable color usually have similar resin acid compositions (Soltes and Zinkel 1989).

2. Neutral Fraction

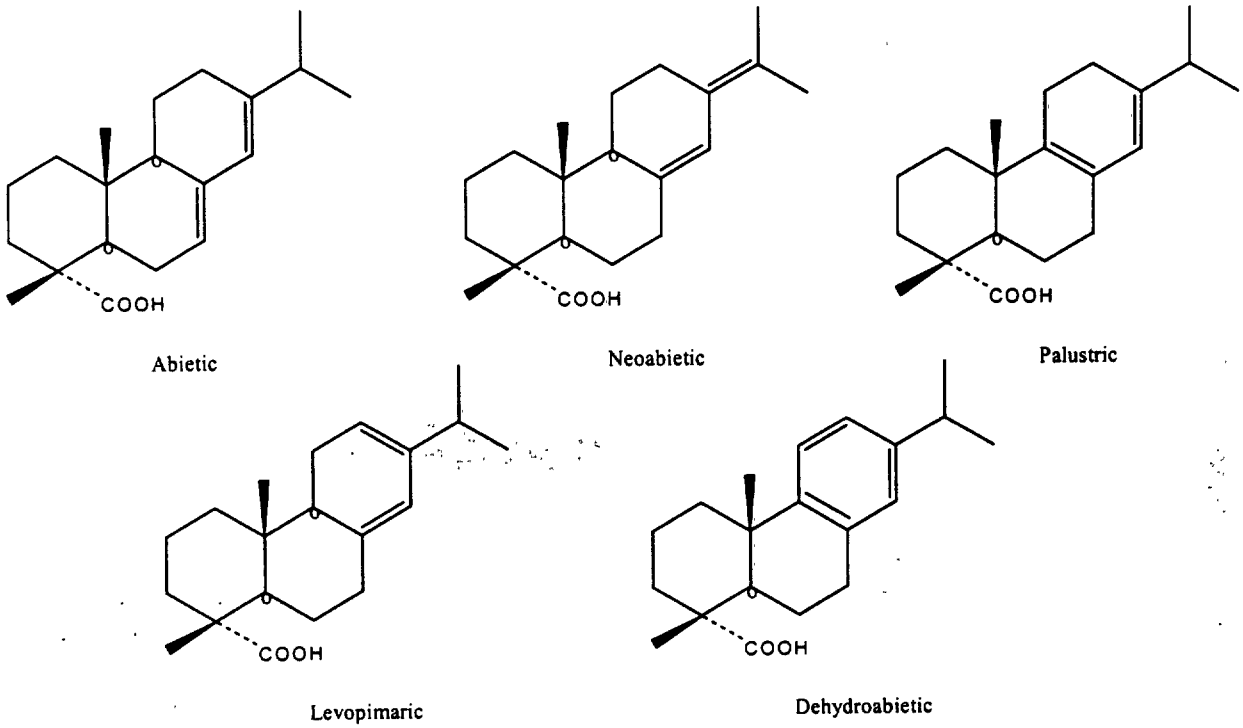
The neutral fraction of gum or wood rosin is composed of esters of resin acids, fatty acids, and unsaponifiables (various other nonacidic compounds). Resin acid esters and fatty acids make up the majority of the neutral fraction (approximately 60%). The composition of the resin acid portion of the esters is similar to the acid fraction. The fatty acid portion is predominantly C_{18} or higher straight-chain acids of various degrees of unsaturation (Soltes and Zinkel 1989). Differences in the neutral fractions of gum and wood rosins are attributable to their source and manufacture. Wood rosin contains small quantities of other organic materials present in the solvent extract of pine stumps and incompletely removed in refining. Gum rosin contains other terpenes and hydrocarbons of generally high molecular weight and low volatility that are not stripped out in turpentine recovery (Soltes and Zinkel 1989).

C. Equivalence Based on Analysis of Rosin Esters

Resinas Sintéticas compared physical/chemical properties, IR and GC spectra of Resina 8/RE (glycerol ester of gum rosin) and ester gum 8BG; Hercules, Inc. glycerol ester of wood rosin product. Physical-chemical properties of typical samples of both products are summarized in Table 4 and these data show that softening point, color, and specific gravity of typical samples of these two products are comparable. Resinas Sintéticas analyzed three samples each of Resina 8/RE and ester gum 8BG by gas chromatography following de-esterification of the samples. The average percent composition for the two products (as an average of three samples) based on area under the peak is summarized in Table 5.

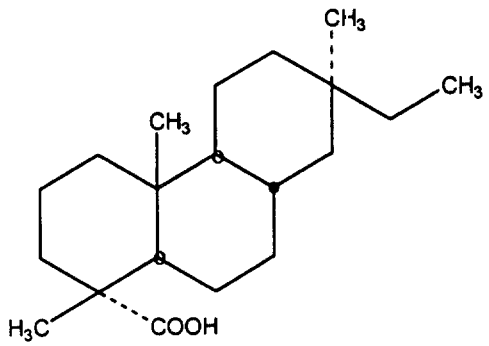
Infrared analyses of Resina 8/RE and ester gum 8BG conducted by Resinas Sintéticas for three samples of each product determined the type of functional groups present as part of the chemical structure of each. This analysis showed that the IR spectra was essentially identical, again indicating the comparability of these two products.

Figure 2
Common Resin Acids of the Abietane Class

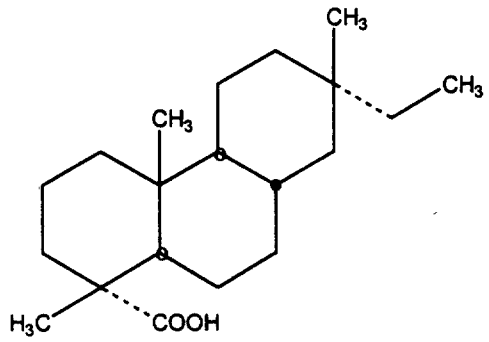


01-7894A\Common Resin Acids

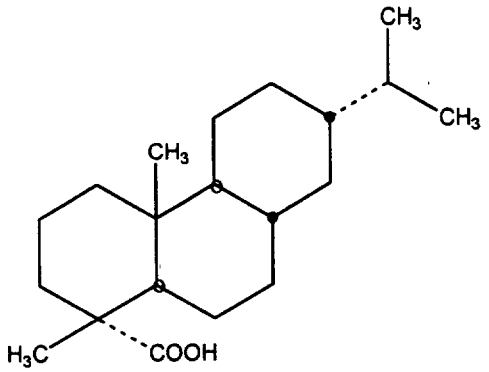
Figure 3
Basic Structures of the Principal Diterpene Resin Acids



