EVALUATION OF THE HEALTH ASPECTS OF CAFFEINE

AS A FOOD INGREDIENT

1978

Prepared for

Bureau of Foods
Food and Drug Administration
Department of Health, Education, and Welfare
Washington, D.C.

Contract No. FDA 223-75-2004
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Life Sciences Research Office
Federation of American Societies
for Experimental Biology
9650 Rockville Pike
Bethesda, Maryland 20014
NOTICE

This report is one of a series concerning the health aspects of using the Generally Recognized as Safe (GRAS) or prior sanctioned food substances as food ingredients, being made by the Federation of American Societies for Experimental Biology (FASEB) under contract no. 223-75-2004 with the Food and Drug Administration (FDA), U.S. Department of Health, Education, and Welfare. 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 Life Sciences Research Office (LSRO), established by FASEB in 1962 to make scientific assessments in the biomedical sciences, is conducting these studies.

Qualified scientists were selected as consultants to review and evaluate the available information on each of the GRAS substances. These scientists, designated the Select Committee on GRAS Substances, were chosen for their experience and judgment with due consideration for balance and breadth in the appropriate professional disciplines. The Select Committee's evaluations are being made independently of FDA or any other group, governmental or nongovernmental. The Select Committee accepts responsibility for the content of each report. Members of the Select Committee who have contributed to this report are named in Section VII.

Tentative reports are made available to the public for review in the Office of the Hearing Clerk, Food and Drug Administration, after announcement in the Federal Register, and opportunity is provided for any interested person to appear before the Select Committee at a public hearing to make oral presentation of data, information, and views on the substances covered by the report. The data, information, and views presented at the hearing are considered by the Select Committee in reaching its final conclusions. Reports are approved by the Select Committee and the Director of LSRO, and subsequently reviewed and approved by the LSRO Advisory Committee (which consists of representatives of each constituent society of FASEB) under authority delegated by the Executive Committee of the Federation Board. Upon completion of these review procedures the reports are approved and transmitted to FDA by the Executive Director of FASEB.

While this is a report of the Federation of American Societies for Experimental Biology, it does not necessarily reflect the opinion of all of the individual members of its constituent societies.

[Signature]
Kenneth D. Fisher, Ph.D., Director
Life Sciences Research Office
FASEB

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I. INTRODUCTION

This report concerns the health aspects of using caffeine as a food ingredient. It has been based partly on the information contained in a scientific literature review (monograph) furnished by FDA (1), which summarizes the world's scientific literature from 1920 through 1974.* To assure completeness and currency as of the date of this report this information has been supplemented by searches of over 30 scientific and statistical reference sources and compendia that are generally available; use of new, relevant books and reviews and the literature citations contained in them; consideration of current literature citations obtained through computer retrieval systems of the National Library of Medicine; recent literature searches by the Toxicology Information Response Center, Oak Ridge, Tennessee; searches for relevant data in the files of FDA; and by the combined knowledge and experience of members of the Select Committee and the LSRO staff. In addition, announcement was made in the Federal Register on April 1, 1977 (42 FR 17526-17529) that opportunity would be provided for any interested person to appear before the Select Committee at a public hearing to make oral presentation of data, information, and views on the health aspects of using caffeine as a food ingredient. Two requests were received. The Select Committee held a hearing on September 26, 1977. Those who requested opportunity to present data, information, and views are identified on page 56. The material presented at the hearing has been considered by the Select Committee in reaching its final conclusions.

As indicated in the Food, Drug, and Cosmetic Act [21 USC 321 (s)], GRAS substances are exempt from the premarketing clearance that is required for food additives. It is stated in the Act and in the Code of Federal Regulations (2) [21 CFR 170.3 and 170.30] that GRAS means 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 credible toxicological testing or, for those substances used in food prior to January 1, 1958, on a reasoned judgment founded in experience with common food use, and 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. FDA (2) recognizes further [21 CFR 170.30] that it is impossible to provide assurance that any substance is absolutely safe for human consumption.

*The document (PB-234 894/4) is available from the National Technical Information Service, U.S. Department of Commerce, P.O. Box 1553, Springfield, Virginia 22161.
The Select Committee on GRAS Substances of LSRO is making its evaluations of these substances in full recognition of the foregoing provisions. In reaching its conclusions on safety, the Committee, in accordance with FDA's guidelines, is relying primarily on the absence of substantive evidence of, or reasonable grounds to suspect, a significant risk to the public health. While the Committee realizes that a conclusion based on such reasoned judgment is expected even in instances where the available information is qualitatively or quantitatively limited, it recognizes that there can be instances where, in the judgment of the Committee, there are insufficient data upon which to base a conclusion. The Committee is aware that its conclusions will need to be reviewed as new or better information becomes available.

In this context, the LSRO Select Committee on GRAS Substances has reviewed the available information on caffeine and submits its interpretation and assessment in this report, which is intended for the use of FDA in determining the future status of this substance.
II. BACKGROUND INFORMATION

Caffeine is the alkaloid 1,3,7-trimethylxanthine. It is one of the xanthine derivatives present up to 1.5 percent in seeds of coffee (Coffee arabica L.) and up to 5 percent in the leaves of tea (Camellia sinensis). It is a component of beverages made from these plants. Caffeine is also a component of chocolate (Theobroma cacao L.) and the kola nut (Cola acuminata Schott and Endl. and related species), the extract of which is used in cola drinks (1-3).

The Food Chemicals Codex (4, 5) specifications for caffeine require that it contain not less than 98.5 percent and not more than the equivalent of 101.0 percent of \( C_8 H_{10} N_4 O_2 \) calculated on the anhydrous basis. The limits for impurities are arsenic (as As), not more than 3 ppm; heavy metals (as Pb), not more than 20 ppm; and lead, not more than 10 ppm. It should pass a specified test for the presence of other alkaloids.

Caffeine is listed in the Code of Federal Regulations (2) as a multiple purpose GRAS food substance, limited to cola-type beverages with a permissible level of up to 0.02 percent [21 CFR 182.1180]. Cola-type beverages are defined in the Code [21 CFR 165.175] as those that shall contain caffeine from kola nut extract and/or other natural caffeine-containing extracts. This regulation also indicates that caffeine may be added to any soda water. According to 21 CFR 165.175 the caffeine concentration in the finished food shall not exceed 0.02 percent by weight.

Kola nut, the dried cotyledons of the seeds of the edible species of the genus Cola, has been chewed as a stimulant by the peoples of West Africa where the plants are native (6). In cola-type beverages aqueous alcoholic extracts of kola nut, containing about 2.35 percent caffeine, are used as a flavor ingredient; the extract is blended in the syrup base such that the final beverage contains about 120 ppm of the extract (7). On this basis the amount of kola nut extract needed for flavoring provides less than 10 percent of the caffeine present in cola-type beverages; the remaining more than 90 percent is added caffeine.

Whether caffeine is added to cola-type beverages primarily for its stimulatory effects or for the enhancement of flavor, is not known to the Select Committee. According to Korab (8) subtle and subliminal flavors are widely appreciated by consumers and caffeine has a modifying effect on other components of a beverage. He believes that there is an effect on flavor if caffeine is omitted. The threshold for detecting the presence of caffeine in liquid foods varies depending on the nature of other substances present, but lies close to the level characteristic of currently produced cola-type beverages. Mackey and Valassi (9) found the threshold for detection of caffeine
in water to be 0.0095 percent; in liquid foods, 0.0184 percent. Pangborn (10) found panelists could distinguish a solution containing 0.0058 percent caffeine from the control. Lyons (11) found that the threshold for detecting a taste difference between an aqueous solution of caffeine and a water control was 0.005 percent caffeine and to distinguish bitterness 0.011 percent caffeine. In another study, Pangborn (12) showed that in aqueous solutions containing threshold and sub-threshold concentrations of caffeine, sucrose, citric acid and salt, all compounds depressed the taste intensity of each other.

