EVALUATION OF THE HEALTH ASPECTS OF CAPRENNIN

January 1991

Prepared for
The Procter & Gamble Company
Winton Hill Technical Center
8300 Center Hill Road
Cincinnati, Ohio 45224
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(CAPROCAPRYLOBEHENIN)

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Prepared by
Kenneth D. Fisher, Ph.D.
FOREWORD

The Life Sciences Research Office (LSRO), Federation of American Societies for Experimental Biology (FASEB), provides scientific assessments of topics in the biomedical sciences. Reports are based upon literature reviews and the scientific opinions of knowledgeable investigators engaged in work in specific areas of biology and medicine.

This report is one of a continuing series concerning the health aspects of food ingredients that may be Generally Recognized as Safe (GRAS) food substances. The Federation recognizes that the safety of GRAS substances is of national significance, and that its resources are particularly suited to marshalling the opinions of knowledgeable scientists to assist in these evaluations.

The LSRO convened an ad hoc Expert Scientific Panel to conduct an evaluation of the health effects of caprenin. This report was prepared for The Procter & Gamble Company, Cincinnati, Ohio by an ad hoc Expert Scientific Panel and edited by Kenneth D. Fisher, Ph.D., Director, LSRO in accordance with a contract between the Company and the LSRO, FASEB. Scientists selected as members of the Panel were chosen for their scientific qualifications, experience, and judgment, with due consideration for balance and breadth in appropriate professional disciplines. Members of the Panel and others who assisted in the preparation of this report are listed in Chapter VII.

In particular, the Panel and LSRO acknowledge the cooperation of scientific staff of the Regulatory and Clinical Development Division, The Procter & Gamble Company, who provided information, data, and studies of caprenin. Specifically, the Panel and LSRO thank L. Kenneth Hiller, Ph.D., John C. Peters, Ph.D., and D. Ronald Webb, Ph.D. for their efforts in collating available materials and in providing background information necessary to the Expert Panel’s deliberations and evaluation.

The Expert Panel met in October and November 1990 to: obtain background information; identify and analyze pertinent literature and experimental studies; develop drafts of the report; and, reach an opinion as to whether the available information and data on the health effects of caprenin are sufficient to meet the regulatory requirements of safety as a GRAS food ingredient. The Expert Panel's evaluation was made independently of The Procter & Gamble Company or any other governmental or nongovernmental groups. The Expert Panel and LSRO accept responsibility for the study conclusions and the accuracy of the report.

This final report was reviewed and approved by the LSRO Advisory Committee (which consists of representatives of each constituent Society of FASEB) under authority delegated by the Federation Board. Upon completion of these review procedures, the report was approved and transmitted to The Procter & Gamble Company by the Executive Director, FASEB.

While this is a report of the Federation of American Societies for Experimental Biology, it does not necessarily reflect the opinion of each individual member of the constituent Societies.

January 31, 1991
Date

Kenneth D. Fisher, Ph.D.
Director
Life Sciences Research Office
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I. INTRODUCTION

This report concerns the health aspects of a triacylglycerol prepared by the esterification of glycerol with capric, caprylic, and behenic acids. The substance, caprocaprylobehenicin, has the proposed common name, "caprenin." The report is based partly on the information contained in a compilation of pertinent literature and in a monographic review of available data and a series of studies provided by The Procter & Gamble Company (1991).

To ensure completeness and currency of this report, this information has been supplemented by the use of generally available scientific and statistical reference sources and compendia; new, relevant books and reviews and the literature citations contained in them; current literature citations obtained through computer retrieval systems of the National Library of Medicine; relevant data in the files of LSRO; relevant regulatory documents of the Food and Drug Administration (FDA); and the combined knowledge and experience of members of the Expert Panel and the LSRO staff.

As indicated in the Food, Drug, and Cosmetic Act [21 USC 321(s)], (U.S. Congress, 1990), GRAS substances are exempt from the premarketing clearance that is required for food additives. This Act and the Code of Federal Regulations [21 CFR 170.3 and 170.30] (Office of the Federal Register, 1990a,b) state that GRAS can mean general recognition of safety by experts qualified by scientific training and experience to evaluate the safety of substances on the basis of scientific data derived from published literature. These sections of the Code also indicate that expert judgment is to be based on the evaluation of results of publicly available credible toxicological testing, which may be corroborated by unpublished studies and data. Further, the Code specifies that expert judgment is to take into account reasonably anticipated patterns of consumption, cumulative effects in the diet, and safety factors appropriate for the utilization of animal experimentation data.

The FDA also specifies that persons seeking affirmation of GRAS status of substances must submit a petition for GRAS affirmation that contains all relevant chemical, physical, and biological data related to the intended uses [21 CFR 170.35] (Office of the Federal Register, 1990c). These data must include a description of the physical and chemical properties of the substance, past, current, or intended use in foods, methods for detecting the substance in foods, information that supports safety and functionality, a statement attesting to the balance and representative nature of the submitted information, and a statement affirming that non-clinical laboratory studies were conducted in compliance with regulations. The petition must also include an environmental assessment or justification for exclusion. Finally, the FDA recognizes [21 CFR 170.30] (Office of the Federal Register, 1990b) that it is impossible to provide assurance that any substance is absolutely safe for human consumption.

The LSRO ad hoc Expert Panel reviewed and evaluated the available information on the safety of caprenin in full recognition of the foregoing provisions. In reaching its conclusions on safety, in accordance with FDA's guidelines, the Expert Panel relied primarily on scientific procedures based on published studies as well as on corroboration by unpublished studies and other information and data. This report is intended for use by The Procter & Gamble Company in submitting a GRAS affirmation petition to FDA on caprenin under the Federal Food, Drug, and Cosmetic Act. The Expert Panel anticipates that its conclusions would be reviewed if new information on safety of the substance becomes available.
II. BACKGROUND INFORMATION

Caprenin is essentially a randomized triacylglycerol of caprylic (C8:0), capric (C10:0) and behenic (C22:0) acids (The Procter & Gamble Company, 1991). Spectroscopic data indicate that the three fatty acids are distributed randomly on the glycerol skeleton resulting in a mixture of triacylglycerols each containing caprylic, capric, and behenic acids. Caprenin also contains diacylglycerol esters of caprylic and capric acids (1 to 3%) as well as stearic acid (1 to 2%), arachidic acid (2 to 5%) and lignoceric acid (1%). These additional fatty acid constituents have been identified as constituents of the food-grade behenic acid used as a raw material (The Procter & Gamble Company, 1991).

Caprenin is prepared by conventional fat processing technology (Sonntag, 1982; The Procter & Gamble Company, 1991) in a manner analogous to that used for the non-catalytic process used in production of glyceryl behenate (Food and Drug Administration, 1987). Glycerol is esterified non-catalytically with behenic acid to form glyceryl monobehenate and subsequently with capric and caprylic acids or their anhydrides. Further purification is accomplished by molecular distillation and one or more of the following procedures: thermal winterization, bleaching, and steam deodorization. The final product is a solid at room temperature that has melting properties, textural and sensory characteristics similar to cocoa butter and other commercially available confectionery fats. However, because of the limited intestinal absorption of behenic acid and the inefficient energy utilization from capric and caprylic acids, caprenin has a metabolizable energy of 5 kcal/g rather than the 9 kcal/g of most other dietary fats (The Procter & Gamble Company, 1991).

Proposed specifications for food-grade caprenin:

<table>
<thead>
<tr>
<th>Ester distribution</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Triacylglycerols</td>
<td>at least 95%</td>
</tr>
<tr>
<td>Diacylglycerols</td>
<td>not more than 2%</td>
</tr>
<tr>
<td>Monoacylglycerols</td>
<td>not more than 1%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Fatty acid distribution (weight basis)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Behenic acid (C22:0)</td>
<td>40 to 54%</td>
</tr>
<tr>
<td>Caprylic acid (C8:0) and</td>
<td></td>
</tr>
<tr>
<td>Capric acid (C10:0)</td>
<td>43 to 55%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Triacylglycerol (carbon number) profile</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>C36 thru C44</td>
<td>at least 90%</td>
</tr>
</tbody>
</table>

| Acid value                             | not more than 1.5 |
| Unsaponifiable material\(^1\)          | not more than 0.5% |
| Moisture                               | not more than 0.1% |
| Residue on ignition                    | not more than 0.5% |
| Heavy metals (as Pb)\(^2\)             | not more than 10 ppm |
| Lead\(^2\)                             | not more than 0.1 ppm |
| Arsenic\(^2\)                          | not more than 0.5 ppm |

\(^1\) The unsaponifiable content as measured is <0.20% and includes primarily C24 to C33 saturated hydrocarbons (The Procter & Gamble Company, 1991).

\(^2\) Specifications consistent with those established for various food-grade fats and oils by the National Research Council (1981).
According to the manufacturer (The Procter & Gamble Company, 1991), the substance is intended for use as a confectionery fat substitute in soft candy (such as traditional candy bars, solid chocolate–type candy; caramel and nougat) and in confectionery coatings of (a) wafers, (b) granola–type bars, (c) confections such as marshmallows, (d) nuts and nut products, such as peanuts, (e) fruits, such as cherries and raisins, (f) snack foods, such as pretzels, and (g) snack cakes and cookies.

The safety evaluation of caprenin by the ad hoc Expert Panel is based on these intended food uses, the consumer exposures that might result from these uses, and the biological effects reported in animals and humans fed various dietary levels of the substance or other triacylglycerols that contain one or more of the acyl groups of caprenin.