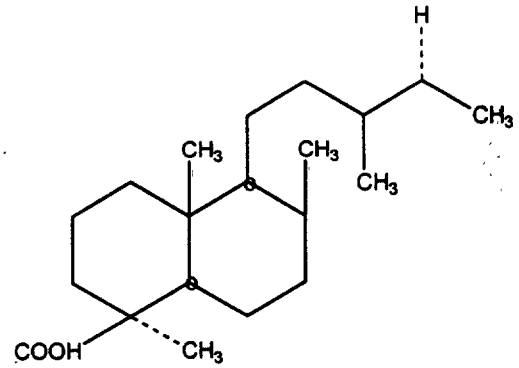
Pimarane



Isopimarane



Abietane



Labdane

01-7894A\Dipertene Resin Acids

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TABLE 3
Typical Percent Composition of the Common Resin Acids in Source Rosins from Various Countries

Resin Acid	Gum Rosins			U.S. Wood Rosin[a]
	U.S.[a]	Mexican[b]	Chinese[b]	
Dihydrodextropimaric	NR	0.3	0.17	NR
Tetrahydropimaric	NR	0.56	0.31	NR
Pimaric	4.5	6.70	11.06	7.1
Sandarcopimaric	1.3	4.16	2.92	2.0
Communic	3.1	NR	NR	NR
Levopimaric	1.8	NR	NR	NR
Palustric	21.2	13.75	13.93	8.2
Isopimaric	17.4	16.02	1.55	15.5
Abietic	23.7	43.14	48.44	50.8
Dehydroabietic	5.3	8.7	11.63	7.9
Neoabietic	19.1	4.96	8.16	4.7

NR = not reported
(a) From Soltes and Zinkel (1989)
(b) From Resinas Sintéticas. Analyses of both Mexican and Chinese gum rosins were conducted in the Resinas Sintéticas laboratory in Morelia, Mexico.

TABLE 4
Comparison of the Typical Physical/Chemical Properties of Resina 8/RE and Ester Gum 8BG[1]

Parameter	Resina 8/RE	Ester Gum 8BG[1]
Acid number	6.3	2.58
Softening point (Ring & Ball) (°C)	84	84.5
Gardner color G'33 (50% toluene)	5	6 (+)
Peroxide index	2.2	17.3
Specific gravity @ 25°C	1.071	1.0884
Specific gravity @ 20°C (50% limonene)	0.9499	0.9492

[1]Hercules, Inc. glycerol ester of wood rosin

TABLE 5[1]
Percent Composition of Resin Acids in Resina 8/RE and Ester Gum 8BG

Peak No.[2]	Resin Acid	Percent of Total in Resina 8/RE	Percent of Total in Ester Gum 8BG
1	Dihydrodextropimaric	0.22%	0.78%
2	Tetrahydropimaric	1.91%	0.56%
3	Pimaric	7.99%	5.17%
4	Sandaracopimaric	9.69%	5.76%
5	Communic	9.14%	10.72%
6	Levopimaric	--	--
7	Palustric	7.87%	5.59%
8	Isopimaric	10.81%	14.97%
9	Abietic	19.56%	19.46%
10	Dehydroabietic	27.01%	34.59%
11	Neoabietic	1.92%	0.55%
	Total	96.12%	98.15%

[1] Values presented in this table are average of three samples
[2] Peak number corresponds to the peaks as identified on GC chromatograms

VI. CORROBORATIVE SAFETY DATA

A. Overview

In order to identify publicly available toxicity data on glycerol ester of gum rosin, ENVIRON conducted a DIALOG search of over 60 databases included in the medicine, toxicology, and food science sets within DIALOG, including MEDLINE® (1966-2002), Toxline® (1965-2002), Cancerlit (1975-2002), Life Sciences Collection (1982-2002), Biosis Previews® (1969-2002), SciSearch® (1974-2002), NTIS (1964-2002), Agricola (1970-2002), Food Science and Technology Abstracts (1969-2002), FOODLINE (1972-2002), and Agris (1974-2002). In addition, the following sources were reviewed:

- Freedom of Information Act (FOIA) requests submitted to the FDA regarding Food Additive Petition (FAP) Nos. 269, 336, 346, 354, 375, and 5A1606.

- National Association of Chewing Gum Manufacturers (NACGM) and European Association of the Chewing Gum Industry (EACGI) (1996).

ENVIRON's online searches of the toxicological and medical literature included the key words "gum rosin," "wood rosin," as well as specific rosin derivatives. Because glycerol esters of gum and wood rosin are essentially equivalent, toxicity data for the wood rosin ester are directly relevant to the glycerol ester of gum rosin. In addition, toxicity studies have been performed on the parent gum and wood rosins; the information from these studies can be used to supplement the more relevant toxicity information on the rosin ester.

B. Pharmacokinetic Data

The Joint FAO/WHO Expert Committee on Food Additives (JECFA 1996a,b) reviewed the results of several unpublished pharmacokinetic studies of glycerol ester of wood rosin submitted in support of the JECFA food additive evaluation of this substance. Overall, these studies show that glycerol ester of wood rosin is stable in the gastrointestinal tract and that only a minor fraction, most likely the monoglycerol ester fraction, undergoes partial hydrolysis.

In the first study summarized by JECFA, Fischer 344 rats (6/sex/group) were fed diets containing ester gum 8BG[8] under two treatment regimes: (1) for 24 hours at dietary concentrations of 7,000 or 28,000 mg/kg diet, or (2) for 10 days at concentrations of 14,000 or 28,000 mg/kg diet (Blair 1995, as cited in JECFA 1996b). After a 24-hour dietary intake, most of the ingested gum was excreted in the feces within 48 to 72 hours. The recovery at the 7,000 mg/kg dietary level was 75% of the amount ingested, whereas recovery at the 28,000 mg/kg level was 95%. After 10 days of intake, recoveries of the gum in the fecal material were about 102% and 91% at the 14,000 and 28,000 mg/kg dietary levels, respectively. These recoveries indicate a low degree of biological conversion or gum resin in the gastrointestinal tract.

In another study, the absorption, metabolism and excretion of [1,3-^{14}C]glycerol ester gum 8BG were studied in Fischer 344 rats (Noker 1996, as cited in JECFA 1996b). Animals received a single dose of about 200 mg/kg labeled compound by gavage after one day (5 male and 5 female rats) or 10 days (5 male rats) of dietary administration of unlabelled compound. In the rats fed ester gum 8BG for one day, most of the dose (>95%) was recovered in the feces or cage rinses. One percent or less of the administered radiolabel was excreted either as carbon dioxide in the expired air or in urine within 120 hours, and only traces (≤0.2% of the total dose) of radiolabel were detected in eight of fifteen carcasses 120 hours after treatment. Similar results were obtained in rats receiving a 10-day dietary administration of unlabelled compound. According to the authors, reverse-phase, high-performance liquid chromatography (HPLC) of fecal extracts indicated that a very small percentage of the administered ^{14}C-gum, probably monoglycerol esters, was hydrolyzed.