The Select Committee is considering in this report only the addition of caffeine to nonalcoholic (cola-type) beverages. This report is not concerned with caffeine as a natural component of coffee or tea. However, since estimates of caffeine consumption from these sources provide a point of orientation in considering the magnitude of total caffeine consumption from all food and beverage sources, the following information is provided: In 1975 the United States imported 2.7 billion pounds of crude coffee, 36 million pounds of roasted or ground coffee, 49 million pounds of instant or soluble coffee, 72 thousand pounds of coffee extract, 159 million pounds of tea, and 1.5 million pounds of caffeine (13). In addition to caffeine, some of these sources may contain other xanthine alkaloids such as theophylline (1,3 dimethylxanthine) and theobromine (3,7 dimethylxanthine) which are pharmacologically similar to caffeine (14).

Therefore, when the health aspects of total exposure of the population to caffeine and other xanthine bases are matters for consideration, account must be taken of consumption from all beverage and food sources and of the biological consequences of this level of exposure. Gilbert* has recently prepared a comprehensive review and evaluation of caffeine from this viewpoint.

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III. CONSUMER EXPOSURE DATA

A subcommittee of the National Research Council (15, 16) surveyed manufacturers concerning the addition of GRAS substances to foods. Based on information supplied, a weighted mean of 0.014 percent was calculated for the maximum level of addition of caffeine to cola beverages. The NRC subcommittee estimated possible average daily intakes of caffeine from Market Research Corporation of America data on the mean frequency of consumption of cola beverages, U.S. Department of Agriculture data on mean portion size, and the assumption that all cola-type beverages contain 0.014 percent caffeine. Mean intakes of caffeine were estimated to be 0.013 mg per kg per day for those 0 to 5 months old, 0.045 mg per kg per day for those 6 to 11 months old, 0.39 mg per kg per day for those 12 to 23 months old, and 0.22 mg per kg per day for those 2 to 65 or more years old. Recalculated on the basis of 0.01 percent caffeine in cola-type beverages, a concentration that appears from what follows to be more realistic, these figures become 0.01, 0.032, 0.28, and 0.16 mg per kg per day, respectively.

Alternative estimates of daily caffeine intake due to consumption of cola beverages have been made based on additional data in the NRC reports and other sources.

Consumption can be estimated from frequency data acquired by the Market Research Corporation of America in a national household menu census involving thousands of respondents (17), and serving size data reported in a U.S. Department of Agriculture survey of 24-hour recalls of food eaten by some 3,000 individuals.* According to these data, adults of 25 or older consume 8 to 12 fluid ounces of cola beverage per drink and this is repeated 4.5 to 6.4 times during a 2-week period. Corresponding figures for 6- to 24-year-olds are 12 ounces and 4.4 to 6.2 times in 2 weeks; for children up to 5 years old, 3.5 to 5 ounces and 4.1 to 5.2 times in 2 weeks. Assuming that the maximum volume for each range is consumed in each case, the amount of caffeine consumed via cola drinks on the day of each drinking would be as shown in Table I.

*Developed for the Select Committee by Food and Drug Administration from raw data in the U.S. Department of Agriculture survey and provided in memorandum from Arletta Beloian to Corbin Miles dated December 11, 1975.
### TABLE I

Estimated Caffeine Consumption at Each Drinking of Cola Beverages

<table>
<thead>
<tr>
<th>Age group</th>
<th>Cola beverage consumed at each drinking</th>
<th>Caffeine consumed at each drinking*</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;5 yr</td>
<td>150 ml</td>
<td>15 mg</td>
</tr>
<tr>
<td>6-24 yr</td>
<td>350 ml</td>
<td>35 mg</td>
</tr>
<tr>
<td>25+ yr</td>
<td>350 ml</td>
<td>35 mg</td>
</tr>
</tbody>
</table>

* Based on 0.01 percent caffeine. Examination of raw data in the National Research Council (NRC) survey (15) by Durward Dodgen, NRC (communicated to the Select Committee on December 9, 1975), indicated that the usual range of caffeine concentration in cola beverages is from 0.011 to 0.015 percent. A consensus of manufacturers of cola beverages (letter from E. E. Lockhart, the Coca Cola Company, Atlanta, Georgia, dated June 27, 1975) indicated that cola beverages usually contain less than 4 mg caffeine per fluid ounce (<0.012 percent).

Since there were repeated drinkings during the 2-week census period, the average daily intake can also be calculated (Table II) from the figures given above, again assuming the maximum of the ranges given in each instance.

### TABLE II

Estimated Caffeine Consumed from Cola Beverages Over a 14-Day Period by Those Who Consume Them

<table>
<thead>
<tr>
<th>Age group</th>
<th>Cola beverage consumed in 14 days</th>
<th>Total caffeine consumed</th>
<th>Caffeine consumed per day*</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;5 yr</td>
<td>770 ml</td>
<td>77 mg</td>
<td>5.5 mg</td>
</tr>
<tr>
<td>6-24 yr</td>
<td>2200 ml</td>
<td>220 mg</td>
<td>15.5 mg</td>
</tr>
<tr>
<td>25+ yr</td>
<td>2260 ml</td>
<td>225 mg</td>
<td>16.0 b mg</td>
</tr>
</tbody>
</table>

* See footnote in Table I.

b Assuming a body weight of 60 kg, consumption would be 0.27 mg per kg per day.
Calculation of a per capita daily intake can be made from annual poundage data provided in the earlier of the two NRC reports (15). Some 1.4 million pounds (0.64 million kg) of caffeine were reported to be added to food in 1970 by those responding to the survey. The NRC subcommittee has estimated that this amount is 90 percent of that actually used by the food industry in all cola beverages. Therefore, that actually used would be about 0.71 million kg. Based on 0.71 million kg annually and a population of 205 million, the per capita intake would be 0.16 mg per kg per day of caffeine from this source. Since the per capita figure includes non-drinkers, it would be expected to be smaller than that given for adults in Table II. In the more recent NRC report (16), new manufacturers' estimates place the annual poundage used in food at 2.0 million (0.91 million kg), making the calculated per capita intake 0.21 mg per kg per day.

Estimates of caffeine consumption from all sources (soft drinks, coffee, tea, chocolate) were presented by Burg (18) at a public hearing before the Select Committee on September 26, 1977. These estimates were derived by Burg from household menu census data obtained by the Market Research Corporation of America in surveying a nationally representative sample (4,000 households, 12,337 individuals) during a 12-month period in 1972-73. The population surveyed was selected to recognize possible differences due to geographic region, city size, household size, age of housewife, and income. Mean consumption of caffeine by consumers of soft drinks from soft drinks alone and from all sources are given in Table III. These estimates were based on detailed records obtained for all foods eaten at home and away from home by individuals in several age groups.

### TABLE III

Mean Consumption of Caffeine by Consumers of Soft Drinks

[Taken from Burg (18)]

<table>
<thead>
<tr>
<th>Age</th>
<th>Caffeine from all sources a mg/kg/day</th>
<th>Caffeine from soft drinks b mg/kg/day</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-11 mo</td>
<td>0.70</td>
<td>0.17</td>
</tr>
<tr>
<td>1-5 yr</td>
<td>1.4</td>
<td>0.49</td>
</tr>
<tr>
<td>6-11 yr</td>
<td>1.0</td>
<td>0.31</td>
</tr>
<tr>
<td>12-17 yr</td>
<td>0.87</td>
<td>0.21</td>
</tr>
<tr>
<td>18+ yr</td>
<td>2.4</td>
<td>0.18</td>
</tr>
</tbody>
</table>

a Includes soft drinks, coffee, tea, chocolate
b Calculation based on portion size estimates of the U.S. Department of Agriculture and an assumed caffeine content of 0.01 percent. While caffeine content of soft drinks cannot exceed 0.02 percent (2), actual caffeine content of the four major caffeine-containing soft drinks are 0.0075, 0.0107, 0.0116, and 0.0127 percent (18).
Burg (18) also derived the data given in Table IV showing mean consumption of caffeine by soft drink consumers in the 75th to 90th, and 90th to 100th percentiles. Comparable data are contained in the 1977 NRC report (16).