Caprenin has no history of use as a food ingredient; however, its components (glycerol, capric, caprylic, and behenic acids) are found in triacylglycerols of many foods, particularly fats and oils, and consumed by humans. For example, human milk contains triacylglycerols that include caprylic acid (0.1 to 0.8%) and capric acid (0.9 to 3.5%) (Hilditch and Williams, 1964); both acids are also present in the fat of bovine milk, butter, and various types of cheese (Kuksis, 1978; Sonntag, 1979a), as well as milk fats of other domestic animals and several vegetable oils (coconut, palm kernel) (Sonntag, 1979b).

Behenic acid is widely distributed in many edible vegetable oils including corn, cottonseed, olive, peanut, rapeseed, safflower, sunflower, soybean and numerous other plant oils (Hilditch and Williams, 1964; Sonntag, 1979b; Spencer et al., 1976). Typically, plant oils contain less than 3% behenic acid; for example, of the domestic edible vegetable oils, peanut oil contains the highest percentage of behenic acid (3.1%) (The Merck Index, 1989). Hilditch and Williams (1964) have reported that some plant species contain up to 34.3% behenic acid in seed fats, and The Merck Index (1989) notes that hydrogenated jamba, mustard seed, and rapeseed oils can contain about 50% behenic acid. Behenic acid is also present in various animal and marine oils (Sebedio and Ackman, 1983a,b; The Merck Index, 1989) as well as animal and human tissues (Kuksis, 1978).

Several enteral products, available as foods for special dietary use [21 CFR 105.3] (Office of the Federal Register, 1990d), and special infant formulas [21 CFR 107.50] (Office of the Federal Register, 1990e) may contain medium–chain triacylglycerols (MCT) as MCT oil, a fraction derived from coconut oil. Commercially available MCT oils contain primarily caprylic (67%) and capric (23%) acids as the fatty acid constituents (Hui, 1988). Exempt infant formulas [21 CFR 107.100] (Office of the Federal Register, 1990f) must have a fat content between 3.3 and 6.0 g per 100 kcal of formula.

Two components of caprenin have been affirmed as GRAS substances. Glycerol is a multiple purpose food ingredient for use without limits other than good manufacturing practices [21 CFR 182.90, 21 CFR 182.1320] (Office of the Federal Register, 1990g,h). Caprylic acid is GRAS for several specific uses including use in soft candy at 0.005% of total fat and oil content [21 CFR 184.1025] (Office of the Federal Register, 1990i). Products containing behenic acid that have been affirmed as GRAS include hydrogenated and superglycerinated hydrogenated rapeseed oil [21 CFR 184.1555] (Office of the Federal Register, 1990j), hydrogenated and partially hydrogenated menhaden oils [21 CFR 184.1472] (Office of the Federal Register, 1990k), and peanut oil and hydrogenated soybean oil migrating from cotton packaging to dry foods [21 CFR 182.70] (Office of the Federal Register, 1990l). Glyceril behenate, a mixture of mono–, di–, and triacylglycerols of behenic acid, is also affirmed as GRAS for use as an aid in excipient formulations [21 CFR 184.1328] (Food and Drug Administration, 1987; Office of the Federal Register, 1990m).
III. CONSUMER EXPOSURE DATA

A. CHRONIC CONSUMPTION OF CONFECTIONERY FATS

1. Estimates based on disappearance data

Potential per capita exposure to caprenin has been estimated from 1987 confectionery fat disappearance data by The Procter & Gamble Company (1991). The data in Table 1 were prepared by the staff of The Procter & Gamble Company; however, the footnotes were added by the Expert Panel. The high estimate of caprenin exposure (1.6 g/capita per day) was made with the assumption that caprenin would replace all cocoa butter and other fats used in the confectionery industry in 1987. The typical estimate (0.4 g/capita per day) was made by The Procter & Gamble Company with the assumption that, because of its reduced caloric value (5 kcal/g) relative to currently used confectionery fats (9 kcal/g), caprenin will achieve the same share (26%) of the confectionery market as diet carbonated soft drinks now hold in the carbonated soft drink market (Anonymous, 1989). Both estimates indicate that current confectionery fat consumption and potential caprenin consumption are relatively low when compared with consumption of total food fats [169 g/capita per day total fat disappearance in 1985 (Putnam, 1989)].

However, the estimated intake of caprenin (g/capita per day) will not be reduced by the percentage that the typical estimate might suggest, unless the consumption of the reduced caloric products is evenly distributed among individuals in the portion of the population that consumes confectionery products. For example, individuals who replace all confectionery products with reduced calorie products would consume as much caprenin as traditional confectionery fat previously consumed.

The Procter & Gamble Company (1991) has compared the potential per capita daily exposures to the fatty acids derived from caprenin (i.e., medium-chain fatty acids and behenic acid) with the background exposure to these fatty acids in the food supply (Table 1). Background exposure to medium-chain fatty acids was based on 1987 per capita consumption of dairy products, coconut and palm kernel oils and their content of capric and caprylic acids. Background exposure to behenic acid was based on 1987 per capita consumption of peanuts, peanut butter, peanut oil, hydrogenated and superglycerinated hydrogenated rapeseed oil, and hydrogenated and partially hydrogenated menhaden oil.

Based on an assumption that candy is the major source of confectionery fat, the Expert Panel calculated the potential per capita exposures to caprenin from candy disappearance data. This alternative approach is based on the 1987 data for candy disappearance (18.4 lb/capita per year) (Putnum, 1989). Estimates of the fraction of candy that contains chocolate are 59% (Pao et al., 1982) and 53% (National Confectioners Association, 1990). The Expert Panel has used the 53% value in the exposure calculations which follow only because it is the most recent figure available. Figures calculated on the basis of the 59% figure would be about 9% higher than those reported in the tables in this chapter. In addition, the calculations reflect that candy containing chocolate has an average chocolate content of 54% which contains 32% cocoa butter; nonchocolate candies contain 5% replaceable confectionery fat (The Procter & Gamble Company, 1991). Based on these data, the unweighted average fat content of candy is calculated to be 11% and per capita consumption of confectionery fat in 1987 from candy was 2.5 g/day. Although not all confectionery fat is used in candy, this value is greater than 1.6 g, the value calculated from the disappearance of confectionery fat in 1987 (Table 1). In the absence of data to the contrary, the Expert Panel assumed that all candies with chocolate had average chocolate contents and all had equal market shares. The difference in the two per capita consumption estimates (2.5 g vs. 1.6 g) suggests that chocolate-containing candies having the largest market shares may have average fat contents less than 11% and that use of the unweighted average probably results in an overestimate of per capita exposure.
Table 1. Estimates of Potential Per Capita Consumption of Caprenin, its Component Fatty Acids, and Background Exposure From Other Dietary Sources.

<table>
<thead>
<tr>
<th>Compound</th>
<th>Per Capita Exposure</th>
<th>Background</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>g/person per day</td>
<td></td>
</tr>
<tr>
<td></td>
<td>High</td>
<td>Typical</td>
</tr>
<tr>
<td>Caprenin</td>
<td>1.6$^2$</td>
<td>0.4$^2$</td>
</tr>
<tr>
<td>Medium-Chain Fatty Acids</td>
<td>0.9$^4$</td>
<td>0.2$^4$</td>
</tr>
<tr>
<td>Behenic Acid</td>
<td>0.9$^4$</td>
<td>0.2$^4$</td>
</tr>
</tbody>
</table>

1 A detailed discussion of the data sources used and assumptions made in calculating these values is provided in The Procter & Gamble Company (1991).

2 The estimates of caprenin were derived from data on the disappearance of cocoa butter and other fats and oils used in the confectionery industry in 1987. For the estimate of high exposure, 100% replacement by confectionery products containing caprenin was assumed. For the estimate of typical exposure, the calculation included an adjustment for a likely market share based on the current share for diet soft drinks in the carbonated soft drink market.

3 Because this substance is not a triacylglycerol found in other fat sources, background exposure is not applicable.

4 These estimates were derived from the per capita exposure estimates for caprenin and the maximum possible levels (% weight) for these fatty acids in the triacylglycerol (55% for medium-chain triacylglycerols and 54% for behenic acid).

5 This estimate was based on 1987 per capita consumption of dairy products, coconut and palm kernel oils, and their content of capric and caprylic acids.

6 This estimate was based on 1987 per capita consumption of peanuts, peanut butter, peanut oil, hydrogenated and superglycerinated hydrogenated rapeseed oil, and hydrogenated and partially hydrogenated menhaden oil.
2. Estimates based on food consumption data

The Expert Panel also calculated an estimate of candy intake and possible caprenin exposure from data reported on consumption of candy by individuals. Data on the actual intake of candy are provided by two food consumption surveys conducted by the U.S. Department of Agriculture: the 1977–78 Nationwide Food Consumption Survey (NFCS) (U.S. Department of Agriculture, 1984) and the 1985 and 1986 Continuing Survey of Food Intakes by Individuals (CSFII) (U.S. Department of Agriculture, 1985, 1986, 1987a,b, 1988). Intake data were collected by means of different protocols in the two surveys; this results in certain ambiguities when comparing the findings. In the 1977–78 survey, intake data were collected for three consecutive days during four consecutive seasons from 37,874 individuals in approximately 15,000 households, one day by interview and two days by diary (Pao et al., 1989). In the 1985 CSFII, the data were collected on six nonconsecutive days over a one-year period from 1,088 women 19 to 50 years of age and 371 of their children one to five years of age. Each day of data was collected using a one-day recall. The first-day data were collected in a personal interview; data for subsequent days were collected by telephone. Data were collected similarly in the 1986 survey for 1,164 women 19 to 50 years of age and 375 of their children one to five years of age. Data were also collected from 1,134 men 19 to 50 years of age interviewed on one day in the summer of 1985 (U.S. Department of Agriculture, 1985, 1986, 1987a,b, 1988). Use of food consumption data for making exposure estimates is discussed by Anderson (1988).