In a separate study, Noker (1996, as cited in JECFA 1996b) found 1.6 to 2.9% of the oral dose of ^{14}C-ester gum in the bile and that all of the radioactivity eluted at the approximate void volume of the column, indicating the presence of hydrolyzed components. The amount of radioactivity in the blood at up to 24 hours accounted for ≤0.1% of the administered dose, while the radioactivity in livers collected from these same rats at 24 hours accounted for 0.1 to 0.2% of the administered dose. Together, these results indicate that very low levels of ^{14}C-ester gum were absorbed, and that ^{14}C-ester gum undergoes little hydrolysis or degradation in the gastrointestinal tract.

In vitro (Tsu-Han Lin,1996, as cited in JECFA 1996b), [1,3-^{14}C]glycerol ester gum 8BG incubated with human fecal extract, simulated gastric fluid, or sterile water (as a negative control) for 24 hours showed no repeatable significant changes over time in

[8] Ester gum 8BG is a commercial food-grade preparation of glycerol ester of wood rosin manufactured by Hercules, Inc.

comparisons to the negative control. These results were consistent with the negligible changes observed in rat studies and indicated that glycerol ester gums should be stable in the human gastrointestinal tract.

Based on the above studies, JECFA (1996b) concluded that food-grade glycerol ester of wood rosin is metabolically stable in the gastrointestinal tract and is essentially non-bioavailable following ingestion. Only a minor fraction, most likely the monoglycerol ester fraction, undergoes partial hydrolysis and accounting for the low amount of radioactivity recovered in blood, liver and bile.

C. Mammalian Toxicity Data

1. Repeat-dose Toxicity Data

a) Glycerol Ester of Gum Rosin

In a 1996 "white paper," the NACGM/EACGI summarized the results of two 90-day toxicity studies of glycerol ester of gum rosin. The study results as reported by the NACGM/EACGI (1996) are as follows:

> Two subchronic toxicity studies were conducted in 1989 in which rats were fed glycerol ester of gum rosin at dietary levels of 0.2, 0.5 and 1% for 90 days. The no-effect level in each study was determined to be 1% in the diet. Although supplemental data included in this report were from studies conducted by Industrial Bio-test[9] these data were from studies conducted at another testing laboratory.

b) Glycerol Ester of Wood Rosin

The toxicity of ester gum 8BG, a glycerol ester of wood rosin, was evaluated in a 13-week dietary toxicity study in Fischer 344 rats (Blair 1991, 1992, as cited in JECFA 1996a). Groups of rats (20 per sex) were fed a diet containing ester gum 8BG at dose levels of 0, 625, 1,250 or 2,500 mg/kg/day.[10] Investigators reported no mortality during the study and no changes in appearance, behavior, ophthalmoscopic examinations,

[9] The primary study reports were considered to be confidential business information and therefore were not available for review by ENVIRON.

[10] These dose levels are comparable to dietary levels ranging from approximately 1% to 5%, assuming a rat body weight of 0.35 kg and food consumption rate of 18 g/day (Derelanko and Hollinger 1995).

hematology or clinical chemistry that were attributable to treatment. Slight, but significant, decreases in body-weight gain were noted in female rats at 1,250 and 2,500 mg/kg/day during the last weeks of the study. These minor effects were considered negligible and likely attributable to dietary dilution. There were no gross or histopathologic changes in any organ that were related to treatment. The no-observed-adverse-effect level ("NOAEL") was determined to be 2,500 mg/kg/day.

2. Genotoxicity Data

The genotoxic potential of glycerol ester of wood rosin has been tested in several *in vitro* assays. Glycerol ester of wood rosin was negative for genotoxic activity in assays with *S. typhimurium* strains TA92, TA94, TA98, TA100, TA1535, TA1537 and TA1538 (Ames assay) both with and without microsomal activation using a rat liver S-9 fraction (Ishidate et al. 1984; Jagannath 1988, both as cited in JECFA 1996a). This wood rosin ester was also negative in a chromosome aberration test with Chinese hamster fibroblast cells, in a cytogenetic assay with Chinese hamster ovary cells (with and without microsomal activation), and in a test for unscheduled DNA synthesis with rat primary hepatocyte cells (Ishidate et al. 1984; Murli 1988; Cifone 1988, all as cited in JECFA 1996a).

3. Supplemental Toxicity Data

In the 1960s, Hercules, Inc. sponsored a comprehensive testing program to evaluate the toxicity of approximately 20 rosins and rosin derivatives in both 90-day and two-year toxicity studies. This testing program included the following toxicity tests on gum rosin, wood rosin and the glycerol ester of wood rosin:

<u>Gum rosin:</u>

- 90-day oral toxicity study in the rat at dietary levels ranging from 0.01 to 5%;
- 2-year oral toxicity study in the rat at dietary levels of 0.05 and 1%; and
- 2-year oral toxicity study in the dog at dietary levels of 0.05 and 1%.

Wood rosin:

- 90-day oral toxicity study in the rat at dietary levels ranging from 0.01 to 5%;
- 2-year oral toxicity study in the rat at dietary levels ranging from 0.05 to 1%; and
- 2-year oral toxicity study in the dog at dietary levels of 0.05 and 1%.

Glycerol ester of wood rosin (i.e., ester gum 8D):

- 90-day oral toxicity study in the rat at dietary levels ranging from 0.01 to 5%.

The experimental animal studies of these rosins and rosin derivatives were conducted for Hercules, Inc. by Industrial Bio-Test Laboratories ("IBT"). The FDA disqualified some IBT studies as a result of an investigation during the 1970s that revealed improper practices in the conduct of some studies by this laboratory. There is no indication that the IBT studies of the rosins were in any way compromised and the data from the IBT studies are consistent with the data from other toxicity studies on wood rosin. Because ENVIRON could not establish that the studies had undergone independent validation, however, they were not relied upon as the basis for the safety evaluation of glycerol ester of gum rosin, but rather were employed as confirmatory evidence to supplement the data from other studies.

Brief summaries of the toxicity studies listed above are presented below. In addition, the available acute toxicity data for wood rosin considered by JECFA are also summarized.

a) Gum Rosin

The toxicity of gum rosin was evaluated in 90-day and two-year oral toxicity studies in the rat and in a two-year oral toxicity study in the dog.

In a 90-day study, Sprague-Dawley rats (10/sex/group) were fed a diet containing 0, 0.01, 0.05, 0.2, 1.0, or 5.0% gum rosin for 90 days (Kay 1960a). At dietary levels up to 1%, there was no mortality and no treatment-related effects on hematology, urinalysis, or gross or histopathology. At the 1% dietary level, body weights and food consumption were depressed, particularly during the first few weeks of the study, consistent with palatability problems. Differences in certain organ weights in the 1% dose group were difficult to interpret because of

depressed body weight, but differences in organ weights were not accompanied by histopathological changes.