**TABLE IV**

Mean Consumption of Caffeine by Consumers of Soft Drinks
[Taken from Burg (18)]

<table>
<thead>
<tr>
<th>Age (yr)</th>
<th>75th to 90th percentile</th>
<th>90th to 100th percentile</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Caffeine from all sources$^a$</td>
<td>Caffeine from soft drinks$^b$</td>
</tr>
<tr>
<td>1-5</td>
<td>2.2 mg/kg/day</td>
<td>0.82 mg/kg/day</td>
</tr>
<tr>
<td>6-11</td>
<td>1.4 mg/kg/day</td>
<td>0.51 mg/kg/day</td>
</tr>
<tr>
<td>12-17</td>
<td>1.3 mg/kg/day</td>
<td>0.37 mg/kg/day</td>
</tr>
<tr>
<td>18+</td>
<td>2.3 mg/kg/day</td>
<td>0.32 mg/kg/day</td>
</tr>
</tbody>
</table>

$^a$ See corresponding footnote, Table III
$^b$ See corresponding footnote, Table III

It is likely that mean caffeine consumption from cola drinks by those who consume them, is of the order of 0.2 to 0.5 mg per kg per day with the highest levels in the 1 to 5 year old age group. For the 75th to 90th percentile, consumption is 0.3 to 0.8 mg per kg per day and for the 90th to 100th percentile, 0.7 to 2 mg per kg per day, again with the higher levels in the 1 to 5 year old age group. These figures are based on a caffeine content of 0.01 percent in cola beverages. If cola beverages should contain the maximum permitted percentage of caffeine of 0.02 percent (2), these figures would be doubled.

By contrast, it can be seen from Tables III and IV that daily consumption of caffeine by cola drinkers from all sources (tea, coffee, chocolate) other than cola beverages is two to four times that consumed as cola beverages by children and adolescents, and four to thirteen times that consumed as cola beverages by adults.

For further comparative purposes the following data are noteworthy:

- Burg (19) surveyed the caffeine content of "variously prepared, average brews" of coffee, tea, and cocoa based on recent analyses. He concluded that an average cup of coffee contains 85 mg of caffeine, of leaf tea approximately 50 mg caffeine, and of cocoa, depending on the source, 5 to 40 mg caffeine. In reporting these values, Burg (19) noted the difficulties in
assessing a "standard cup" and the significance of the brewing methods on the concentration of caffeine in the final beverage as consumed.

• It is estimated by the International Coffee Organization (20) that in 1974, 2.25 cups of coffee were consumed daily by persons 10 years of age and older in the United States. Children 10 to 14 years old averaged 0.11 cup per day, youths 15 to 19 years old, 0.46 cups per day. Thus, at 85 mg caffeine per cup, coffee drinking by the 175 million persons over 9 years of age* would result in a daily per capita intake of about 190 mg (about 3 mg per kg) of caffeine; for 10 to 14 year olds, about 9 mg (about 0.2 mg per kg); for 15 to 19 year olds, about 40 mg (about 0.7 mg per kg).

• Calculations can also be made from other data from the Pan American Coffee Bureau report (21). About 62 percent of all persons in the United States drink coffee; those who do, consume 3.65 cups daily, amounting to a daily intake of 310 mg (about 5 mg per kg for adults) caffeine from this source.

For the purposes of this report, the Select Committee considers that for most consumers the intake of caffeine due to drinking cola beverages is of the order of 0.3 mg per kg per day and that for only a small (less than 10 percent) number of consumers could caffeine intakes from this source be as high as 1.8 mg per kg per day. The corresponding range of intakes of caffeine by cola drinkers from all other sources (given in Tables III and IV) are 1 to 2 and 2 to 3 mg per kg per day, respectively.

* Telephone information from U.S. Census Bureau.
IV. BIOLOGICAL STUDIES

Absorption, metabolism, and excretion

Animal studies: Burg and Werner (22) intubated adult male CD-1 mice with 5 to 25 mg per kg body weight of doubly-labeled \(^{14}\)C, \(^{3}\)H-caffeine to trace subsequent metabolic events. The animals were killed at various times from 5 minutes to 24 hours after dosing and organ homogenates were assayed for radioactivity. Within 5 minutes of dosing, caffeine rapidly entered all organs and tissues, and after 1 hour, distributed in proportion to tissue water. The half-life of caffeine in all organs was less than 3 hours. The major metabolite was found to be 1,7-dimethylxanthine. Little 1-methyluric acid was present in the tissues. The authors suggest that their data indicate that a barrier in brain and testes may impede accumulation of caffeine in those organs. In another experiment adult male CD-1 mice which had received up to 25 mg caffeine per kg per day in their drinking water since weaning were given a single 10 mg per kg dose of caffeine labeled in the 1-methyl position with \(^{14}\)C. Twenty-four hours later the mice were sacrificed by quick-freezing and transections made for radioautography. No significant difference in distribution of caffeine was observed as compared to animals receiving caffeine for the first time.

Bernthal and Christensen (23) have shown that peak caffeine concentrations following an oral dose of 1.5 mg per kg of caffeine in rats are 3.15 \(\mu\)g per ml in plasma, and 0.46 to 1.1 \(\mu\)g per g in the brain.

Experiments with dogs receiving 4 mg caffeine per kg body weight intravenously indicated a half-life of about 5 hours and showed the distribution of caffeine to be in approximate proportion to the water content of the tissues (24). In contrast, Burg et al. (25) found caffeine half-life, administered in a single oral dose, to be 11 hours in the plasma of squirrel monkeys and 2.4 hours in rhesus monkeys but metabolic products in both were found to be the same and similar to those for mice.

Burg and Stein (26) found the main excretory route for caffeine in male CD-1 mice to be urinary. Intubated, doubly-labeled \(^{14}\)C, \(^{3}\)H caffeine was almost entirely absorbed from the gastrointestinal tract with little appearing in the feces. Of the total radioactivity of the caffeine given to mice, 64 to 90 percent was recovered in the urine, chiefly as metabolites; 1,7-dimethylxanthine, 3-methylxanthine, 7-methylxanthine, 1,3-dimethyluric acid, and 1-methyluric acid. Only 3 to 6 percent of the total administered caffeine appeared in the urine as unchanged caffeine. Within 8 hours of dosing with 25 mg per kg of radiolabeled caffeine, 80 percent of the metabolites had been excreted in the urine.
Khanna et al. (27) administered intraperitoneally 40 mg per kg of tritiated caffeine to male rats and found 37 percent of the radioactivity excreted as chloroform-methanol soluble substances in the urine in 24 hours. About 8.8 percent was unchanged caffeine. The main urinary metabolite (11.4 percent) was unidentified; other metabolites included p-xanthine (8.8 percent), theobromine (5.1 percent), theophylline (1.2 percent), and another unidentified substance (1.3 percent). Rao et al. (28) characterized the main unidentified metabolite as 1,3,7-trimethylxanthine and the minor unidentified metabolite as 3,6,8-trimethylallantoin. Sved et al. (29) found theophylline in plasma 5 to 7.5 hours after an oral dose of 300 mg caffeine.

Recently, Kamei et al. (30) have described three sulfur-containing metabolites of caffeine, namely, α-[7-(1,3 dimethylxanthinyl)]-methyl methyl sulfoxide and the corresponding sulfide and sulfone, in the 48-hour urine samples of the horse, rabbit, rat, and mouse. The compounds were identified by isolation, mass spectrography and chromatography, and confirmed by synthesis. The caffeine was orally administered but the doses were not indicated.

**Human studies:** Axelrod and Reicenthal (24) administered oral doses of 7 mg per kg caffeine to three men. Peak plasma levels occurred about 1 hour after dosing. After an intravenous dose of 500 mg caffeine (7 mg per kg) only about 0.5 to 1.5 percent was excreted unchanged in the urine, and the plasma half-life was about 3.5 hours.