The Expert Panel has utilized the USDA survey data to compare candy intake data obtained for one day in the spring in each of the surveys (Table 2). Although the mean consumption of candy by all individuals for one day in the spring was greater in 1985 and 1986 than in 1977, the mean intake per eater was less except for women 19 to 50 years of age in 1986. Mean intake per eater was obtained by dividing mean intake of all individuals in the population surveyed by the fraction of the population that reported candy consumption. The lower mean intake per eater resulted from the greater percentage of the population that reported eating candy in 1985 and 1986 as compared with 1977. Percentage differences between intakes per eater were less than percentage differences between intakes of all individuals in 1977 and 1985 or 1986. It should be noted that changes in mean daily intakes of all individuals as given in Table 2 for the one day in the 1977 and 1985 surveys are not consistent with changes in candy disappearance data for those years; that is 16.8 lb/capita in 1977 and 18.4 lb/capita in 1986 (Putnam, 1989), an increase of only 10.1%.

If the data collected on all days of the four seasons in the 1977 and 1986 surveys are considered, the percentage of candy eaters is increased for all gender/age groups. Similarly, the mean intake/person per day for each age group is decreased when compared with intakes calculated from the one day intake data shown in Table 2. Thus, in the 1977 survey (Pao et al., 1982), eater participation of children one to five years of age as candy eaters increased to 19.6% and mean intake decreased to 15.7 g/person per day. Similarly, in the 1986 survey (U.S. Department of Agriculture, 1987b, 1988), participation of children one to five years of age as eaters increased to 49.2% and mean intake for this group decreased to 10.2 g/person per day.

Pao et al. (1982) have reported data from the 1977–78 NFCS for both average candy intake/person per day at selected percentiles for 16 gender/age groups and acute exposure at selected percentiles as measured by g/person per eating occasion. Reports of the 1985 and 1986 CSFII provide intake data for only three gender/age groups and do not report quantity consumed per eating occasion. For these reasons the Expert Panel selected data on candy consumption from the 1977–78 NFCS for estimation of confectionery fat consumption and potential exposure to caprenin.

The average, 50th percentile, and 90th percentile consumption of candy and confectionery fat in grams, and also confectionery fat consumption in g/kg body weight (bw) for individuals in 11 gender/age groups who ate candy at least once in the three days of the 1977–78 NFCS are presented in Table 3. In making these calculations, the Expert Panel assumed that all candy contained fat and
Table 2. Candy Intakes of Selected Groups on One Day in Spring of 1977, 1985, and 1986.

<table>
<thead>
<tr>
<th>Gender/Age Groups</th>
<th>Mean Intake of All Individuals in the Survey Population</th>
<th>Mean Intake/Eater (Percent Eaters)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1977$^1$ 1985$^1$ 1986$^2$</td>
<td>1977 $^1$ 1985 $^1$ 1986 $^2$</td>
</tr>
<tr>
<td>Children 1–5 yrs</td>
<td>4          8          7</td>
<td>44$^3$ (9.0)$^1$ 34$^3$ (23.8)$^1$ 36$^3$ (19.3)$^2$</td>
</tr>
<tr>
<td>Women 19–50 yrs</td>
<td>2          5          6</td>
<td>44 (4.5) 37 (13.6) 53 (11.4)</td>
</tr>
<tr>
<td>Men 19–50 yrs</td>
<td>2          4          NA</td>
<td>44 (4.6) 37 (10.8) NA</td>
</tr>
</tbody>
</table>

3 Calculated as (mean intake of all individuals/% eaters) x 100.
Table 3. Daily Consumption of Confectionery Fat by Candy Eaters.¹

<table>
<thead>
<tr>
<th>Gender/Age Groups</th>
<th>Body Weight kg</th>
<th>Intake/Person</th>
<th>Average</th>
<th>50th Percentile</th>
<th>90th Percentile</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Candy Fat</td>
<td>g</td>
<td>g</td>
<td>g/kg</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>g</td>
<td>g/kg</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>g</td>
<td>g/kg</td>
</tr>
<tr>
<td>Children, 1–2</td>
<td>11.1</td>
<td>15</td>
<td>1.7</td>
<td>0.15</td>
<td>9</td>
</tr>
<tr>
<td>Children, 3–5</td>
<td>16.6</td>
<td>16</td>
<td>1.8</td>
<td>0.11</td>
<td>11</td>
</tr>
<tr>
<td>Children, 6–8</td>
<td>22.6</td>
<td>19</td>
<td>2.1</td>
<td>0.09</td>
<td>13</td>
</tr>
<tr>
<td>Males, 9–14</td>
<td>38.5</td>
<td>26</td>
<td>2.9</td>
<td>0.08</td>
<td>18</td>
</tr>
<tr>
<td>Females, 9–14</td>
<td>39.3</td>
<td>24</td>
<td>2.6</td>
<td>0.07</td>
<td>16</td>
</tr>
<tr>
<td>Males, 15–18</td>
<td>63.8</td>
<td>28</td>
<td>3.1</td>
<td>0.05</td>
<td>19</td>
</tr>
<tr>
<td>Females, 15–18</td>
<td>55.8</td>
<td>23</td>
<td>2.5</td>
<td>0.05</td>
<td>15</td>
</tr>
<tr>
<td>Males, 19–34</td>
<td>76.6</td>
<td>29</td>
<td>3.2</td>
<td>0.04</td>
<td>19</td>
</tr>
<tr>
<td>Females, 19–34</td>
<td>62.7</td>
<td>20</td>
<td>2.2</td>
<td>0.04</td>
<td>14</td>
</tr>
<tr>
<td>Males, 35–64</td>
<td>79.5</td>
<td>26</td>
<td>2.9</td>
<td>0.04</td>
<td>18</td>
</tr>
<tr>
<td>Females, 35–64</td>
<td>68.0</td>
<td>19</td>
<td>2.1</td>
<td>0.03</td>
<td>13</td>
</tr>
</tbody>
</table>

¹ Candy consumption of individuals who ate candy at least once in the 3-day USDA 1977–78 Nationwide Food Consumption Survey (Puo et al., 1982). Average fat content of candy was assumed to be 11% (see text).

² Body weights for gender/age groups were calculated from the 50th percentiles of NCHS growth curves for ages 1–18 years, as included in Block and Shils (1988). Body weights for adult males and females were calculated from NHANES I and NHANES II body weight data as presented in Frisancho (1990).
the average fat content was 11% (see calculations on p.5). Confectionery fat consumption in g/kg bw was greatest for children one to two years of age; average, 50th percentile, and 90th percentile fat intakes for this age group were 0.15, 0.10, and 0.35 g/kg bw, respectively. Although males 19 to 34 years of age consumed the largest amounts of candy, intakes per kg bw were one-fourth to one-third that of one to two year-old children. Intakes decreased fairly uniformly with age for both males and females, reaching values of 0.03, 0.02, and 0.06 g/kg bw for females 35 to 64 years of age. However, the values in Table 3 may underestimate potential chronic exposure to caprein because the estimates do not include possible contributions of products other than candy that might contain caprein (e.g., snack foods with confectionery coatings). Even so, these figures also may overestimate caprein intake because the Expert Panel assumed all chocolate-containing candies had the same market share in calculating the average chocolate content of candy (see p.5).

Earlier in this section, the Expert Panel presented a comparison of per capita availability of confectionery fat with that of all edible fats based on disappearance data. Another comparison can be derived from food intake data in which confectionery fat consumption by candy eaters is compared with the consumption of all dietary fats by the total population. This comparison is provided in Table 4 for selected age groups based on data from the 1977–78 NFCS. In Table 4, the average confectionery fat intake by candy eaters as a percent of average intake of all fats by the total population is greatest for children 1 to 5 years of age (3.5 to 5.3%). For the other age groups, the average intake is about 3.0% of the intake of all fats. It should be noted that the values for the intake of all fats for the various age groups may not necessarily parallel the total fat consumption by candy eaters in the corresponding age groups.

B. ACUTE EXPOSURE TO CONFECTIONERY FATS

Estimates of potential acute exposure to caprein were derived from the amounts of candy consumed per eating occasion by individuals who reported eating candy at least once in three days in the 1977–78 NFCS as reported by Pao et al., 1982. The Expert Panel assumed, for purposes of calculation, that the relatively high intakes per eating occasion at the 90th percentiles occurred only once in the three days of the survey. However, comparison with quantities consumed on one day by consumers who ate candy on only one day indicates that this was not the case. Hence, some users may have eaten candy on more than one day or on more than one occasion on a single day in the three-day period.

The calculations of fat intake values given in Table 5 include the assumption that all candy eaten was chocolate candy containing 32% fat. This probably overestimates acute confectionery fat consumption by some of the candy eaters as some chocolate candy contains less than 32% confectionery fat, and not all candy contains chocolate.

These estimates suggest that children one to two years of age have the highest potential intake of caprein per eating occasion when expressed on a g/kg bw basis (Table 5). Average, 50th and 90th percentile intakes of confectionery fat for children one to two years of age were 0.84, 0.49, and 1.6 g/kg bw, respectively. The corresponding potential exposures to fatty acids derived from caprein at these percentiles were calculated to be 0.46, 0.27, and 0.88 g/kg bw for medium-chain fatty acids and 0.45, 0.26, and 0.86 g/kg bw for behenic acid, respectively.