In a two-year toxicity study with the same material, Sprague-Dawley rats (30/sex/group) were fed diets containing 0, 0.05, or 1% gum rosin (Kohn 1962a). At the 1% dietary level, body weights were significantly lower than controls throughout the study, which was attributed to feed palatability problems. There were no significant differences in survival, hematology, urinalysis, gross or histopathology, or tumor incidence. Some sporadic differences in organ to body weight ratios were noted, but in the absence of any accompanying pathology, were not considered to be of toxicological significance.

In the two-year dog study, animals (3/sex/group) were fed diets containing 0, 0.05 or 1.0% gum rosin (Kohn 1962b). The test article had no effect on growth, food consumption, survival, hematology, urinalysis, liver or kidney function, organ weights, or gross or histopathology. The NOAEL in this study was 1.0% in the diet .

b) Wood Rosin

The acute toxicity of pale wood rosin was examined in several rodent species. Oral LD_{50} values for the mouse, rat, and guinea pig were reported to be 4,100, 8,400, and 4,100 mg/kg, respectively (Hercules, Inc. 1974, as cited in JECFA 1996a).

In the 90-day study, Sprague-Dawley rats (10/sex/dose) were fed a diet containing 0, 0.01, 0.05, 0.2, or 1.0% N-wood rosin (equivalent to 0, 6.4, 36, 119, or 674 mg/kg/day, respectively) for 90 days (Kay 1960b; JECFA 1996a). A 5% dose group was also included, but was discontinued early in the study because all animals in this group died during the first eight days of the treatment period attributed to the very low food consumption during the first week of the study due to palatability problems. At dietary levels up to 1%, there was no mortality and no significant differences in hematology or urinalysis. Body weights and food consumption were significantly reduced in male and female rats at the 1.0% dose level throughout the study, suggesting palatability as the principal reason for weight depression in this group. Liver to body weight and brain to body weight ratios for male and female rats were significantly

increased at the 1.0% dietary level. No gross or histopathological lesions related to wood rosin were observed in any of the treated animals.

The toxicity of wood rosin was also examined in two-year studies in the rat and beagle dog. Sprague-Dawley rats (30/sex/group) were fed dietary levels of 0, 0.05, 0.2 or 1% rosin for 24 months (equivalent to 0, 24, 88 or 434 mg/kg/day) (Kohn 1962c; JECFA 1996a). Five animals from each group were sacrificed at 12 months for gross and histopathologic examination. At the 1% level, body weights were significantly lower than controls at both 12 and 24 months. Decreased body weights were again attributable to feed palatability problems and resulting reduced food consumption. There were no significant differences in mortality, hematology, urinalysis, gross or histopathology, or tumor incidence. Some sporadic differences in organ to body weight ratios were noted, but were not considered to be of toxicological significance.

In the two-year dog study, animals (3/sex/group) were fed diets containing 0, 0.05 or 1.0% N-wood rosin (equivalent to 0, 14 or 260 mg/kg/day) (Kohn 1962d; JECFA 1996a). Food consumption appeared to be somewhat decreased in the high-dose males, consistent with feed palatability problems; however, a clear treatment-related effect on body weight gain was not discernible. The study authors concluded that the NOAEL in this study was 1.0%.

c) Glycerol Ester of Wood Rosin

In a 90-day toxicity study, Sprague-Dawley rats were fed ester gum 8D[11] at dietary levels of 0, 0.01, 0.05, 0.2, 1.0, or 5.0% (equivalent to 0, 6, 31, 120, 630 or 2,660 mg/kg/day (Kay 1960c; JECFA 1996a). No mortality occurred among treated or control animals, and there were no significant effects on body weight, food intake, hematology, urinalysis, or gross or histopathology at dietary levels up to and including 1.0%. At the 5.0% dietary level, food consumption was slightly lower than controls but the glycerol ester of wood rosin had remarkably lower toxicity than the non-esterified product that cause mortality due to low dietary intake at this dose level. The 1.0% treatment level (630 mg/kg/day) was the NOAEL.

d) Discussion

In general, the toxicity of gum and wood rosins appears to be similar. Both rosins depressed body weight gain and food consumption at levels of 1% in the diet in the rat, but not in the dog. This weight loss, which was severe enough at the 5% dietary level to cause mortality in all rats, was consistent with a diet that was not palatable to the animals. These palatability problems at the highest dietary levels tested in the IBT studies (1% and 5%) complicate interpretation of the findings. However, neither gum or wood rosin caused any systemic toxicity or histopathological changes in rats or dogs.

Esterification appears to reduce the toxicity of these rosins (or at least minimize palatability problems). In the 90-day IBT study of glycerol ester of wood rosin, no effects were observed at dietary levels of up to 1%, and no mortality was observed at the 5% level. In response to FAP 85 requesting approval for the use of glycerol ester of wood rosin as a density adjuster for citrus oils, the FDA stated, "previous evaluations (FAP 269 and 334) of the safety of a large number of rosins and modified rosins have indicated that the esterification does not cause an increase in the toxicity of a basic rosin..."[12]

The findings in the IBT studies are consistent with the conclusions from the more recent studies at other laboratories on the commercial food-grade product, i.e., that rosin and the glycerol esters of rosin, regardless of whether it is gum or wood, produces no systemic toxicity in experimental animals. Effects are principally limited to reduced body weight gain, which may be secondary to problems with the palatability of a diet containing high levels of the test material.

4. Dermal Reactions to Rosin and Glycerol Esters of Rosin

Numerous patch testing studies have shown that rosin, glycerol esters of rosin and various constituents in rosin produce dermal contact sensitization in animals (JECFA 1966a; Hausen and Mohnert 1989; Shao et al. 1993; Gäfvert et al. 1994; Hausen et al. 1989; and Färm 1997) as well as in humans (JECFA 1996a; Hausen and Mohnert 1989; Shao et al. 1993; Gäfvert et al. 1994; Hausen et al. 1989; and Färm 1997). Induction of

[11] Ester gum 8D is a glycerol ester of wood rosin manufactured by Hercules, Inc.

dermal sensitization reactions requires occluded skin contact with high exposure concentrations (10 and 20% in animal and human tests, respectively) and extended exposure times (standard procedure is 24 hours covered with a patch). There is no evidence that either wood rosin or gum rosins are potential sensitizers following oral ingestion of rosin glycerol esters in beverages. There was no indication of sensitization potential via the oral route following ingestion of glycerol esters in 90 day or 2 year feeding studies in rats or dogs fed diets containing up to 1 to 5% glycerol esters of gum or wood rosin.

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ATTACHMENT 1

PROJECTED INTAKES OF GLYCEROL ESTER OF GUM ROSIN FROM THE INTENDED USE IN CITRUS BEVERAGES

ATTACHMENT 1

PROJECTED INTAKES OF GLYCEROL ESTER OF GUM ROSIN FROM THE INTENDED USE IN CITRUS BEVERAGES

A. Introduction

This attachment summarizes ENVIRON International Corporation's analyses of the projected intakes of glycerol ester of gum rosin associated with its use in citrus beverages.