The plasma level time-courses of caffeine in male human subjects, given caffeine orally, intramuscularly, or intravenously were studied by Sant'Ambrogio et al. (31). Doses varied from 6 to 9 mg per kg body weight. After oral administration, the plasma levels of caffeine peaked at 30 minutes; intramuscular injection produced peaks at 60 minutes. After intravenous injection, half of the caffeine dose diffused into tissues in about 1.5 minutes. The metabolic half-life of caffeine in man was found to be about 3 hours. Similar results were obtained by Chvasta and Cooke (32) who found in six healthy volunteers that 16 percent of an oral dose of 3 mg caffeine per kg was absorbed after 20 minutes. Other recent human studies have indicated a caffeine half-life of 4 hours (33), 3.8 hours (34), 5 hours (29), 5.6 hours (35), and 5 hours (36). Parsons et al. (36, 37) observed that plasma half-life of caffeine received in utero by human full-term neonates averaged 80 hours and that in pregnant women (38 to 40 weeks post-conception) the apparent plasma half-life after receiving caffeine was 18 hours (36). Neims and Aranda (38) found the half-life of caffeine to be 97.5 hours in premature infants with a clearance rate about one-fifteenth that of adults. The greater half-life was attributed to slower renal excretion in the newborn than in adults. However, half-life and clearance rate for caffeine were found to equal that of the adult about 6 months after birth. Half-life of caffeine in females during the third trimester of pregnancy was found to be four times that in non-pregnant females, with a return to normal values 6 weeks postpartum.
Peak steady state plasma concentrations of caffeine, ranging from 5 to 18 μg per ml, were attained within 2 hours in premature newborns given 2.5 mg of caffeine citrate per kg per day orally to treat apnea. Christensen and Whitsett (34) found peak plasma caffeine levels in man after oral administration of 1.1, 2.2, 4.4, and 8.8 mg per kg to be 1.2, 2.4, 5.7, and 14.5 μg per ml, respectively.

Goldstein and Warren (39) showed that caffeine equilibrates freely between plasma and tissue water of the human ovary and testis as determined by intravenous infusion of surgical specimens. Caffeine was also found to equilibrate freely between maternal plasma and the 7 to 8-week-old fetus. The authors conclude that the gonads and the products of conception in those who consume caffeine are exposed to the concentrations of the alkaloid that are reached in the extracellular body water.

Caffeine in the body tissues of a presumed suicide from an overdose of caffeine was determined by Parish et al. (40) to be distributed in the following tissues in decreasing concentration: stomach, liver, kidney, and brain. Comparative studies of rats killed by an oral dose of 1 g caffeine per kg body weight showed a similar distribution of caffeine in these organs.

Buchanan et al. (41) in 1945 investigated the possibility that some caffeine metabolites are converted to uric acid because some reports noted an increased uric acid excretion following caffeine and theophylline ingestion (coffee and tea) but not from theobromine ingestion (cocoa). Using a more specific uricase enzymatic procedure, it was demonstrated that total uric acid excretion over a 24-hour period is increased little, if at all, by oral caffeine (about 15 mg per kg body weight), or by theophylline. Weinfeld and Christman (42) studying the urinary metabolites of human subjects given 1 g doses of caffeine, confirmed that no appreciable uric acid is excreted. The principal urinary excretion product of caffeine was shown to be 1-methyl-uric acid; a sequence of metabolic events was postulated. In a related study by Warren (43) a two-stage system for thin-layer chromatographic separation was devised and applied to blood samples from human volunteers ingesting 500 mg of caffeine. Both caffeine and paraxanthine (1, 7-dimethylxanthine) appeared in red cells and plasma within 3 hours and disappeared from blood extracts within 24 hours. It was concluded that the first step in caffeine metabolism in man appears to be the removal of the 3-methyl group to yield 1, 7-dimethylxanthine.

Christensen and Whitsett (34) found little difference in pharmacokinetic parameters regardless of whether caffeine was administered to men as a solution or as coffee. This coincides with the animal studies of Czok et al. (44) who found no difference in the physiological disposition of radioactivity in rats whether radiolabeled caffeine was administered as caffeine solution or as coffee. However, when administered as tea, a decreased rate of uptake
from the gastrointestinal tract and longer retention in the tissues was observed. By contrast, Marks and Kelly (45) found no difference in the rate of increase of caffeine in the venous blood of human volunteers after oral administration of coffee or tea containing equivalent amounts of caffeine. When given as cola-type beverage, caffeine plasma levels increased at a slower rate, peaking at 60 minutes as compared to 30 minutes for coffee or tea. Houston and Levy (46) suggest that the slower rate of absorption of caffeine from soft drinks may be due to a decrease in gastric motility and emptying rate caused by soft drinks.

Horning et al. (47) and Horning (48) in testimony before the Select Committee at its public hearing on September 26, 1977, supplemented subsequently (49), presented data on human mother-infant pairs comparing caffeine concentration in breast milk and in maternal and neonatal plasma. Samples analyzed on the third, fourth, and fifth neonatal days showed that neonatal caffeine concentration in plasma (0.75 to 2.7 mg per l) was significantly lower than that of the breast milk (1.3 to 6.9 mg per l). The concentration of caffeine in neonatal plasma was similar to that of maternal plasma. While level of caffeine in breast milk was equal to or greater than the level in maternal plasma, there was no evidence of sequestering of caffeine in breast milk. The highest caffeine concentration observed in breast milk was 8.05 mg per l. Assuming consumption of 150 ml of breast milk per kg per day, the intake of an infant under such circumstances would be about 1.2 mg per kg per day. It was also noted that of several hundred neonates observed, all excreted caffeine in the urine during the first few days after birth indicating that they were exposed to caffeine in utero.

These and other data on the comparative absorption, distribution, metabolism, and excretion of caffeine in man have been summarized by Burg (50). It is evident that ingested caffeine is absorbed, metabolized and excreted in the urine as xanthine derivatives. The half-life in the plasma and most organs is of the order of 3 to 5 hours.

Acute toxicity

Animal studies: Table V summarizes the data on acute toxicity of caffeine in animals.

Studies have also been made on the effects of various factors on caffeine toxicity. Scott et al. (55) found the acute toxicological properties of synthetic and natural caffeine to be identical; the intravenous LD₅₀ in mice was 76 mg per kg for the synthetic and 79 mg per kg for the natural caffeine. The effect of age on caffeine toxicity in rats was studied by Poe and Johnson (56) who found that sensitivity is greater in old animals; the intraperitoneal LD₅₀ was 200 mg per kg for rats 1.5 months old, 205 mg for rats 2 to 4 months old, and 167 mg for rats 6 to 9 months old. Kuftinec and Mayer (57)
# TABLE V