Only limited comparisons can be made between the estimates of acute exposure by the Expert Panel in Table 5, and those by The Procter & Gamble Company (1991). Percentiles of candy intake selected, gender/age groupings, and assumptions about proportion of chocolate-containing candy consumed and the fat content of that candy all differed. These factors make direct comparisons impossible. However, for the 90th percentile estimates of acute exposure, both sets of calculations assumed that all candy consumed was chocolate which contained 32% fat. The gender/age groups
Table 4. Comparison of Intake of Confectionery Fat by Candy Eaters With Intake of All Fats by Total Population.

<table>
<thead>
<tr>
<th>Gender/Age Groups</th>
<th>Confectionery fat</th>
<th>All fats, Total population</th>
<th>Percent³</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Candy eaters¹</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Children, 1–2</td>
<td>1.7</td>
<td>32.0</td>
<td>5.3</td>
</tr>
<tr>
<td>Children, 3–5</td>
<td>1.8</td>
<td>50.9</td>
<td>3.5</td>
</tr>
<tr>
<td>Males, 15–18</td>
<td>3.1</td>
<td>116.5</td>
<td>2.7</td>
</tr>
<tr>
<td>Females, 15–18</td>
<td>2.5</td>
<td>78.5</td>
<td>3.2</td>
</tr>
<tr>
<td>Males, 19–34</td>
<td>3.2</td>
<td>111.8</td>
<td>2.9</td>
</tr>
<tr>
<td>Females, 19–34</td>
<td>2.2</td>
<td>73.3</td>
<td>3.0</td>
</tr>
<tr>
<td>Males, 35–64</td>
<td>2.9</td>
<td>105.6</td>
<td>2.8</td>
</tr>
<tr>
<td>Females, 35–64</td>
<td>2.1</td>
<td>70.9</td>
<td>3.0</td>
</tr>
</tbody>
</table>

¹ Data from Table 3.


³ (Confectionery fat/all fats) x 100.
Table 5. Estimates of Acute Exposure to Confectionery Fat.

<table>
<thead>
<tr>
<th>Gender/Age Groups</th>
<th>Body Weight(^3) kg</th>
<th>Average 50th</th>
<th>90th</th>
<th>Average 50th</th>
<th>90th</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>g/person per eating occasion</td>
<td></td>
<td>g/kg bw per person per eating occasion</td>
<td></td>
</tr>
<tr>
<td>Children, 1–2</td>
<td>11.1</td>
<td>9.3</td>
<td>5.4</td>
<td>18.2</td>
<td>0.84</td>
</tr>
<tr>
<td>Children, 3–5</td>
<td>16.6</td>
<td>10.6</td>
<td>9.0</td>
<td>19.2</td>
<td>0.64</td>
</tr>
<tr>
<td>Children, 6–8</td>
<td>22.6</td>
<td>12.2</td>
<td>9.6</td>
<td>23.7</td>
<td>0.53</td>
</tr>
<tr>
<td>Males, 9–14</td>
<td>38.5</td>
<td>16.3</td>
<td>11.5</td>
<td>36.2</td>
<td>0.41</td>
</tr>
<tr>
<td>Females, 9–14</td>
<td>39.3</td>
<td>14.1</td>
<td>9.6</td>
<td>27.2</td>
<td>0.36</td>
</tr>
<tr>
<td>Males, 15–18</td>
<td>63.8</td>
<td>17.0</td>
<td>11.8</td>
<td>33.6</td>
<td>0.27</td>
</tr>
<tr>
<td>Females, 15–18</td>
<td>55.8</td>
<td>15.0</td>
<td>10.9</td>
<td>33.3</td>
<td>0.27</td>
</tr>
<tr>
<td>Males, 19–34</td>
<td>76.6</td>
<td>17.0</td>
<td>12.5</td>
<td>36.2</td>
<td>0.22</td>
</tr>
<tr>
<td>Females, 19–34</td>
<td>62.7</td>
<td>13.1</td>
<td>10.2</td>
<td>27.2</td>
<td>0.21</td>
</tr>
<tr>
<td>Males, 35–64</td>
<td>79.5</td>
<td>17.0</td>
<td>12.2</td>
<td>32.6</td>
<td>0.21</td>
</tr>
<tr>
<td>Females, 35–64</td>
<td>68.0</td>
<td>12.5</td>
<td>9.6</td>
<td>26.9</td>
<td>0.18</td>
</tr>
</tbody>
</table>

1. Calculated from data on candy consumption (quantity consumed per eating occasion) from the USDA 1977–78 Nationwide Food Consumption Survey, (Pao et al., 1982).
2. Assumes all candy eaten was chocolate containing 32% fat.
3. Body weights for gender/age groups were calculated from the 50th percentiles of NCHS growth curves for ages 1–18 years, as included in Block and Shils (1988). Body weights for adult males and females were calculated from NHANES I and NHANES II body weight data as presented in Frisancho (1990).
that can be compared most directly are the 13 to 18 year olds of both sexes combined by The Procter & Gamble Company and the 15 to 18 year old males and 15 to 18 year old females used by the Expert Panel in their estimates. Assuming that both eating day and eating occasion are surrogate measures of acute exposure, the 90th percentile intake was estimated to be 38 g/person per eating day for 13 to 18 year olds of both sexes (The Procter & Gamble Company, 1991) and 33.6 and 33.3 g/person per eating occasion for males and females 15 to 18 years of age, respectively, by the Expert Panel.
IV. BIOLOGICAL STUDIES

A. DIGESTION, ABSORPTION, AND METABOLISM

Lingual lipase, released during chewing, initiates hydrolysis of triacylglycerols in the stomach to release fatty acids and partial acylglycerols (Dupont, 1990). Digestion by pancreatic lipase–colipase continues in the duodenum and yields mainly free fatty acids and 2-monoacylglycerols (Dupont, 1990; Patton, 1981). Small fractions of the 2-monoacylglycerols are further hydrolyzed to glycerol and fatty acids.

Short- and medium-chain triacylglycerols are rapidly hydrolyzed by both lingual and pancreatic lipases (Bach and Babayan, 1982; Greenberger et al., 1966; Pike and Brown, 1984). In contrast, the long-chain triacylglycerols are digested predominantly by pancreatic lipase (Carroll, 1958; Greenberger et al., 1966; Hamosh, 1990).

The short- and medium-chain fatty acids are soluble in aqueous medium and are, for the most part, transported by the portal circulation (Hyun et al., 1967; Sickinger, 1975). Because of their relatively rapid absorption, transport, and metabolism, the medium-chain triacylglycerols have been used extensively as sources of energy in various enteral products for special dietary purposes (Bach and Babayan, 1982).

Digestion and absorption of triacylglycerols of long-chain saturated fatty acids are slower than those of medium-chain triacylglycerols. This is due to their relative insolubility, the need for reesterification to triacylglycerols and the formation of chylomicrons in the intestine and subsequent transport of chylomicrons via the lymphatic system to the systemic circulation (Dupont, 1990; Patton, 1981).

Caprylic and capric acids hydrolyzed from triacylglycerols are oxidized predominantly to carbon dioxide, acetate, and ketone bodies by the hepatocytes (Bach and Babayan, 1982). Small quantities of short- and medium-chain fatty acids may bypass the liver and reach the peripheral tissues directly where they are oxidized in an analogous manner. Both medium- and long-chain fatty acids in triacylglycerols of chylomicrons are released by the action of lipoprotein lipase (Dupont, 1990). Fatty acids enter cells and are reesterified to triacylglycerols, incorporated into phospholipids of membranes, serve as precursors for eicosanoids, or are used as energy sources (Dupont, 1990). The rate of β-oxidation by the mitochondria and peroxisomes depends in part on the chain length and degree of unsaturation of the fatty acid (Bach and Babayan, 1982; Alexson and Cannon, 1984).

Alexson and Cannon (1984) have shown that among the C4 to C22 fatty acids, capric and caprylic acids are oxidized by mitochondria isolated from brown adipose tissue of female Sprague–Dawley rats at rates of about 80% and 60%, respectively, relative to that of myristic acid (C14:0) which had the most rapid rate (178 nmol/min per mg protein).

While Alexson and Cannon (1984) found essentially no β-oxidation of behenic acid when incubated in vitro with peroxisomal fractions, earlier studies of Bernhard and Vischer (1946) provided evidence of β-oxidation of ethyl behenate by rats. The latter investigators observed that male white rats (strain not identified) fed a diet containing 5% deuterated ethyl behenate and 5% olive oil or a diet with 10% deuterated ethyl behenate alone absorbed 40% of the behenate. Bernhard and Vischer (1946) concluded that the labeled C12, C16, and C14 fatty acids found in carcass lipids were products of β-oxidation of the behenic acid. Indirect evidence for β-oxidation of behenic acid can be derived from the 91-day feeding studies of Nolen (1981), in which the animals consumed diets containing approximately 3.3% behenic acid derived from hydrogenated rapeseed oil. At autopsy, liver:body
weight ratios were normal. These observations suggest that excessive induction of liver enzymes sufficient to increase liver weights did not occur, and that the normal pathways of β-oxidation were probably present.