B. Overview of the 94-96 CSFII

ENVIRON intake estimates were based on data contained in the 1994-96 Continuing Surveys of Food Intakes by Individuals (94-96 CSFII) (ARS 1998). The 94-96 CSFII is the most recent complete data set from national food consumption surveys conducted by the U.S. Department of Agriculture (USDA). The 94-96 CSFII was a three-year survey in which data were collected from a stratified area probability sample of individuals residing in households in the U.S. Households represented a cross-section of the population of the 50 states and the District of Columbia.

The 94-96 CSFII obtained individual food consumption data for two non-consecutive days; the second day was three to ten days after the first. Each day's intake was collected by trained interviewers using a 24-hour recall of foods and beverages consumed the previous day.

The 94-96 CSFII was not designed to be self-weighting. Weights were developed by USDA to adjust for over- and under-representation of certain population subgroups in the unweighted sample due to the sample design (children, minority respondents, and low-income households were oversampled), non-response, and unequal interviewing across seasons and days of the week.

Individuals were surveyed in all four seasons and on all days of the week. In addition to information on food consumption, the survey collected extensive physiological and demographic data such as sex, age, self-reported height and weight, ethnic group, pregnancy and lactation status, household income, and urbanization category of the household. This information permits assessment of food consumption by specific population groups of interest.

Food intake was recorded by time of day and by eating occasion (breakfast, brunch, lunch, dinner, supper, snack, and extended eating occasion) as defined by the respondent. Separate entries were made in the survey database for each food consumed according to a system developed by USDA. There are approximately 6,000 separate 7-digit food codes in the database, representing nine major food groups. Quantities of foods and beverages consumed were

recorded as reported, in household measures, weights, dimensions or common units (e.g., slice, piece). All quantities were converted to grams by USDA.

The survey also identified the source of food, i.e., eaten at home, taken from home and eaten away from home, or never brought into the home. When foods were obtained and eaten away from home, the location was specified as restaurant, cafeteria, school, day-care center, community feeding program, vending machine, store, or someone else's home. Foods obtained from fast-food restaurants were identified as eaten at home or away from home.

Foods that were consumed together were coded to indicate the type of grouping, such as sandwiches, salads or breakfast cereal dishes (e.g., cereal, milk, sugar, fruit). This facilitates analyses of intakes from such combination dishes.

Approximately 15,000 individuals were interviewed in the three years of the survey. This resulted in 29,710 person days of consumption for all individuals, 14,518 person days for females, and 15,192 person days for males.

C. Intake Estimates for Glycerol Ester of Gum Rosin

ENVIRON estimated the projected intake of glycerol ester of gum rosin by assuming that this material was present in all citrus beverages at a concentration of 100 ppm. The food codes included in this analysis are identified in Table A.

TABLE A Citrus Beverages from the 94-96 CSFII Assumed to Contain Glycerol Ester of Gum Rosin	
Food Code	**Food Name**
92431000	Carbonated Juice Drink, NS as to Type of Juice
92432000	Carbonated Citrus Juice Drink
92510910	Grapefruit Juice Drink
92511000	Lemonade, Frozen Concentrate, Not Reconstituted
92511010	Lemonade
92511020	Lemon-Limeade
92511110	Limeade
92511190	Orange Juice Drink
92511200	Orange-Mango Juice Drink
92511220	Orange Drink (include Orange Ade, Yaba Daba Dew)
92511230	Orange-Apricot Juice Drink
92511240	Orange-Lemon Drink
92511250	Citrus Fruit Juice Drink (Incl. 5-Alive)
92511260	Orange-Cranberry Juice Drink
92511270	Orange-Peach Juice Drink
92511280	Orange-Grape-Banana Juice Drink
92511350	Orange-Raspberry Juice Drink
92520910	Lemonade, Low Calorie
92530410	Citrus Drink w/Vitamin C Added
92530810	Grapefruit Juice Drink w/Vitamin C Added
92530910	Lemonade w/Vitamin C Added
92531010	Orange Drink & Orangeade w/Vitamin C Added
92531020	Orange Breakfast Drink, From Frozen Concentrate
92531030	Orange Breakfast Drink
92531110	Pineapple-Grapefruit Juice Drink w/Vit C Added
92531120	Pineapple-Orange Juice Drink w/Vitamin C Added
92531150	Pineapple-Orange-Grapefruit Juice Drink w/Vitamin C
92541020	Lemonade-Flavored Drink, From Powder, w/Sugar & Vit C
92541040	Lemonade-Flavored Drink, From Powder, Lo Cal, w/Vit C
92550300	Grapefruit Juice Drink, Low Calorie, w/Vitamin C
92551600	Citrus Juice Drink, Low Calorie
92552050	Orange Breakfast Drink, Low Calorie
92552100	Orange-Cranberry Juice Drink, Low Cal, w/Vit C Added
92570100	Fluid Replacement, Electrolyte Solution (Incl. Pedialyte)
92570500	Fluid Replacement, 5% Glucose in Water
92582100	Citrus Juice Drink, Calcium Fortified
92582110	Orange Breakfast Drink, Calcium Fortified

The resulting intake estimates associated with use in citrus beverages for the average and 90th percentile consumer of citrus beverages and intakes expressed on a per capita basis are shown in Table B.

TABLE B.
Estimated Intake of Glycerol Ester of Gum Rosin Associated with its Intended Use in Citrus Beverages

Age Group	Eating Occasion	Intake for Mean User (mg/day)	Intake for 90th Percentile User (mg/day)	Mean Intake per Capita (mg/day)	% Consumer Days
Total Population	per day	43.3	75.0	2.5	5.89
Females	per day	38.8	62.3	2.2	5.69
Males	per day	47.5	94.0	2.9	6.09

ATTACHMENT 2

COPY OF PERSONAL COMMUNICATION ON REGULATORY STATUS OF GLYCEROL ESTER OF GUM ROSIN IN MEXICO: MEXICAN GENERAL DIRECTORATE OF HEALTH

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ENVIRON

FAP 2T2715

OFFICE OF THE COMMISSIONER, FOOD & DRUG ADMINISTRATION

GLYCEROL ESTER OF WOOD ROSIN - AMEND 121.1084; ADJUSTER OF CITRUS BEVERAGES

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VOLUME 1 OF 1

BF

November 23, 1970

Glycerol ester of wood rosin as a density adjuster for citrus oils
CFR 121.1084; FAP 85)

XX

TO: Dr. Leo Friedman, Director
Division of Toxicology (DF-140)

THRU: Dr. H. Blumenthal, Chief
Petitions Review Branch (DF-143)
Division of Toxicology

CFR 121.1084 states that the glycerol ester of wood rosin may be used to adjust the density of citrus oils used in the preparation of beverages. There are no limits on the amounts to be used. The original Notice of Filing of Petition (January 26, 1963; 28 FR 727), indicated a proposed use level at 60 ppm in still and carbonated beverages, alcoholic beverages, and fruit drinks. Division of Food, in a memo dated 2-5-63, (FAP 85) indicated a maximum use level of 100 ppm.