## Acute Toxicity of Caffeine in Animals

<table>
<thead>
<tr>
<th>Animal</th>
<th>Route</th>
<th>Measurement</th>
<th>Dosage (mg/kg)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mouse</td>
<td>sc</td>
<td>LD</td>
<td>180-190</td>
<td>51</td>
</tr>
<tr>
<td>Mouse</td>
<td>ip</td>
<td>MLD</td>
<td>220</td>
<td>51</td>
</tr>
<tr>
<td>Mouse</td>
<td>ip</td>
<td>LD</td>
<td>500</td>
<td>51</td>
</tr>
<tr>
<td>Mouse</td>
<td>ip</td>
<td>LD</td>
<td>250</td>
<td>51</td>
</tr>
<tr>
<td>Mouse</td>
<td>iv</td>
<td>LD&lt;sub&gt;50&lt;/sub&gt;</td>
<td>100</td>
<td>51</td>
</tr>
<tr>
<td>Mouse, male</td>
<td>or</td>
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<td>127</td>
<td>52</td>
</tr>
<tr>
<td>Mouse, female</td>
<td>or</td>
<td>LD&lt;sub&gt;50&lt;/sub&gt;</td>
<td>137</td>
<td>52</td>
</tr>
<tr>
<td>Rat</td>
<td>or</td>
<td>LD&lt;sub&gt;50&lt;/sub&gt;</td>
<td>200</td>
<td>51</td>
</tr>
<tr>
<td>Rat</td>
<td>or</td>
<td>LD&lt;sub&gt;50&lt;/sub&gt;</td>
<td>233</td>
<td>51</td>
</tr>
<tr>
<td>Rat</td>
<td>or</td>
<td></td>
<td>192</td>
<td>53</td>
</tr>
<tr>
<td>Rat</td>
<td>or</td>
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<tr>
<td>Rat, male</td>
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<tr>
<td>Rat, female</td>
<td>or</td>
<td>LD&lt;sub&gt;50&lt;/sub&gt;</td>
<td>247</td>
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<td>Rat</td>
<td>sc</td>
<td>LD</td>
<td>70-130</td>
<td>51</td>
</tr>
<tr>
<td>Rat</td>
<td>sc</td>
<td>LD</td>
<td>250</td>
<td>51</td>
</tr>
<tr>
<td>Rat</td>
<td>ip</td>
<td>MLD</td>
<td>210-280</td>
<td>51</td>
</tr>
<tr>
<td>Rat</td>
<td>iv</td>
<td>LD&lt;sub&gt;50&lt;/sub&gt;</td>
<td>105</td>
<td>51</td>
</tr>
<tr>
<td>Guinea pig</td>
<td>sc</td>
<td>MLD</td>
<td>200-240</td>
<td>51</td>
</tr>
<tr>
<td>Guinea pig</td>
<td>ip</td>
<td>MLD</td>
<td>220-250</td>
<td>51</td>
</tr>
<tr>
<td>Rabbit</td>
<td>or</td>
<td>MLD</td>
<td>290-350</td>
<td>51</td>
</tr>
<tr>
<td>Rabbit</td>
<td>or</td>
<td>LD</td>
<td>350-360</td>
<td>51</td>
</tr>
<tr>
<td>Rabbit, male</td>
<td>or</td>
<td>LD&lt;sub&gt;50&lt;/sub&gt;</td>
<td>246</td>
<td>52</td>
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<tr>
<td>Rabbit, female</td>
<td>or</td>
<td>LD&lt;sub&gt;50&lt;/sub&gt;</td>
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<td>52</td>
</tr>
<tr>
<td>Rabbit</td>
<td>sc</td>
<td>MLD</td>
<td>200-300</td>
<td>51</td>
</tr>
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<td>sc</td>
<td>LD</td>
<td>270-280</td>
<td>51</td>
</tr>
<tr>
<td>Rabbit</td>
<td>im</td>
<td>LD</td>
<td>200</td>
<td>51</td>
</tr>
<tr>
<td>Rabbit</td>
<td>iv</td>
<td>LD</td>
<td>80-100</td>
<td>51</td>
</tr>
<tr>
<td>Cat</td>
<td>or</td>
<td>MLD</td>
<td>100-150</td>
<td>51</td>
</tr>
<tr>
<td>Cat</td>
<td>sc</td>
<td>MLD</td>
<td>150</td>
<td>51</td>
</tr>
<tr>
<td>Cat</td>
<td>sc</td>
<td>LD</td>
<td>150-155</td>
<td>51</td>
</tr>
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<td>Cat</td>
<td>ip</td>
<td>MLD</td>
<td>180-200</td>
<td>51</td>
</tr>
<tr>
<td>Cat</td>
<td>iv</td>
<td>MLD</td>
<td>80-100</td>
<td>51</td>
</tr>
<tr>
<td>Cat</td>
<td>iv</td>
<td>LD&lt;sup&gt;b&lt;/sup&gt;</td>
<td>175</td>
<td>51</td>
</tr>
<tr>
<td>Dog</td>
<td>or</td>
<td>MLD</td>
<td>140-150</td>
<td>51</td>
</tr>
<tr>
<td>Dog</td>
<td>sc</td>
<td>MLD</td>
<td>500</td>
<td>51</td>
</tr>
<tr>
<td>Dog</td>
<td>sc</td>
<td>LD</td>
<td>110</td>
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<td>175</td>
<td>51</td>
</tr>
<tr>
<td>Hamster, male</td>
<td>or</td>
<td>LD&lt;sub&gt;50&lt;/sub&gt;</td>
<td>230</td>
<td>52</td>
</tr>
<tr>
<td>Hamster, female</td>
<td>or</td>
<td>LD&lt;sub&gt;50&lt;/sub&gt;</td>
<td>249</td>
<td>52</td>
</tr>
</tbody>
</table>

*Median lethal dose

Reference indicates this as an average lethal dose
studied oral caffeine toxicity in mice with an hereditary obese-hyperglycemia syndrome, and found them to be more sensitive than normal, lean mice; the \( \text{LD}_{50} \) under conditions of ad libitum feeding was 80 mg per kg as compared to 400 mg per kg for lean animals. Muller and Vernikos-Danellis (58) found that increased environmental temperature and dehydration increased caffeine mortality in mice. Temperature increase and dehydration had an additive effect. However, the effect on drug toxicity was not entirely predictable when several other stressful stimuli were combined. Beliles (59) determined mortality after intravenous administration of caffeine to pregnant and non-pregnant mice; the \( \text{LD}_{50} \) values were not significantly different (96 and 89 mg per kg, respectively). A review of the literature on these and other factors influencing caffeine toxicity has been published by Peters (60).

**Acute toxicity**

**Human studies:** In human adults, the usual pharmacologically active oral dose of 200 mg caffeine (3.3 mg per kg) produces cerebral and cardiac stimulation; effects are observable at a dose of about 2.5 mg per kg (38, 61, 62). Ingestion of caffeine in doses up to 10 g has caused convulsions and vomiting with complete recovery in 6 hours (63). The fatal acute oral dose of caffeine in humans appears to be greater than 10 g (170 mg per kg) (62).

**Chronic studies**

Bachmann et al. (64) found no growth retardation in weanling rats of either sex when caffeine was fed in drinking water, 40 to 50 mg per kg body weight daily, for 26 weeks (10 males) or 11 weeks (10 females). Reproductive capacities were not impaired and no pathological changes were observed.

The influence of starvation or inanition on the toxicity of caffeine was studied by Peters (65) using female Wistar albino rats. A variety of treatments with normal diets with and without caffeine (185 mg per kg body weight per day) and reduced food intake diets plus caffeine for 14 days were studied. Reducing food intake increased the caffeine toxicity (weight loss, diuresis followed by oliguria, hair loss, self mutilation*, death due to cachexia), but in general the effects were not appreciable unless food intake approached zero.

Boyd et al. (66) found growth of Wistar rats over a period of 100 days to be inhibited only at caffeine oral dose levels above the \( \text{LD}_{50} \), 100 days (150 mg per kg). Polydipsia and diuresis were common at the \( \text{LD}_{50} \) level and above. At dose levels approaching the \( \text{LD}_{100} \), 100 days, blepharitis, alopecia, and dermatitis were observed and histopathologic studies revealed adrenocortical hyperplasia, thymic atrophy, and hyperemia and congestion of many organs.

Scott and Chen (67) fed rats caffeine in their food in concentrations of 0.02 to 0.50 percent for 28 days. There was no retardation in weight gain at levels as high as 0.1 percent (about 100 mg per kg body weight) but definite retardation at the 0.5 percent level (about 500 mg per kg). Autopsy of animals fed 0.5 percent caffeine showed slight pulmonary edema and congestion in one of five animals and hydronephrosis in one of five; the other three animals were normal.

Eichler and Mügge (68) injected rats subcutaneously daily with 100 mg caffeine per kg body weight for four generations. No adverse effects on fertility or mortality, and only temporary weight loss were observed.

Strubelt et al. (69) administered caffeine solution as drinking water to Wistar rats for 6 to 7 months. Daily caffeine intake ranged from 35 to 60 mg per kg body weight. Parameters studied were: red and white cell blood count; urinalysis; serum concentrations of glucose, free and esterified fatty acids, cholesterol, glutamic-oxaloacetic transaminase, and glutamic-pyruvic transaminase; weights of organs; fat and triglyceride content of the livers; histological examination of livers, hearts, and kidneys. Caffeine exerted no influence on body weight. Animals receiving caffeine revealed no toxic effects. There was no lipolytic action of caffeine. Serum glucose concentrations in caffeine-consuming rats were slightly lower at the end of the experiment than those of the water drinking controls.

Special studies

**Ulcerogenesis:** In investigating a possible relationship between caffeine and the pathogenesis of peptic ulcers, Roth and Ivy (70) injected intramuscularly in 22 cats a mixture of caffeine, beeswax and mineral oil. Daily, or slightly less frequent, injections equivalent to 300 mg caffeine (about 55 to 85 mg per kg body weight per day) produced bleeding erosions or ulcers in the stomach mucosa of the antrum and prepylorus in half of the animals; multiple lesions were observed in five of the cats. These changes were not observed in controls receiving injections of the beeswax and mineral oil alone. The same investigators (71) found that caffeine in a dose of 250 mg given to dogs (weights not indicated) subcutaneously, intramuscularly, or intravenously did not stimulate gastric secretion, whereas a dose of 65 to 125 mg caffeine given intravenously or by pyloric intubation to cats provoked marked increase in gastric secretion. Caffeine (250 mg) given by gastric intubation or intramuscularly to 11 human subjects also produced marked stimulation of gastric secretion. Ulcerogenic effects of caffeine have also been noted in guinea pigs (72).