In a seven- to eight-day fat balance study with male Sprague-Dawley rats, Carroll (1958) found that 7% of the free behenic acid fed at 1370 mg/day was absorbed. Mattson and Streck (1974) reported 24% absorption of behenate from 2-behenoyl diilinolein fed by gavage in male Sprague-Dawley rats based on 24-hour lymph recovery data. Nolen (1981) reported 12-17% absorption of behenic acid by Sprague-Dawley rats fed hydrogenated rapeseed oil and superglicerinated hydrogenated rapeseed oil as their sole dietary fat (15% by weight) for 10 days during a 91-day feeding trial. However, when mixed with liquid soybean oil (7.5% experimental fat and 12.5% soybean oil), behenic acid absorption was 31% and 42% from hydrogenated rapeseed and superglicerinated rapeseed oil, respectively. These levels of absorption are analogous to the 40% reported by Bernhard and Vischer (1946). Bézard and Sawadogo (1983) found that 58.9% of the behenic acid from peanut oil fed to male Wistar rats for 17 weeks was absorbed. These results are similar to those of Tso et al. (1984), who observed 1.8 mass percent behenic acid in lymph fat of male Sprague-Dawley rats after an intraduodenal infusion of peanut oil. Because peanut oil typically contains 3 to 4% behenic acid, absorption of about 50% would account for the indicated level of recovery in lymph lipids. This variability in the percentage of behenic acid absorbed may be explained primarily by the form of the behenic acid administered even though the experimental procedures differed.

Finally, Kokatnur et al. (1985) have reported behenic acid present in sphingomyelin isolated from amniotic fluid of 14 healthy pregnant women (4.3% of total fatty acids) and 11 diabetic pregnant women (2.9% of total fatty acids). These investigators were exploring the origin and composition of sphingomyelin during pregnancy. They found a wide distribution of C_{14} to C_{24} fatty acids in sphingomyelin derived both from fetal pulmonary epithelial cells and from maternal tissues. They suggested that the fatty acid distribution found in amniotic sphingomyelin was analogous to that found in maternal tissues.

Data from studies on digestion, absorption, and metabolism of caprenin are equivalent to those obtained from studies of capric, caprylic, and behenic acids as well as the triacylglycerols containing these fatty acids. Swift et al. (1991) studied the effects of intake of a structured triacylglycerol (STL) on plasma lipids and lipoproteins of 10 healthy men. The STL contained caprylic, capric, and behenic acids but was not identical to the completely randomized triacylglycerol, caprenin. The subjects were fed liquid diets containing 40% of total energy as a long-chain triacylglycerol (C16:0-C18:0) (LCT), a medium-chain triacylglycerol (C8:0-C10:0) (MCT), or STL (80% STL and 20% soybean oil) for six days. Each subject received each diet in random order for six-day periods over five weeks. The C8:0 and C10:0 fatty acids of the STL were absorbed and transported after digestion in a manner similar to that of the C8:0 and C10:0 fatty acids from MCT, but the behenic acid of the structured triacylglycerol was poorly absorbed.

The investigators reported several diet-associated changes in serum lipids and lipoproteins. Total fasting plasma cholesterol was not altered by any of the three diets; however, HDL cholesterol was decreased 14% by the STL diet (p<0.05), and 15% by the MCT diet (p<0.01), but was unchanged by the LCT diet. Fasting plasma triglycerides were increased 42% by the MCT diet (p<0.01), but were not altered by either the STL or LCT diets. Neither the STL nor MCT diets produced changes in fasting lipoprotein lipid composition; however, during the LCT diet, VLDL became enriched in triglyceride, and LDL became enriched in cholesterol. Finally, total triglyceridemia (defined as the total mass of triacylglycerols in the plasma for six hours following the meal) induced by the meal on day six was similar for all three diets. However, the postprandial hypertriglyceridemia (defined as the extent of the increase in plasma triacylglycerols above fasting values after the meal) was significantly greater for the LCT diet than for either STL or MCT diets, which were similar. Swift
et al. (1991) also measured the fatty acid composition of chylomicrons isolated three to four hours after the meal on day six in three of the test subjects. They found that 8% of the chylomicron fatty acids was C\textsubscript{22}, compared with the 26% behenic acid in the STL meal.

Most data on excretion of various fatty acids have been derived from fat balance studies. For example, Carroll (1958) found no caprylic or capric acid in the feces of male Sprague–Dawley rats consuming diets containing these free fatty acids. However, when the animals were fed diets containing 10% behenic acid, 93% of the quantity ingested was excreted over a 7 to 8 day period. Bézard and Sawadogo (1983), in a 17–week feeding study of male Wistar rats fed 15% peanut oil diets, reported 7.5% of the ingested fat was recovered in feces. They estimated the excretion of behenic acid to be 41.1% of the quantity ingested.

Normal adults excrete less than 5% of ingested fat in the feces (Riley and Glickman, 1979). Greater proportions of long–chain saturated fatty acids are excreted than short– and medium–chain or unsaturated fatty acids because of the reduced absorption of the longer–chain fatty acids (Thomson and Dietschy, 1981). Adults excrete 4 to 6 g of fecal fat per day of which 80% is fatty acids (Carey, 1983; Patton, 1981).

In a recent study of fat balance in humans fed caprenin, 71% of the behenic acid of caprenin was excreted over a nine–day period by 10 healthy men and 10 healthy women (The Procter & Gamble Company, 1991).

B. ACUTE TOXICITY

Data on the acute oral toxicity of caprenin are lacking; however, data on acute oral toxicity of the component substances provide information that suggests acute toxicity is unlikely. Available data are noted in Table 6. A number of foods contain the fatty acids found in caprenin. For example, coconut oil contains 5 to 9% caprylic acid and 6 to 10% capric acid. Oral LD\textsubscript{50} values for coconut oil have been reported to exceed 5.0 g/kg bw for rats (Cosmetic Ingredient Review Expert Panel, 1986). Further, no acute oral toxicity of foods such as peanut oil and hydrogenated fish oils that contain about 2 to 3% behenic acid has been reported.

No significant adverse effects were reported in 10 men (mean body weight = 79.7 kg) consuming diets (mean daily caloric intake 2730 kcal) containing 32% fat as a structured lipid which was 23.5% caprylic, 22.8% capric and 26.4% behenic acids (Swift et al., 1991). Similarly, no significant adverse effects were observed during a 5–day feeding trial with caprenin fed as a confectionary fat to 10 women at 1.3g/kg bw per day and 10 men at 1.1 g/kg bw per day (The Procter & Gamble Company, 1991).

C. SUBCHRONIC TOXICITY

No reports on the subchronic oral toxicity of caprylic or capric acid in animals or humans have been found. The nutritive value of medium–chain triacylglycerol (MCT) oils in animals and in humans has been evaluated in a number of studies. MCT oil is a triacylglycerol containing caprylic (67 to 75%) and capric (22 to 23%) acids (Greenberger and Skillman, 1969; Hui, 1988). MCT oil is derived primarily from coconut oil by hydrolysis and steam distillation. The volatile fraction is used in reesterification to produce triacylglycerols containing C\textsubscript{8} and C\textsubscript{10} fatty acids (Greenberger and Skillman, 1969). Thus, studies on MCT oil, and secondarily on coconut oil, are pertinent to the possible toxicity of triacylglycerols containing caprylic and capric acids.
Table 6. Acute Oral Toxicities (LD$_{50}$) of Caprenin Constituents.

<table>
<thead>
<tr>
<th>Compound</th>
<th>Animal</th>
<th>LD$_{50}$ (g/kg)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glyceryl Behenate</td>
<td>Rat</td>
<td>&gt;5.0</td>
<td>Rondot, 1980</td>
</tr>
<tr>
<td>Capric Acid</td>
<td>Rat</td>
<td>3.7</td>
<td>Smyth et al., 1962</td>
</tr>
<tr>
<td>Caprylic Acid (mixed isomers)</td>
<td>Rat</td>
<td>10.1</td>
<td>Jenner et al., 1964</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1.4</td>
<td>Smyth et al., 1962</td>
</tr>
<tr>
<td>Glycerin$^1$</td>
<td>Rat</td>
<td>27.2</td>
<td>Hine et al., 1953</td>
</tr>
<tr>
<td></td>
<td></td>
<td>27.5</td>
<td>Smyth et al., 1941</td>
</tr>
<tr>
<td></td>
<td>Guinea Pig</td>
<td>7.8</td>
<td>Smyth et al., 1941</td>
</tr>
<tr>
<td></td>
<td></td>
<td>10.0</td>
<td>Hine et al., 1953</td>
</tr>
<tr>
<td></td>
<td>Mouse</td>
<td>19.3</td>
<td>Latven and Molitor, 1939</td>
</tr>
<tr>
<td></td>
<td></td>
<td>20.7</td>
<td>Anderson et al., 1950</td>
</tr>
<tr>
<td></td>
<td></td>
<td>23.0</td>
<td>Hine et al., 1953</td>
</tr>
<tr>
<td></td>
<td></td>
<td>26.1</td>
<td>Kudo and Ito, 1972</td>
</tr>
<tr>
<td></td>
<td></td>
<td>31.5</td>
<td>Fischer et al., 1949</td>
</tr>
</tbody>
</table>

$^1$ Data cited in Select Committee On GRAS Substances, 1975.
Several investigators fed hydrogenated oils (e.g., hydrogenated rapeseed oil) and triacylglycerols containing behenic acid to experimental animals in efforts to establish nutritional and toxicological properties. These studies are identified in Table 7.

The majority of these studies did not include complete histopathological examination at autopsy; however, few if any overt adverse effects were observed. Harris and Mosher (1940) noted fatty deposits in livers of male and female Wistar rats fed diets containing 25% coconut oil for 90 days, but these changes were considered to have no toxicological significance. Nolen (1981) found significantly lower serum phospholipids in female rats that were fed superglycerinated hydrogenated rapeseed oil diets than in control animals that were fed refined rapeseed oil. No evidence of gross pathology or histopathology was found after staining with H&E or Sudan IV stain. Tissue hyperlipidosis was not observed in rats that consumed either the hydrogenated rapeseed oil or the superglycerinated hydrogenated rapeseed oil diets.