Data relating to the safety of the glycerol ester of wood rosin and the wood rosin were submitted with FAP 269 and 336. The no effect levels were set at 1% (90 day study) and 0.2% (2 yr study) respectively (see memo of K. P. Mera and J. McLaughlin, FAP 269 and 336). These levels would not provide sufficient margin of safety for the proposed use of the additive. The memo of April 8, 1968 contains an error relating to use levels. I have re-evaluated the data submitted in these petitions and consider the 'no-effect' level in a 90-day study in rats with glycerol ester of wood rosin to be 5%, and a two-year study in rats and dogs with the wood rosin to be 1%.

In the case of glycerol ester of wood rosin, groups each of 20 rats equally divided by sex were maintained on diets containing 0.01, 0.05, 0.2, 1 and 5% of the glycerol ester of wood rosin ([redacted]) and the usual observations were made with respect to growth, food consumption, incidence of mortality, status of hematopoietic and urinary system. At the conclusion of test, pathological studies, including microscopic examination of tissues and organs of animals from each of the five test groups were made. The original evaluation of this petition indicated that there was a depressant effect on growth and food intake at the 5%, and this appears to be the only adverse effect noted. However, re-examination of the data indicates that at the 5% level, weight gain in both male and female rats, was equal to a slightly better than controls, although food consumption in test animals at this level was slightly less than controls. This effect was considered to be due to or slightly higher oil content in the test diet. There was

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some variation in absolute organ and relative organ weights, but none of these effects appeared to be dose related. The 'no-effect' level of the [redacted] in this study, should be considered 5% of the diet.

In the case of the wood rosin ([redacted]), two 2-year studies were reported, one with rats, the other with dogs. In the case of rats, 5 groups each of 60 rats (equally divided by sex), were maintained on diets containing 0 (two test groups), or 0.05, 0.2 and 1% of the test material. The usual observations were made with respect to growth, food consumption, mortality, incidence of tumors, status of hematopoietic and urinary systems. An interim gross and microscopic pathologic study was carried out at 12 months, and at the termination of the study all surviving rats were autopsied, and selected rats from each group, subjected to complete histopathologic studies. In the original evaluation of this study it was stated that at the 1% dietary level growth, food consumption and utilization showed a 'lag effect.' Other effects noted at the 1% level were related to organ weights and considered of decreased weight of spleen in females, of heart in males and females, and an increase in weight of liver (males and females), and gonads and brain (males). No other adverse effects were noted. The mean body weight gains on test males (1% level) was 402g compared to controls, 414 and 422g. In the case of the test females (1% level), mean body weight gain was 205g, compared to controls, 220 and 236g. In the case of female rats, the decreased weight may be due to slightly decreased food intake (5720g for week 1-52, as compared to control intake of 6645 or 6101g). The variation in organ weight was most marked at the 1% level and although the organ body weight ratios of liver at the 1% level (females), and gonads (male) showed some differences from control, the organ/brain weight ratios were comparable to controls and showed no significant differences when compared with controls. Further, none of these minor weight variations in the organs were related to any histologic changes, nor was there any compound related trend.

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In the case of the dog study, groups each of 6 dogs (3 of each sex), were maintained on diets containing 0.05 and 1% of [redacted], and one group of 12 dogs (6 of each sex) was maintained for controls. During the test period growth, food consumption, incidence of mortality and reactions were studies. Liver and kidney tests, and a complete study of blood and urine was also made. At termination of the study gross and microscopic pathology was carried out. In the previous evaluation the only effects reported at the 1% level were related to organ weight ratios, specifically to slight increases in liver and kidney, and a decrease in brain weight when compared to respective controls. However, although a consideration of the mean values may indicate slight differences, consideration of the standard deviations reported, show that there is sufficient variation to indicate that this is not a significant problem. Based on these considerations, the no-effect level for wood rosin in a two-year feeding study with rats and dogs is 1%.

a) long term (lifetime) feeding of glycerol ester of wood rosin - no effect [illegible]
2 year study (dogs + rats) with wood rosin - no effect 1%

Since previous evaluations (FAP 269 and 336) of the safety of a large number of rosins and modified rosins have indicated that the esterification does not cause an increase in the toxicity of a basic rosin, the studies with wood rosins provide a basis for accepting a "no-effect" level of 1% for the glycerol ester of wood rosin.

On the basis of a 100-fold margin of safety, this would equate to 100 ppm of the diet. It is estimated that use in packaging would account for 5 ppm. Since the maximum estimated intake of soft drink is 1.5 liters, this would permit a use level of approximately 65 ppm. The petitioner (FAP 8S, Jan. 22, 1960), stated that the, "Range of Glycerol Abietate in the finished beverage is 30 to 60 ppm. However, we request a tolerance up to 100 ppm." Presumably, the latter request is to obviate problems that might arise due to inherent error in metering equipment during the addition of the additive to the soft drink. Since DF, in a memo dated February 5, 1963, indicated that ordinarily the expected use level will 60 ppm, there would be no objection to permitting a maximum use level of 100 ppm. However, since it is possible that the glycerol ester of wood rosins is used at much higher levels than in the proposal (a recent FAP, relating to glycerol ester of tall oil, indicated levels for a similar purpose could range from 160-320 ppm), it is recommended that the regulation be amended to include an upper limit on the level of use of glycerol ester of wood rosin, i.e., 100 ppm. If the petitioner requests use at higher levels, because of the high intake of the products containing this additive, we recommend the petitioner submit reproduction studies and adequate toxicological studies at suitable dietary levels.

FAP 269 336

sufficient for use of 65 ppm in soft drinks

Recommendations:

(1) Based on a 'no-effect' level of 1%, it is proposed that CFR 121.1004(b) be modified to read "It is used to adjust the density of citrus oils used in preparation of beverages in an amount not to exceed 100 ppm of the finished product."

(2) DFCT should concur that a maximum permitted use level of 100 ppm of glycerol ester of wood rosin in soft drink, would result in an average expected use level in all soft drinks at 65 ppm.

(3) If higher use levels are requested then adequate toxicological studies including reproduction studies, at a suitable dietary level be submitted.