Wald et al. (73) found in human volunteers that 150 to 300 mg of caffeine (about 2.5 to 5 mg per kg body weight) perfused into the jejunum produced a striking reversal of the net jejunal absorptive state of 0.5 ml
per cm per hr to a net fluid excretion of 6 ml per cm per hr with return to the normal absorptive state within 35 minutes after dosing. The authors suggest that some symptoms of patients with functional diarrhea may be attributable to increased intestinal secretion due to caffeine ingestion.

Giddings et al. (74) intubated 34 albino rats with 75 mg caffeine per kg body weight daily for 8 to 20 weeks. Microscopic gastric erosions and a single small ulcer were seen in only three animals. In a second study, 26 cats were intubated with 75 mg caffeine per kg daily for 3 weeks without inducing gastric erosions or ulcers. However, Pfeiffer and Gass (75) produced stimulation in gastric acid secretion by intramural injection of caffeine solutions (1 µg to 1 mg) into the submucosa of the everted stomachs of fasted rats. Intramurally injected caffeine caused gastric acid secretion in rats that were vagotomized to prevent normal gastric secretion, leading the authors to suggest that the mode of action of caffeine in gastric ulcerogenesis is through stimulation of acid secretion mediated by intramural myenteric plexuses within the stomach.

The Select Committee considers that the etiopathic implication of caffeine in the induction or exacerbation of peptic ulcer is not well founded.

Carcinogenesis: Very recent studies of Takayama and associates, reported in Food Chemical News (76) and referred to by Burg (18) at the public hearing on caffeine before the Select Committee on September 26, 1977, have apparently shown that rats given caffeine solutions in lieu of drinking water for 15 months (doses of the order of 150 to 250 mg caffeine per kg body weight per day) develop cancer of the pituitary, thyroid, mammary glands and uterus. The results of this study are being submitted for publication and full details are not yet available (77). No other studies of the carcinogenicity of caffeine per se have been found by the Select Committee. It is to be noted, however, that several studies (18, 78-80) in rats and mice fed caffeine in daily doses up to 200 mg per kg body weight as coffee for 2 or more years have failed to demonstrate the development of pathological lesions; epidemiological studies (81-83) have failed to demonstrate a causal relationship in man between coffee drinking and cancer. Kihlman (6) believes most of the available evidence suggests that caffeine, rather than being a carcinogen or co-carcinogen, may have anticarcinogenic effects.

Mutagenesis: Genetic or chromosomal changes following exposure to caffeine have been seen in bacteria, fungi and higher plants and in some mammalian cells in vitro (84, 85). Clarke and Wade (86) studying Escherichia coli K-12 found that 1 mg of caffeine per ml of medium produced frameshift reversions and suggested that caffeine's mutagenic action in bacteria generally is of the frameshift type. Ostertag et al. (87) found that caffeine caused isococcus chromosome breakage in HeLa cells in culture, proportional to the caffeine concentration up to 10 mg (10,000 µg) per ml. No translocations
were observed at a caffeine level of 0.5 mg per ml (the lowest dose studied) and few at higher levels. Caffeine is believed to be capable of inducing pre-mutations in germ cells and that such mutagenic change could accumulate in men (88). Preliminary examination of human populations has not confirmed this possibility (89). Thayer et al. (90) found no increase in incidence of chromatid breaks in HeLa cells in vitro after continuous exposure to 20 μg caffeine per ml for as long as 9 weeks (48 cell divisions). The authors indicate that this level of caffeine corresponds to several times the transitory plasma peak levels attainable in man after ingestion of eight cups of coffee. Weinstein et al. (91) found lymphocytes from human volunteers who consumed 200 mg caffeine four times a day for 1 month to manifest no significant increase in chromosome damage. McCann et al. (92) found caffeine to be non-mutagenic in the Salmonella/microsome test.

Weinstein et al. (93) found 52 percent of the metaphase chromosomes were damaged, compared to about 2 percent in controls, when human lymphocyte cultures were treated with 750 μg of caffeine per ml at the 48th hour of culture and examined after the 72nd hour.

Slizynski (94) cultured mouse testes cells at 35°C in a saturated caffeine solution (about 20 percent caffeine) and found chromosomal aberrations (stickiness, clumping, and fragmentation) in spermatogonial cells and also abnormalities in mature sperm. Cytostatic or mitostatic properties of caffeine were observed in human lymphocyte cultures by Timson (95). The degree of mitotic inhibition was related to the concentration of the caffeine: 10^{-4}M solutions (about 20 μg caffeine per ml) were ineffective; 10^{-3}M solutions partly inhibited and 10^{-2}M solutions (about 2000 μg per ml) completely inhibited mitosis. Caffeine produced no significant aberration in the anaphase chromosomes of human embryonic lung cells in culture at levels up to 20 μg per ml (96).

Despite an indication that caffeine may exhibit genetic activity in some of these in vitro studies, the in vivo investigations, summarized below, have failed to demonstrate mutagenic effects of caffeine.

Caffeine was found to be inactive at a dose of 200 mg per kg body weight in the host mediated assay for mutagenicity in mice using strains of Salmonella typhimurium and Saccharomyces cerevisiae (96). It produced no significant aberration in bone marrow metaphase chromosomes in rats at a dosage of 200 mg per kg body weight. It was considered to be non-mutagenic in the dominant lethal assay in rats at a level of 200 mg per kg body weight.

Cattanach (97) obtained negative results in efforts to induce translocations in mouse chromosomes of the type reducing male fertility. Male mice given 0.3 percent caffeine in the drinking water for 3 months (about 300 mg caffeine per kg per day) were bred to virgin females and several subsequent generations of male offspring were tested for fertility. Only in
the original caffeine-treated parents was there some reduction in fertility, but this effect diminished upon cessation of the caffeine treatment.

Wyrobek and Bruce (98) observed no elevation in levels of sperm abnormalities in mice following intraperitoneal administration of 100 to 200 mg caffeine per kg body weight daily for 5 consecutive days.

Lyon et al. (99) gave male and female mice, as drinking water, a 0.1 percent solution of caffeine from the time of mating; the offspring were continued on the same regime. The dosage was estimated to be about 250 mg per kg body weight per day. The mutation rate of the experimental animals, as measured by dominant lethals, did not differ significantly from the known spontaneous rate. A total of about 64,000 progeny were observed. The caffeine treatment did not noticeably affect reproduction; mice kept on 0.1 percent caffeine solution throughout life continued to breed satisfactorily.

Adler (100) studied the mutagenic effects of caffeine on spermatogenesis in male mice given a single dose of 250 mg per kg intraperitoneally. The males were mated to virgin females. No significant differences in implantational egg losses were observed, but the males copulated less frequently. Adler and Röhrborn (101) found that caffeine (3 to 305 mg caffeine per kg body weight per day) given to 3-week-old male mice in drinking water for 245 to 350 days, had no distinct effect on the induction of chromosomal aberrations. The appearance of univalent chromosomes more frequently in the meiotic spermatogonial chromosomes of the treated males than in the controls was regarded by the authors as a fortuitous occurrence rather than an effect of the caffeine. Röhrborn (102) fed male mice low doses of caffeine for periods of from 245 to 351 days. Several concentrations of caffeine were given in the drinking water, making intakes range from 3.4 to 514 mg per kg body weight per day. Virgin females were mated with treated males, and on the 15th day of pregnancy were sacrificed. Using the increased number of dead uterine implants as the criterion for induced dominant lethal mutations, the investigators were unable to demonstrate a significant mutagenic effect of caffeine.

Epstein et al. (103) studied mutagenicity in Swiss male mice given caffeine orally in the drinking water for 8 weeks and by single dose intraperitoneal injection. The oral dose (estimated from consumption of 6.4 ml of 0.1 percent caffeine solution per mouse daily) was about 320 mg per kg body weight per day; the injections ranged from 168 to 240 mg per kg. In each instance, the males were bred to virgin females; after 13 days, the females were autopsied and early and late fetal deaths determined. The authors concluded that caffeine administered to male mice acutely or for 8 weeks prior to mating produced no mutagenic effect. Epstein and his associates (104, 105) also administered single intraperitoneal doses of caffeine (LD₅₀ or LD₂₅ level) to mature male mice which were sequentially mated with untreated females. The females were dissected on day 13 of pregnancy and examined for early fetal deaths and living implants. Caffeine produced no mutagenic effects nor did it enhance the effects of low doses of known mutagens.
Thayer and Kensler (106) gave male mice caffeine in the drinking water for 8 weeks. Caffeine intakes ranged from about 4 to 122 mg per kg body weight per day. After 8 weeks the males of each generation were mated to untreated females and the mutation index data from females and offspring were found to be not significantly different from the controls.