Nolen (1981) also observed that relative ovary weights (g/kg body weight) of female Sprague–Dawley rats fed the hydrogenated rapeseed oil and superglycerinated hydrogenated soybean oil diets were significantly greater (p<0.05) than those of control female rats fed either refined rapeseed oil or refined soybean oil (ratios of 1.4 and 1.5 vs. 1.1 and 1.0, respectively) but not significantly different from those of females fed hydrogenated soybean oil. He concluded that these relative ovary/body weight changes were toxicologically insignificant because ovaries from animals in both treatment groups were histologically normal at autopsy. In a 16–week study, no significant gross pathological or histopathological changes were observed when diets containing hydrogenated or superglycerinated hydrogenated rapeseed oils were consumed (Nolen, 1981). No microscopic changes were detected in the ovaries of rats fed either type of hydrogenated rapeseed oil.

Svaar et al. (1980) found lipidosis and vacuolization in cardiac muscle cells, as well as atrophic muscle fibers around fat droplets in cardiac muscle cells of female Norwegian Landrace pigs fed various fats at 16% of the diet [rapeseed oil, fish oil, partially hydrogenated fish oil (2.2% behenic acid), partially hydrogenated soybean oil (0.5% behenic acid), and lard]. These investigators were unable to establish a relationship between incidence and severity of cardiac lesions and the type of fat in the diet.

Caprenin was fed to groups of 15 weanling male and 15 female Crl:CD®BR rats in a semipurified diet (Purina Basal Diet #5755) for 28 days (Osheroff, 1990). Caprenin was added at 0, 5, 10, or 15% (w/w), and corn oil (Pure Dukes Corn Oil) was added at 18, 13, 8, or 3% (w/w), respectively to maintain the total fat content of the diet at 18% and to provide essential fatty acids. Caloric densities ranged from 4500 kcal/kg for the corn oil diet to 3900 kcal/kg for the 15% caprenin diet. Levels of caprenin intake (g/kg bw per day) calculated from feed consumption and body weight data were 16.1 g for males and 21.4 g for females (average = 18.8 g/kg bw per day) during the first week of feeding (5 week–old rats). During the fourth week of the feeding trial, the average caprenin intake was 11.4 g/kg bw per day (males 10.9 g and females 11.8 g).

No deaths occurred in the four treatment groups during the 28–day study. At the termination of the study, 10 of the 15 rats in each treatment group were bled for hematological and serum chemistry analyses and all animals were then sacrificed for gross necropsy and histopathological examination of tissues.

No adverse clinical signs, observations, or ophthalmoscopic findings were evident. Further, no gross evidence of adverse effects in the postmortem studies was reported. Some depression in total body weight gains of males, but not females, was associated with the quantity of feed consumed, the deposition of carcass fat, and the differing caloric content of the diets. These results were consistent with physiological responses to feeding MCT reported by other investigators (Baba et al., 1982; Geliebter et al., 1983).
Table 7. Subchronic Toxicity Studies in Animals with Caprenin Constituents and Related Materials (see text for discussions of principal findings).

<table>
<thead>
<tr>
<th>Compound Fed</th>
<th>Animal Species</th>
<th>Percentage in Diet</th>
<th>Duration of Study</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>MCT Oil</td>
<td>Rat</td>
<td>20</td>
<td>10–12 mo.</td>
<td>Kaunitz et al., 1958a,b</td>
</tr>
<tr>
<td></td>
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<td></td>
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¹ The triacylglycerol contained C8:0, C10:0, and C22:0 fatty acids; the percentage in the diet is the figure for the structured triacylglycerol.

² Nolen (1981) fed a diet with 20% fat composed of 7.5% hydrogenated rapeseed oil (HRSO) and 12.5% soybean oil (SBO). The hydrogenated rapeseed oil contained 43.9% behenic acid. The percentage in the diet is the figure for behenic acid.

³ Nolen (1981) fed a diet with 20% fat composed of 7.5% superglycerinated hydrogenated rapeseed oil (SGHRSO) and 12.5% SBO. The superglycerinated hydrogenated rapeseed oil contained 42.1% behenic acid. The percentage in the diet is the figure for behenic acid.

⁴ Nolen (1981) in a second study fed a diet with 15% HRSO containing 29.8% behenic acid. The percentage in the diet is the figure for behenic acid.

⁵ Nolen (1981) in a second study fed a diet with 15% SGHRSO containing 30.6% behenic acid. The percentage in the diet is the figure for behenic acid.

⁶ Svaar et al., (1980) fed female pigs diets with 16% partially hydrogenated capelin oil (2.2% behenic acid) for periods of 1, 6, 26, and 52 weeks. The percentage in the diet is the figure for behenic acid.
Statistically significant increases in hemoglobin values occurred in female rats fed 10% caprenin and in mean platelet count of male rats fed 15% caprenin (Osheroff, 1990). Neither change was considered toxicologically significant because of the absence of a dose-related response. Statistically significant increases in mean blood urea nitrogen values in male rats fed 5, 10, or 15% of the test substance in the diet were related to increased protein intake from increased food consumption.

Statistically significant increases in serum alanine aminotransferase (ALAT) levels were found in female rats fed 10% caprenin and male and female rats fed the 15% level. Elevation of ALAT is generally considered an indication of hepatic injury. The occurrence of hepatic injury in laboratory animals may be explained by several mechanisms that include alteration of the levels of circulating hepatic enzymes, changes in hepatic excretory function, alteration of chemical composition of the liver, or histological evidence of qualitative or quantitative injury. Enzymes that reflect hepatotoxicity include: enzymes that are elevated primarily in the presence of cholestatic injury (alkaline phosphatase, 5'-nucleotidase, gamma glutamyltransferase); enzymes that are elevated primarily in the presence of parenchymal disease (alanine aminotransferase); enzymes that are elevated only in the presence of hepatic injury since they are found only in the liver (sorbitol dehydrogenase, ornithine carbamyl transferase); and enzymes that are depressed in the presence of hepatotoxicity (cholinesterase). Certain enzymes are non-specific and reflect damage to hepatic and or nonhepatic tissues (aspartate aminotransferase, lactate acid dehydrogenase) (Balazs et al., 1961; Zimmerman, 1978).

Elevation of serum ALAT was the only notable response reported in this study. Neither alteration in serum aspartate aminotransferase (ASAT) nor alkaline phosphatase levels was found nor were changes in serum bilirubin levels observed. Further, no histopathological changes were observed. These results suggest that the observed increases in serum ALAT levels were not due to the test material but probably associated with biochemical adaptation to the diet. Serum ALAT levels increased by twofold in both male and female rats. This probably represents a physiological response to diets that provided more protein as usable calories but relatively fewer total calories than the corn oil control.

ALAT values are positively related to dietary protein intake (Knox and Greengard, 1965; Rosen et al., 1959; Schimke, 1962). Data from this 28-day study show that serum ALAT levels are positively correlated with mean protein intake for both male and female rats. Knox and Greengard (1965) also reported this correlation previously and noted that it was more evident with female rats than with males. Clapp (1980) noted that serum ALAT levels increased threefold (relative to controls) when rats were maintained on weight-restrictive diets. In the 28-day feeding study with caprenin, male rats had reduced body weight gains (Osheroff, 1990). Thus, the reported increase in serum ALAT levels in the caprenin feeding trial probably is associated with increased consumption of protein from overall increased feed consumption rather than the presence of dietary caprenin, per se.

Subchronic toxicity has not been reported in studies with experimental diets containing medium-chain triacylglycerols. For example, MCT oil has been used to provide 30 to 75% of daily caloric intake of humans without adverse effects for periods of up to 30 days (Barr et al., 1985; Beveridge et al., 1959; Hashim et al., 1960; Hill et al., 1990; Mascioli et al., 1989; Sarda et al., 1987; Sulkers et al., 1989).

Coconut oil is recognized as a source of dietary saturated fatty acids and has been used in human studies of serum lipid changes and cholesterol metabolism. Intake levels of 15 to 40% of total daily energy intakes for periods up to six months have been reported (Ahrens et al., 1957; Anderson et al., 1957; Grande et al., 1961; Hegsted et al., 1965; Malmros and Wigand, 1957; Reiser et al., 1985). With the exception of elevation of total serum cholesterol levels in certain studies (an anticipated effect of certain long-chain fatty acids), no adverse health effects were reported.
No reports of subchronic toxicity of pure behenic acid in humans have been found. Available information is related to foods containing behenic acid. Although the duration of feeding was not reported, Kadam and Salunkhe (1984) reported no adverse health effects in malnourished children fed full-fat winged bean flour that supplied 1.2 g of the seed oil containing 160 to 180 mg of behenic acid/kg bw per day. Conner et al. (1964) fed six healthy adult men diets that contained peanut butter as 40% of the daily fat calories for periods of four weeks. Based on a 3000 kcal/day diet, the maximum behenic acid intake would be 3.2 g/person per day. No adverse health effects were noted.

Peanut oil, (about 3.1% behenic acid) has also been consumed by humans at levels of 20 to 40% of daily calories for periods of four weeks to 25 months (Ahrens et al., 1957; Harris and Connor, 1990; Lassere et al., 1984). Such diets would include about 1.9 to 3.8 g behenic acid/person per day. No adverse effects were associated with consumption of peanut oil containing behenoyl glycerides.