S. I. Shibko, Ph.D.
DT/PRS (DF-148)

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[redacted]

cc: [redacted]

SIShibko:dps 11-23-70

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ATTACHMENT 3

COPIES OF FDA MEMORANDA ON REGULATORY STATUS OF GLYCEROL ESTERS OF GUM ROSIN CITED IN DOCUMENT

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FAP 2T2715

OFFICE OF THE COMMISSIONER, FOOD & DRUG ADMINISTRATION

GLYCEROL ESTER OF WOOD POSIN - AMEND 121.1084: ADJUSTER OF CITRUS BEVERAGES

000056

VOLUME 1 OF 1

BF 2

November 23, 1970

Glycerol ester of wood rosin as a density adjuster for citrus oils
CFR 121.1084; FAP 85)

XX
TO: Dr. Leo Friedman, Director
Division of Toxicology (DF-140)

THRU: Dr. H. Blumenthal, Chief
Petitions Review Branch (DF-143)
Division of Toxicology

CFR 121.1084 states that the glycerol ester of wood rosin may be used to adjust the density of citrus oils used in the preparation of beverages. There are no limits on the amounts to be used. The original Notice of Filing of Petition (January 26, 1963; 28 FR 727), indicated a proposed use level at 60 ppm in still and carbonated beverages, alcoholic beverages, and fruit drinks. Division of Food, in a memo dated 2-5-63, (FAP 85) indicated a maximum use level of 100 ppm.

Data relating to the safety of the glycerol ester of wood rosin and the wood rosin were submitted with FAP 269 and 336. The no effect levels were set at 1% (90 day study) and 0.2% (2 yr study) respectively (see memo of K. P. Misra and J. McLaughlin, FAP 269 and 336). These levels would not provide sufficient margin of safety for the proposed use of the additive. The memo of April 3, 1968 contains an error relating to use levels. I have re-evaluated the data submitted in these petitions and consider the 'no-effect' level in a 90-day study in rats with glycerol ester of wood rosin to be 5%, and a two-year study in rats and dogs with the wood rosin to be 1%.

In the case of glycerol ester of wood rosin, groups each of 20 rats equally divided by sex were maintained on diets containing 0.01, 0.05, 0.2, 1 and 5% of the glycerol ester of wood rosin [redacted]) and the usual observations were made with respect to growth, food consumption, incidence of mortality, status of hematopoietic and urinary system. At the conclusion of test, pathological studies, including microscopic examination of tissues and organs of animals from each of the five test groups were made. The original evaluation of this petition indicated that there was a depressant effect on growth and food intake at the 5%, and this appears to be the only adverse effect noted. However, re-examination of the data indicates that at the 5% level, weight gain in both male and female rats, was equal to a slightly better than controls, although food consumption in test animals at this level was slightly less than controls. This effect was considered to be due to or slightly higher oil content in the test diet. There was

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[redacted]

Best available copy.

some variation in absolute organ and relative organ weights, but none of these effects appeared to be dose related. The 'no-effect' level of the [redacted] in this study, should be considered 5% of the diet.

In the case of the wood rosin ([redacted]), two 2-year studies were reported, one with rats, the other with dogs. In the case of rats, 5 groups each of 60 rats (equally divided by sex), were maintained on diets containing 0 (two test groups), or 0.05, 0.2 and 1% of the test material. The usual observations were made with respect to growth, food consumption, mortality, incidence of tumors, status of hematopoietic and urinary systems. An interim gross and microscopic pathologic study was carried out at 12 months, and at the termination of the study all surviving rats were autopsied, and selected rats from each group, subjected to complete histopathologic studies. In the original evaluation of this study it was stated that at the 1% dietary level growth, food consumption and utilization showed a 'lag effect.' Other effects noted at the 1% level were related to organ weights and considered of decreased weight of spleen in females, of heart in males and females, and an increase in weight of liver (males and females), and gonads and brain (males). No other adverse effects were noted. The mean body weight gains on test males (1% level) was 402g compared to controls, 414 and 422g. In the case of the test females (1% level), mean body weight gain was 205g, compared to controls, 236 and 256g. In the case of female rats, the decreased weight may be due to slightly decreased food intake (5720g for week 1-52, as compared to control intake of 6443 or 6101g). The variation in organ weight was most marked at the 1% level and although the organ body weight ratios of liver at the 1% level (females), and gonads (male) showed some differences from control, the organ/brain weight ratios were comparable to controls and showed no significant differences when compared with controls. Further, none of these minor weight variations in the organs were related to any histologic changes, nor was there any compound related trend.

In the case of the dog study, groups each of 6 dogs (3 of each sex), were maintained on diets containing 0.05 and 1% of [redacted], and one group of 12 dogs (6 of each sex) was maintained for controls. During the test period growth, food consumption, incidence of mortality and reactions were studies. Liver and kidney tests, and a complete study of blood and urine was also made. At termination of the study gross and microscopic pathology was carried out. In the previous evaluation the only effects reported at the 1% level were related to organ weight ratios, specifically to slight increases in liver and kidney, and a decrease in brain weight when compared to respective controls. However, although a consideration of the mean values may indicate slight differences, consideration of the standard deviations reported, show that there is sufficient variation to indicate that this is not a significant problem. Based on these considerations, the no-effect level for wood rosin in a two-year feeding study with rats and dogs is 1%.

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[redacted]

9) long [illegible] - no effect 5%
2 year [illegible] (dog + rat) [illegible] wood rosin - no effect 1%

Since previous evaluations (FAP 369 and 396) of the safety of a large number of rosins and modified rosins have indicated that the esterification does not cause an increase in the toxicity of a basic rosin, the studies with wood rosins provide a basis for accepting a "no-effect" level of 1% for the glycerol ester of wood rosin.

On the basis of a 100-fold margin of safety, this would equate to 100 ppm of the diet. It is estimated that use in packaging would account for 5 ppm. Since the maximum estimated intake of soft drink is 1.5 liters, this would permit a use level of approximately 65 ppm. The petitioner (FAP 85, Jan. 22, 1960), stated that the, "Range of Glycerol Abietate in the finished beverage is 30 to 60 ppm. However, we request a tolerance of up to 100 ppm." Presumably, the latter request is to obviate problems that might arise due to inherent error in metering equipment during the addition of the additive to the soft drink. Since DF, in a memo dated February 5, 1963, indicated that ordinarily the expected use level will be 60 ppm, there would be no objection to permitting a maximum use level of 100 ppm. However, since it is possible that the glycerol ester of wood rosins is used at much higher levels than in the proposal (a recent FAP, relating to glycerol ester of tall oil, indicated levels for a similar purpose could range from 160-320 ppm), it is recommended that the regulation be amended to include an upper limit on the level of use of glycerol ester of wood rosin, i.e., 100 ppm. If the petitioner requests use at higher levels, because of the high intake of the products containing this additive, we recommend the petitioner submit reproduction studies and adequate toxicological studies at suitable dietary levels.

Recommendations:

(1) Based on a 'no-effect' level of 1%, it is proposed that CFR 121.1004(b) be modified to read "It is used to adjust the density of citrus oils used in preparation of beverages in an amount not to exceed 100 ppm of the finished product."

(2) DFCT should concur that a maximum permitted use level of 100 ppm of glycerol ester of wood rosin in soft drink, would result in an average expected use level in all soft drinks at 65 ppm.

(3) If higher use levels are requested then adequate toxicological studies including reproduction studies, at a suitable dietary level be submitted.