Aeschbacher et al. (107) using a dominant lethal test in mice designed to achieve maximum sensitivity, found no evidence of mutagenic induction of dominant lethals, pre-implantation egg loss, or depression of the fertility of females by caffeine at daily oral doses as high as 112 mg per kg. It was also shown that caffeine did not accumulate in testicular tissues, the maximum concentration achieved being 10 μg per g or about 1/100th that required to cause chromosome aberrations in cultured mammalian cells.

Thayer and Palm (108) in a recent review concluded that caffeine is a weak mutagen in some non-mammalian systems, but that the mutagenic significance of caffeine to man has not been established as being either of great concern or as being dismissible.

Kihlman (6), in a comprehensive review, has concluded that the available experimental evidence indicates that caffeine has no mutagenic or chromosome damaging effects in man as a result of normal consumption of caffeine-containing beverages and medical preparations.

Teratogenesis: Fabro and associates (109-111) gave labeled caffeine (1-methyl-14C) orally in a dose of 3.5 mg per kg body weight to 6-day pregnant New Zealand white rabbits. Significant amounts of radioactivity were found after 6 hours not only in the maternal plasma and endometrium but also in the pre-implantation blastocyst and in the uterine secretion indicating that the developing embryo is exposed to caffeine throughout pregnancy. Similar behavior was exhibited by nicotine, and such other compounds as DDT and barbital in rabbits and in a number of other species. However, caffeine (25 mg per kg body weight) intubated daily in pregnant New Zealand white rabbits on days 4, 5, 6, and 7 of gestation produced no difference in the percentage of implanted ova as compared to controls when the animals were killed and examined on the eighth dose (112).