D. CHRONIC TOXICITY

Harkins and Sarett (1968) evaluated the nutritional efficacy of an MCT oil that contained about 75% caprylic and 25% capric acids. Weanling Wistar rats of both sexes were fed a diet containing 19.6% of this preparation and 2.5% safflower oil (to supply essential fatty acids) for 47 weeks. Control animals were fed diets containing oleo fat, butter fat, or coconut oil plus 2.5% safflower oil. The daily intake of caprylic acid is estimated to have been approximately 7.5 g/kg bw and that of capric acid, about 2.5 g/kg bw. The experimental diet supported normal growth and development although the weight gain was slightly but not statistically significantly less than that of rats receiving other sources of dietary fat. Histological studies showed normal intestinal and liver sections in experimental and control animals; however, rats fed the experimental diet had less carcass fat and smaller epididymal fat pads after 47 weeks than control animals. Kaunitz et al. (1958a) had also observed that male Sherman albino rats fed 20% MCT oil (constituents not further identified) for 52 weeks had lower final body weights than those of control animals fed 20% lard. These differences were statistically significant; however, no differences in survival were noted; no necropsy data were reported.

Gopalan et al. (1974) investigated the effects of feeding mustard oil (20% w/w in a diet containing 18% protein) on the heart, liver, adrenals, and sartorii muscles of adult male monkeys (Macaca radiata). Mustard oil was reported to contain 40 to 44% erucic acid and 2 to 3% behenic acid. Peanut oil and hydrogenated peanut oil were fed as reference edible oils because they are widely consumed in India. Each fat was fed for one year to groups of eight monkeys. Sera samples were collected at intervals of 2 months and at the time of sacrifice, and the sera were analyzed for total cholesterol, phospholipids, aspartate aminotransaminase (ASAT) and alanine aminotransferase (ALAT).

In monkeys fed peanut oil, both ASAT and ALAT activities increased significantly (p<.05) at 10 months over those measured at the start of the study (69 ± 22.5 vs. 15 ± 4.1 and 113 ± 41.8 vs. 18 ± 7.0, respectively); however, decreased enzyme activities observed at 12 months (ASAT = 32 ± 9.9; ALAT = 46 ± 14.7) were not significantly different from initial values (ASAT = 15 ± 4.1; ALAT = 18 ± 7.0). ALAT activity in monkeys fed hydrogenated peanut oil increased significantly at 10 months (74 ± 20.3 vs. 17 ± 4.4) (p<0.01) and 12 months (68 ± 63.3 vs. 17.4 ± 4.4) (p<0.05). Gopalan et al. (1974) did not comment on the biological significance of these increases in enzyme activity; however, these increases were similar to those observed by other investigators (Knox and Greengard, 1965; Rosen et al., 1959; Schimke, 1962) and can be explained in terms of dietary adaptation. Differences in heart and liver weights of the monkeys fed mustard oil, peanut oil, and hydrogenated peanut fat were not significant after one year of feeding the three diets. Histologically, the liver, adrenals and sartorii muscles were normal in all groups. Plasmic vacuolation of the right and left ventricular myocardium and myocardial fibrosis were observed in the hearts of the group fed mustard oil. Fatty acid composition of the organs examined was not determined.
Kracht et al. (1974) fed male and female rats (strain not identified) unheated soybean oil and unheated partially hydrogenated peanut oil as control treatments in a study of the toxicity of deep-fried fats. The internal organs of two generations of rats that had been fed diets containing up to 10% of these two oils over their entire life span were examined microscopically at natural death. Animals lived as long as 1,110 days. Forty-nine male and 34 female rats fed the unheated partially hydrogenated peanut oil and 39 male and 47 female rats fed unheated soybean oil were examined. The differences in number of rats per group resulted from failure to notice deaths before autolysis had advanced too far for necropsy. The percent of animals with pathological conditions in several organs was greater in those fed peanut oil than in animals fed soybean oil; however, the incidence of benign and malignant tumors was lower in animals fed peanut oil. Because partially hydrogenated peanut oil differs in composition from soybean oil in respects other than its behenic acid content, the pathologic differences cannot be associated with the behenic acid content alone.

E. OTHER CONSIDERATIONS

1. Adverse reactions

Available information on possible allergic reactions and hypersensitivity to caprenin is limited. No overt signs or symptoms of adverse idiosyncratic or hypersensitive reactions directly attributable to caprenin were reported in a five-day study of 10 men and 10 women each consuming 427 g of a chocolate-flavored test confection containing caprenin as 84% of the confectionery fat during the five-day period (The Procter & Gamble Company, 1991). The average total caprenin consumed in the 427 g of test confection was 120 g. Of the 41 adverse experiences reported by 14 of the 20 subjects, 34 were considered "slight" (83%), four moderate (10%) and three (7%) severe. The severe adverse experiences included migraine headache in one woman during the pretreatment period and menstrual cramps in two women during the five-day caprenin feeding trial. Moderate adverse experiences included headache in one woman during the post-treatment phase, atopic dermatitis in one woman in the caprenin feeding period, diarrhea in one woman during the post-treatment period, and vascular flushing in one man in the post-treatment period. Thus, of the seven reported instances of moderate or severe symptoms experienced by two of 10 men and four of 10 women, only five events occurred during the treatment or post-treatment phases and two of these (menstrual cramps) are unrelated to the feeding trial. The 15 adverse gastrointestinal experiences that occurred in 11 subjects were classified as slight; 13 occurred during the treatment or post-treatment phases. Eight of the 15 reported experiences involved constipation and related symptoms, a condition reported frequently in subjects confined to metabolic wards.

The extent of gastrointestinal discomfort and other consequences (e.g., trouble sleeping, headache, or fatigue) was also assessed in the 10 men studied by Swift et al. (1991). The study involved three six-day periods during which subjects were fed maintenance energy-level diets containing 40% of calories as soybean oil (LCT), MCT oil, or an 80:20 mixture of behenic acid-substituted MCT (BMCT) and soybean oil. The BMCT product was "caprenin-like" in that it contained caprylic, capric and behenic acids. The investigators monitored gastrointestinal discomfort because diets containing 200 g/day of fat as MCT used in previous studies (Hill et al., 1989) evoked complaints of gastrointestinal discomfort, primarily nausea, cramps, and diarrhea.

Similar observations have been reported in many studies and are attributed to the high osmotic load following rapid hydrolysis of short- and medium-chain triacylglycerols in the stomach and duodenum. For these reasons, a daily discomfort questionnaire was used by Swift et al. (1991) in the study of the BMCT material (The Procter & Gamble Company, 1991). Data from these questionnaires indicate that consumption of more than 100 g/day of BMCT for seven days did not result in significant gastrointestinal discomfort when compared to effects reported with MCT or LCT diets. As expected, gastrointestinal discomfort did occur initially with MCT and BMCT diets but subsided with apparent adaptation to the diet over the seven-day period. None of the other
adverse experiences (trouble sleeping, headache, fatigue) associated with consumption of the BMCT diet was significant clinically.

Taken together, these data from two studies provide no evidence of significant adverse reactions that are directly attributable to the BMCT or the caprenin in the diets. Rather, the reactions may be attributed to conditions of the feeding trials such as high osmotic loading, lack of physical exercise, and idiosyncratic responses.

2. Carcinogenicity

There are no data available on possible carcinogenicity of caprenin. Potential carcinogenicity of a chemical can be determined by both in vitro and in vivo testing. Definitive in vivo tests typically involve exposing animals to various doses of a substance for the lifetime or a major portion of the lifetime (e.g., two years in rodents). The nature of the components of caprenin does not suggest carcinogenic potential. Further, studies on related substances and components noted in this report failed to identify carcinogenic potential.

3. Developmental toxicity, mutagenicity, neurobehavioral toxicity, reproductive effects

No studies of developmental toxicity, mutagenicity, neurobehavioral toxicity, or adverse reproductive effects have been reported for caprenin. However, some investigations of these concerns have been conducted with its constituents. Kaunitz et al. (1958b) reported that Sherman rats maintained on diets containing 20% MCT oil supplemented with linoleic acid (0.09 or 2.0% of the diet) produced normal litters.

Harkins and Sarett (1968) fed groups of 15 male and 15 female rats an MCT oil containing 75% caprylic and 25% capric acid. During the 47-week study, animals received diets with 40% of calories as fat. After three weeks of consuming the MCT or other experimental diets, the animals were mated. The average number of pups per litter and the birth weights of the offspring from dams fed the MCT did not differ from those fed control diets. During lactation, dams receiving the MCT diet produced less milk of lower fat content than the control animals. Prior to weaning, the weight gain of the treated pups was less but after weaning, growth of offspring of rats fed MCT compared favorably with that of offspring of control animals. No other effects on reproduction were reported.

Caprylic acid (Litton Bionetics, Inc., 1976) exhibited no mutagenic activity in microbial assays with and without metabolic activation. The indicator microorganisms were Saccharomyces cerevisiae, strain D4 and Salmonella typhimurium, strains TA-1535, -1537, -1538.

4. Effects on lipid metabolism

Swift et al. (1991) observed a significant decrease in plasma HDL cholesterol (1.06 to 0.91 mmol/L) in 10 men who consumed diets containing BMCT and soybean oil (80:20) as 40% of total energy for six days. Similar decreases (1.11 to 0.94 mmol/L) were observed in the subjects when the diet contained 40% MCT. There was no statistically significant change in LDL cholesterol after these men received the BMCT diet for six days. This diet did produce a modest postprandial hypertriglyceridemia and low levels of chylomicrons. The investigators suggested that further studies are needed to assess the atherogenic potential of MCT and BMCT diets. The Expert Panel agrees that information on the effects of long-term caprenin ingestion on plasma lipids and lipoproteins in humans would be of interest.
5. **Effects on membranes**

Behenic acid is present in animal and plant phosphatides (Sonntag, 1979b) and in sphingomyelin (Kokatnur et al., 1985) of amniotic fluid, erythrocytes, and liver cells. Max et al. (1978) reported that behenic acid is a normal constituent of the phosphatidylcholine in rat intestinal brush border cell membranes. Presumably, dietary behenic acid is incorporated into body phospholipids; however, there are no data on whether incorporation of behenic acid into phospholipids is in accord with, greater than, or less than what would be expected based on the behenate content of the diet.