S. I. Shibko, Ph.D.
DT/PRS (BF-148)

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[redacted]

cc: [redacted]

SIShibko:dps 12-23-70

[redacted]

January 14, 1971

BF-117

Additional evaluation of FAP 85. Glycerol ester of wood rosin (GEWR)
Fritzsche
Mr. Schaefer, DRPC (BF-320)

DT/PRB has asked for FAPEB concurrence that a maximum use level of 100 ppm of GEWR in soft drinks would result in an average expected use level in all soft drinks at 65 ppm (see memo 11/23/70).

If a person drank only citrus beverage containing the maximum level of GEWR, then naturally, he would consume 100 ppm of GEWR. However, GEWR is used only in citrus flavored beverages. The proposed maximum permitted use level of GEWR is 100 ppm; based on the fact that only a portion of all beverages consumed are citrus flavored and if one assumes that this would not exceed 65% of all soft drinks, then the average expected use level in all soft drinks would not exceed 65 ppm. The 65% is certainly very exaggerated, for the citrus flavored beverages to arrive at an average consumption expectancy.

I called Mr. Harry Korab, of Soft Drink Bottlers Assoc. He states that 60% of all soft drinks are cola beverages, 15% are 7-Up type beverages (do not use GEWR) and only 10-15% of all beverages sold use GEWR, GETO or * BVO to adjust density of the citrus oils. From these figures then, the average would come out to 15 ppm rather than 65 ppm.

M. Prochazka:sl

cc BF-148
BF-100
BF-112
BF-117

* GETO - Glycerol Ester of Tall Oil

UNITED STATES GOVERNMENT

Memorandum

TO : O/C, FA DATE: February 5, 1963

FROM : Division of Food FAP #85 AF 2-241

SUBJECT: Final evaluation of FAP #85. Use of glyceryl abietate in citrus oils for beverages. H. Kohnstamm & Company.

This petition has been reviewed with regard to Section 121.51(c) A, B, C and D of the food additive regulations. The requirements in these areas have been met, and we therefore recommend that a regulation issue if the Division of Pharmacology has concluded that this use is safe.

A. Identity. The additive is a glyceride of abietic acid. There is no question concerning identity, and the name proposed is satisfactory.

B. Amount and purpose. The additive is added to citrus oils in order to adjust their densities. Oils with adjusted densities do not ~~[illegible]~~ rise to surface as rapidly as the untreated oils. ~~When~~ these treated oils are used as flavoring oils for soda water beverages they may contribute up to 100 ppm of additive to the beverage. Ordinarily, the concentration of the additive in the beverage will be approximately 60 ppm.

C. Intended effect. The intended effect has been demonstrated

D. Analytical method. A method for the determination of the amount of additive in beverages is not available. However, the proposed use of the additive is "self-limiting," and we do not think a method is required at this time.

M.P. Morris

MPMorris:sl 2/5/63

RDIngit:PSJorgensen

cc: DF
DP
BPS
F
FAP #85

000061

052

OPTIONAL FORM NO. 10
5010-104

UNITED STATES GOVERNMENT

Memorandum

H. Kohnstamm & Co., Inc.
161 Ave. of the Americas
New York 13, N.Y.
(AP 2-214) (FAP 85)

TO : COMMISSIONER OF FOOD AND DRUGS

DATE: April 18, 1963

FROM : Frederick A. Cassidy
Food Additive Petitions Control Branch

BRIEFING MEMORANDUM

SUBJECT: Glyceryl Abietate
Food Additive Petition No. 85

This order represents one of the early petitions. While received on February 3, 1961, it was not filed until January 26, 1963. The delay was occasioned by the need to review data which was then being compiled.

Data has been reviewed, and this use of glyceryl abietate in citrus oils for beverage flavoring has been established as safe to the satisfaction of Division of Pharmacology. No tolerance is imposed because the use is essentially self limiting.

Division of Food concurs that the additive accomplishes its intended effect, which is to adjust the densities of citrus oils. Because its use is essentially self limiting, no analytical method is required.

Recommendation:

We recommend that the attached order be signed and published.

APPROVED:

E. T. Wulfsberg
~~Food and Drug Officer~~
Food Additive Petitions Control Branch

Attachment

CONFIDENTIAL

000062

UNITED STATES GOVERNMENT

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

Memorandum

TO : Petitions Control Branch (SC-13)

DATE: May 19, 1969

FROM : Drs. K. P. Misra & J. McLaughlin
Division of Pharmacology and Toxicology
Petitions Review Branch (SC-970)

SUBJECT : Amend regulation 121.1059 (Chewing gum base) to include glycerol ester of tall oil rosin, having an acid number of 5-12, a softening point (ring and ball) of 80-88°C, and a color of N or paler as an alternate substitute for glycerol ester of gum (or wood) rosin.

FOOD ADDITIVE PETITION NO. 9A-2402
(Evaluation of 3-31-69 submission)

American Cyanamid Company
Wayne, New Jersey 07470
(AF 14-731)

Regulation 121.1059 presently allows "glycerol ester of gum (or wood) rosin". The petitioner now proposes to include "glycerol ester of tall oil rosin" as an alternate substitute for the presently listed and derived from gum or wood rosins. The rosin ester will be used in the same manner and amount as the presently regulated rosin esters derived from gum or wood.

The Division of Food Chemistry and Technology (SC-470) observes (SC-470 memo to Petitions Control Branch (SC-13) of May 1, 1969) that the IR spectra of the glycerol ester of tall oil rosin and glycerol ester of wood rosin are almost identical. The difference in softening points could be traced to differences observed between Hercules method of assay of softening point and that of the standard ASTM ring and ball point method. SC-470 seeks additional details about the antioxidant that is used as a stabilizer for this rosin ester.

The petition contains an acute oral LD_{50} data and it is greater than 10 gm/kgm in rat, when given as a 10% corn oil dispersion.

Since the proposed glycerol ester of tall oil rosin is essentially identical in IR spectra, with glycerol ester of wood rosin and this leads SC-470 to suggest that both esters would have essentially similar chemical and physical properties, we would, in context with the toxicity data that we have in FAP nos. 269 and 336, concur that both esters would have essentially similar toxicological behavior as well.

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[redacted]

PCB

MAY 29 1969

HELP ELIMINATE WASTE HEW COST REDUCTION PROGRAM

CONCLUSION:

Since SC-470 can observe that glycerol ester of tall oil rosins are essentially identical in physical and chemical properties with those of glycerol ester of gum rosin, we are inclined to concur that both will have similar toxicological character. Thus, if the regulation would delete the use of antioxidant, and insert, "purified by steam stripping" we would find the proposal safe and suitable for regulation. The basis of safety would be our prior evaluations on the safety of rosins.

INIT:HBlumenthal 5/22/69

cc: SC-570
SC-470
FAP No. 9A-2402
FAP Nos. 269 & 336 → memo Nov. 23-1970

KPMisra/JMcLaughlin:dps 5-19-69

SUBMISSION END