The effect, if any, that incorporation of behenate into phospholipids may have on membrane function is unknown. Bkle (1990) and Nkaido (1990) have noted that permeability of procaryotic and eucaryotic cell membranes to various substances is influenced by the fatty acid composition of the membrane (e.g., degree of fatty acid unsaturation, cis vs. trans configuration). Research on the effects of incorporation of various levels of long-chain fatty acids such as behenic acid into membrane phospholipids on membrane fluidity and function is desirable.

6. **Effects on mineral and vitamin balance**

The possible effects of caprenin on absorption of minerals and fat-soluble vitamins were also considered by the Expert Panel. Important factors in this regard are the consumption level of caprenin, the degree to which fatty acids freed from caprenin are absorbed, and the ability of fatty acids from caprenin to interact with micronutrients. The relatively low absorption of behenic acid may lead to formation of insoluble soaps with cationic minerals that are then excreted in the feces. Studies conducted on zinc and iron absorption in rats fed diets containing full-fat winged bean flour which is relatively rich in behenic acid, suggest that interference of behenate with absorption of these minerals is negligible (Hettiarachchy and Erdman, 1984). The anticipated consumption level of caprenin and the probability that caprenin-containing confections will not normally be consumed with major meals further diminish the possibility that behenate in caprenin could have a significantly adverse effect on mineral absorption.

Four factors lessen concerns in regard to interactions with fat-soluble vitamins: 1) the anticipated low level of consumption of caprenin, 2) the likelihood that the ability of the medium-chain fatty acids of caprenin to serve as solvents for absorption of fat-soluble vitamins will counteract behenate's inadequacy in this regard, 3) behenate's inability to serve as a solvent for fat-soluble vitamins lessens its ability to carry fat-soluble vitamins into the feces, and 4) caprenin-containing confections will not normally be consumed with major meals, thus lessening the interaction of caprenin with fat-soluble vitamins. This conclusion is supported by the work of Blaskovits et al. (1987) who found that absorption and accumulation of vitamin A in liver of male LATICYF rats were related to the oils in which the vitamin A was administered and the chain length of the fatty acids in the oils. They found that vitamin A appeared rapidly in the blood of animals treated with sunflower, rapeseed, or coconut oils, or emulsions of capric, palmitic, or behenic acids. Liver vitamin A levels were increased by 45% sixteen hours after gavage with the behenic acid emulsion and were equivalent to the increase observed with the sunflower oil emulsion.
7. **Ketogenic effects of caprenin**

The hydrolysis and subsequent oxidation of caprylic and capric acids from caprenin would be expected to produce some increase in plasma ketone bodies, but the extent of this effect should be relatively small and of no clinical significance. In a six-day study with 10 healthy men fed a diet containing either soybean oil or a caprenin-like fat containing 46% C8:0 and C10:0, plus 26% C22:0 fatty acids by weight, there was only a slight increase in β-hydroxybutyrate in the plasma (The Procter & Gamble Company, 1991).

The medium-chain fatty acid intake derived from ingestion of caprenin would be relatively low. The estimated 90th percentile acute exposure (g/person per eating occasion) ranges from 18.2 g for children 1 to 2 years of age to 32.6 g for males 35 to 64 years of age (see Table 5). The MCFA would be consumed as a part of a confection containing insulinogenic sugars which would counterbalance the ketogenic effect of the MCFA intake. The risk of significant ketoacidosis from caprenin should be negligible in healthy individuals and type II diabetic patients. MCFA-containing foods would be expected to be mildly ketogenic in type I diabetic patients with low insulin secretion and decreased peripheral utilization of ketones. These patients, however, usually are on prescribed or carefully controlled diets which limit products expected to contain high levels of sucrose such as candy.
V. OPINION OF THE EXPERT PANEL

A. CONCLUSIONS

Caprenin is a randomized triacylglycerol of caprylic (C8:0), capric (C10:0), and behenic (C22:0) acids. Although this triacylglycerol does not occur in currently consumed edible fats and oils, its component fatty acids are widely distributed at low levels among edible animal fats and vegetable oils. Caprenin is prepared by conventional fat-processing technology, is semi-solid at room temperature, has functional and sensory properties similar to those of cocoa butter, and has potential use as a confectionery fat. Because of low absorption of behenic acid and the inefficient energy utilization of capric and caprylic acids, the substance has a caloric density of about 5 kcal/g rather than 9 kcal/g for conventional dietary fats.

The anticipated uses of caprenin are as a confectionery fat in soft candy (such as candy bars, caramel and nougat) and in confectionery coatings of various products, replacing cocoa butter and other fats. Potential usage levels indicate that average chronic exposures for younger children (1 to 5 years of age), older children (6 to 14 years of age), adolescents (15 to 18 years of age), and adults (19 to 64 years of age) would range from 0.15 to 0.11, 0.09 to 0.07, 0.05, and 0.04 to 0.03 g/kg bw per day, respectively. Average acute exposures for these same age groups would be highest for children 1 to 2 years of age (0.84 g/kg bw per day), ranging progressively downward to 0.22 to 0.18 g/kg bw per day for adults 19 to 64 years of age. Chronic intakes of heavy consumers (90th percentile) for the same age groups would range from 0.35 g/kg bw per day for children 1 to 2 years of age down to 0.09 to 0.06 g/kg bw per day for adults. Acute exposures for the same age groups would be 1.6 and 0.47 to 0.40 g/kg bw per day for the same age groups. By comparison, the average confectionery fat consumption by children 1 to 2 years of age who eat candy is about 5.3% (1.7 g/person per day or 0.15 g/kg bw per day) of the average daily intake of all fats. For adults, the average confectionery fat consumption is about 3% (2.1 to 3.2 g/person per day or 0.03 to 0.04 g/kg bw per day) of the average daily fat intake.

There is no evidence of significant adverse health effects in the available information on caprenin or its constituent moieties at the estimated potential levels of consumption. Experimental studies with laboratory animals and humans reviewed in detail in this report have shown that caprenin is digested, absorbed, and metabolized by the usual pathways of triacylglycerol metabolism. As with other triacylglycerols, the medium-chain fatty acid components are readily absorbed, while the long-chain component, behenic acid, is absorbed more slowly and less completely.

In subchronic feeding trials with caprenin in four-week-old weanling rats that consumed an average of 18.8 g/kg bw per day during week 1 and 11.4 g/kg bw per day during week 4, no evidence of adverse effects was observed during feeding or found in subsequent histopathological examinations. Similar experimental feeding trials with related substances such as behenyl glyceride in rats and hamsters, hydrogenated rapeseed oil and superglycerinated hydrogenated rapeseed oil (91 and 117 days in rats), and various fish oils containing 2.2% behenic acid (30 weeks in rats; up to 52 weeks in pigs and monkeys) revealed no evidence of toxicity specifically related to the behenic acid present in the experimental diets. Similarly, studies of the possible toxicity of diets containing about 20% of an MCT (a mixture of 75% caprylic and 25% capric acid) fed to rats for 47 weeks provided no evidence of adverse effects on growth and development.

Long-term toxicity studies with monkeys fed mustard oil (2 to 3% behenic acid) and peanut oil (about 3% behenic acid) for 12 months revealed no histopathological evidence of toxic effects attributable to behenic acid. In a two-generation study in which rats in the control groups were fed hydrogenated peanut oil (estimated to contain about 3% behenic acid), no behenic acid-related effects were identified at autopsy.
The data reviewed in the course of preparing this report did not raise concerns about possible effects of caprenin on mineral and vitamin balances or with ketogenesis. One human feeding study reported a decrease in HDL cholesterol, a modest postprandial hypertriglyceridemia, and low levels of chylomicrons following feeding of a diet which contained 80% of the fat as a structured triacylglycerol containing behenic and medium-chain fatty acids. By comparison, anticipated uses of caprenin as a confectionery fat would constitute an intake of about 3% of the daily dietary fat of candy eaters, and less for infrequent eaters. Nevertheless, it would be of interest to obtain information on the long-term effects of caprenin ingestion on lipoprotein metabolism in humans.

Based on the available information and evaluation of the biological effects of caprenin, the Expert Panel concludes that:

*The available information supports a Generally Recognized as Safe (GRAS) classification of caprenin when used at levels that might reasonably be expected in its intended uses as a confectionery fat in soft candy and confectionery coatings.*

B. RECOMMENDATIONS

While there is no evidence in the available scientific information to suggest adverse health effects, the Expert Panel strongly recommends that, if caprenin is marketed for its intended uses, a mechanism should be provided for consumer comment; specifically, a toll-free number should be made available via labeling information. Consumer comments to the manufacturer which are also made available to the Food and Drug Administration, would provide an additional follow-up measure to the assurance of safety evidenced by the information and data evaluated by the Expert Panel.

The Expert Panel also suggests that, in due course, as time permits, studies should be conducted to identify the effects of dietary saturated long-chain fatty acids such as behenic acid, on phospholipid membrane fluidity and function in mammalian cells. Available information also suggests that triacylglycerols containing medium-chain fatty acids, when consumed over extended periods, influence levels of blood lipoproteins. Possible changes in circulating levels of various blood lipoproteins following consumption of triacylglycerols such as caprenin should be explored. Finally, data on possible gastrointestinal effects of caprenin in humans following periods of chronic ingestion at dosages that approximate levels of intended use should be obtained under controlled conditions.
VI. REFERENCES CITED


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