From examination of Table VI it is obvious that positive teratogenic effects have been reported by some investigators. In many of the studies caffeine was given by other than the oral route, including injection into the fetus. Teratogenic effects in oral studies varied with the time period over which the dose was administered, the gestational period when administered, the strain of animal, and the method of oral administration (intubation or feeding). At oral doses of 50 mg per kg body weight and lower, teratogenic effects were generally absent. At oral doses up to 75 mg per kg body weight, teratogenic effects were neither consistent nor striking. In one study (116)
<table>
<thead>
<tr>
<th>Species (strain)</th>
<th>Route</th>
<th>Dose (mg/kg)</th>
<th>Conditions</th>
<th>Results</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mouse (SMA)</td>
<td>ip</td>
<td>250</td>
<td>Single injection, once during 7th to 15th days of gestation</td>
<td>Day 7 to 12, 3 to 18% embryonic deaths; Day 10 to 14, 18 to 43% malformations and hematomas</td>
<td>113</td>
</tr>
<tr>
<td>Mouse (NMRI)</td>
<td>ip</td>
<td>250</td>
<td>Single injection, Days 10 to 13 of gestation</td>
<td>Malformations and hematomas</td>
<td>114</td>
</tr>
<tr>
<td>Mouse (NMRI) (feed or water)</td>
<td>or</td>
<td>50</td>
<td>Daily, 14 days prior to conception to 14th or 18th days of gestation</td>
<td>Malformations in 7 of 757; 0 of 747 in controls</td>
<td>115</td>
</tr>
<tr>
<td>Mouse (NMRI) (Balb-C, CNRS)</td>
<td>(intubated)</td>
<td>50</td>
<td>Daily during the 6th to 18th days of gestation</td>
<td>Malformations in 1 of 38; 0 in 1,000 controls</td>
<td>116</td>
</tr>
<tr>
<td>Mouse (Swiss)</td>
<td>or</td>
<td>50</td>
<td>Daily during the 6th to 18th days of gestation</td>
<td>No malformations in 116 fetuses</td>
<td>116</td>
</tr>
<tr>
<td>Mouse (ICR-JCL)</td>
<td>ip</td>
<td>200 - 250</td>
<td>Single injection on 12th day of gestation</td>
<td>Malformations 18 to 69%, controls, 0%; micrognathia, club foot, cleft palate, hematomas</td>
<td>117</td>
</tr>
<tr>
<td>Mouse (ICR-JCL)</td>
<td>sc</td>
<td>200</td>
<td>Single injection on 12th day of gestation</td>
<td>14% dead or resorbed; 7% in controls; 21% malformations, 0% in controls</td>
<td>118</td>
</tr>
<tr>
<td>Mouse (ICR-JCL)</td>
<td>ip</td>
<td>200</td>
<td>Single injection on 12th day of gestation</td>
<td>8% dead or resorbed, 7% in controls; 18% malformations, 1% in controls</td>
<td>118</td>
</tr>
<tr>
<td>Mouse (ICR-JCL)</td>
<td>ip</td>
<td>100</td>
<td>Two injections, 2 hours apart on 12th day of gestation</td>
<td>14% dead or resorbed, 9% in controls; 7% malformations, 0% in controls</td>
<td>118</td>
</tr>
<tr>
<td>Mouse (ICR-JCL)</td>
<td>ip</td>
<td>100</td>
<td>Two injections, 4 hours apart on 12th day of gestation</td>
<td>15% dead or resorbed, 7% in controls; 6% malformations, 0% in controls</td>
<td>118</td>
</tr>
<tr>
<td>Mouse (Swiss, CNRS)</td>
<td>or</td>
<td>75</td>
<td>Daily from 5th day of gestation to sacrifice</td>
<td>No increase in resorptions; Malformations in 8 of 439; 5 of 1,022 in controls</td>
<td>119</td>
</tr>
<tr>
<td>Mouse (White)</td>
<td>sc</td>
<td>250 - 800</td>
<td>Single injection between 7th and 14th days of gestation</td>
<td>Malformations only at days 11 to 14</td>
<td>120</td>
</tr>
<tr>
<td>Species (strain)</td>
<td>Route</td>
<td>Dose (mg/kg)</td>
<td>Conditions</td>
<td>Results</td>
<td>Ref.</td>
</tr>
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</tr>
<tr>
<td>Mouse (Balb-C)</td>
<td>or</td>
<td>50 - 75</td>
<td>Administered daily on 5th to 18th day of gestation</td>
<td>70 to 75% resorptions but no ectrodactyly</td>
<td>121</td>
</tr>
<tr>
<td></td>
<td>(intubated)</td>
<td></td>
<td></td>
<td>No embryotoxicity or ectrodactyly</td>
<td></td>
</tr>
<tr>
<td>Mouse (Swiss)</td>
<td>or</td>
<td>50</td>
<td>Administered daily on 5th to 18th day of gestation</td>
<td>Malformations preceded by hematoma in fetuses</td>
<td>121</td>
</tr>
<tr>
<td></td>
<td>(intubated)</td>
<td></td>
<td></td>
<td>No anatomical abnormalities</td>
<td>122</td>
</tr>
<tr>
<td>Mouse (White)</td>
<td>sc</td>
<td>400</td>
<td>Single injection on 12th, 13th or 14th days of gestation</td>
<td>No effects on maternal or fetal survival; no malformations</td>
<td>123</td>
</tr>
<tr>
<td>Mouse (CD-1)</td>
<td>or</td>
<td>4 - 5</td>
<td>Daily, continuously from 4 weeks prior to mating through 4 generations</td>
<td>45% fetal deaths, hemorrhage, limb defects; teratogenic effect on fetal lens not dose related</td>
<td>124</td>
</tr>
<tr>
<td></td>
<td>(drinking water)</td>
<td>12 - 18</td>
<td></td>
<td>33% fetal deaths in treated, 31% in controls; hemorrhage, limb defects, cataracts</td>
<td>125</td>
</tr>
<tr>
<td></td>
<td></td>
<td>25 - 39</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mouse (CD-1)</td>
<td>or</td>
<td>0.36 - 36</td>
<td>Daily on 6th through 15th days of gestation</td>
<td>Cleft palate in 21%; &lt;1% in controls</td>
<td>126</td>
</tr>
<tr>
<td></td>
<td>(intubated)</td>
<td></td>
<td></td>
<td>45% fetal deaths, hemorrhage, limb defects; teratogenic effect on fetal lens not dose related</td>
<td></td>
</tr>
<tr>
<td>Mouse (ICR-JCL)</td>
<td>ip</td>
<td>200</td>
<td>Single injections on 13th day of gestation</td>
<td>33% fetal deaths in treated, 31% in controls; hemorrhage, limb defects, cataracts</td>
<td></td>
</tr>
<tr>
<td>Rat (Carworth)</td>
<td>Fetal</td>
<td>0.025 - 0.3</td>
<td>Single injection on 16th, 17th, 18th, or 19th day of gestation</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>injection (per fetus)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rat (Holtzman)</td>
<td>Fetal</td>
<td>0.050</td>
<td>Single injection on 17th day of gestation</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>injection (per fetus)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rat (Wistar)</td>
<td>or</td>
<td>75 - 150</td>
<td>Daily from 8 days prior to mating to term</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>(intubated)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rat (Br 46, Wistar II)</td>
<td>or</td>
<td>56 - 240</td>
<td>Daily, 6th to 16th days of gestation</td>
<td>At 130 mg/kg 2% malformations, 0.12% in controls (none at lower doses?)</td>
<td>126</td>
</tr>
<tr>
<td></td>
<td>(intubated)</td>
<td></td>
<td></td>
<td>Malformations 0 in 190</td>
<td></td>
</tr>
<tr>
<td>Rat (Wistar, several sources)(intubated)</td>
<td>or</td>
<td>25</td>
<td>Daily, 2nd to 15th days of gestation</td>
<td>Ectrodactylia in 57 of 256 in 2 lines; 2 of 173 in 2 other lines</td>
<td>121</td>
</tr>
<tr>
<td></td>
<td></td>
<td>125</td>
<td>Daily, 2nd to 15th day of gestation</td>
<td>17% resorptions, 6% in controls; 3% malformed; edema</td>
<td>128</td>
</tr>
<tr>
<td>Rat (Sprague-Dawley)</td>
<td>or</td>
<td>ca 200</td>
<td>Daily, 1st day of gestation to term</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>(0.25% in diet)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Species (strain)</td>
<td>Route</td>
<td>Dose (mg/kg)</td>
<td>Conditions</td>
<td>Results</td>
<td>Ref.</td>
</tr>
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</tr>
<tr>
<td>Rat (Sprague-Dawley)</td>
<td>or (intubation)</td>
<td>30</td>
<td>Daily, 5 weeks prior to mating, throughout gestation and until 27 days after parturition</td>
<td>Absence of supraoccipital bone in 5.8%; slightly higher incidence of cryptorchism and delayed ossification of ribs and vertebrae.</td>
<td>52</td>
</tr>
<tr>
<td>Rat (Sprague-Dawley)</td>
<td>or (intubation)</td>
<td>30</td>
<td>Daily, 5 weeks prior to mating, throughout gestation and until 27 days after parturition</td>
<td>Slightly higher incidence of cryptorchism and delayed ossification of ribs and vertebrae</td>
<td>52</td>
</tr>
<tr>
<td>Rat (Sprague-Dawley)</td>
<td>or ca 400 (0.5% in diet)</td>
<td></td>
<td>Daily, 1st day of gestation to term</td>
<td>38% resorptions, 6% in controls; 57% malformations; edema</td>
<td>128</td>
</tr>
<tr>
<td>Rat (Sprague-Dawley)</td>
<td>or ca 400 (0.5% in diet)</td>
<td></td>
<td>Daily, 1st to 7th days of gestation</td>
<td>11% resorptions, 6% in controls; 10% malformations, 1.2% in controls</td>
<td>128</td>
</tr>
<tr>
<td>Rat (Sprague-Dawley)</td>
<td>or ca 400 (0.5% in diet)</td>
<td></td>
<td>Daily, 8th to 14th days of gestation</td>
<td>28% resorptions, 6% in controls; 14% malformations, 1.2% in controls</td>
<td>128</td>
</tr>
<tr>
<td>Rat (Sprague-Dawley)</td>
<td>or ca 400 (0.5% in diet)</td>
<td></td>
<td>Daily, 15th to 21st days of gestation</td>
<td>No increased resorptions or malformations over controls</td>
<td>128</td>
</tr>
<tr>
<td>Rat (Holzer)</td>
<td>ip 20 - 80</td>
<td></td>
<td>Daily, in 4 doses each 24 hours, from day 0 through day 20 of gestation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rat (Sprague-Dawley)</td>
<td>or (intubated)</td>
<td>180</td>
<td>Daily, 6th to 16th days of gestation</td>
<td>Increased fetal deaths and malformations; dwarfs</td>
<td>130</td>
</tr>
<tr>
<td>Rat (Wistar)</td>
<td>or (intubated) 0.23 - 22.5</td>
<td></td>
<td>Daily, 6th through 15th days of gestation</td>
<td>No increase in malformations</td>
<td>124</td>
</tr>
<tr>
<td>Rat</td>
<td>or ca 120 (0.18% in diet)</td>
<td></td>
<td>Daily from 2 weeks prior to mating through 2 pregnancies</td>
<td>No increase in malformations; 131 increased fetal resorption in F-Ib generation</td>
<td>129</td>
</tr>
<tr>
<td>Species (strain)</td>
<td>Route</td>
<td>Dose (mg/kg)</td>
<td>Conditions</td>
<td>Results</td>
<td>Ref.</td>
</tr>
<tr>
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<td>-----------------------------------------------------------------------------</td>
<td>--------------------------------------------------------------------------</td>
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</tr>
<tr>
<td>Hamster (Golden)</td>
<td>or</td>
<td>0.3 - 30</td>
<td>Daily, 6th through 10th day of gestation</td>
<td>No increase in malformations</td>
<td>124</td>
</tr>
<tr>
<td></td>
<td>(intubated)</td>
<td></td>
<td>Daily, 1st to 25th day of gestation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rabbit (Common strain</td>
<td>or</td>
<td>100</td>
<td>Daily, 6th through 18th day of gestation</td>
<td>Ectodactyly in 6 of 64</td>
<td>121</td>
</tr>
<tr>
<td>various origins)</td>
<td>(intubated)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rabbit (Dutch belted)</td>
<td>or</td>
<td>0.325 - 32.5</td>
<td></td>
<td>No increase in malformation at any dose; increased maternal mortality at higher dose</td>
<td>124</td>
</tr>
<tr>
<td></td>
<td>(intubated)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chick embryo</td>
<td>Injection into</td>
<td>10 - 100</td>
<td>Injections into unincubated eggs and eggs after 96 hours incubation</td>
<td>No evidence of toxicity or teratogenicity below 100 mg/kg</td>
<td>132</td>
</tr>
<tr>
<td></td>
<td>air cell or yolk</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chick embryo</td>
<td>Injection into</td>
<td>0.05 - 20</td>
<td>Injections into unincubated eggs and eggs after 96 hours incubation</td>
<td>No evidence of teratogenicity at any dose; some evidence of toxicity on yolk administration, 0 hours</td>
<td>133</td>
</tr>
<tr>
<td></td>
<td>air cell or yolk</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
dose-related resorption and malformation responses were observed in Wistar rats intubated with doses from 75 to 150 mg per kg body weight daily from 8 days before mating to term. It is to be noted that Jacobson (134) believed, because of species differences and the lack of direct evidence in humans, that pregnant women in the first trimester should limit caffeine intake to no more than 0.25 mg per kg per day as a safeguard against caffeine-induced defects in offspring. Jacobson derived this figure by assuming the no-effect level for caffeine's interference with reproduction to be 25 mg per kg per day and dividing this by 100.

Nomura (135) observed that 50 mg of caffeine per kg body weight injected intramuscularly at 6 hour intervals in pregnant mice (day 9 to day 11 of gestation) within 24 hours following injections of urethane reduced the frequency of fetal malformations but malformation frequency was increased when caffeine injections followed x-ray treatment.

In a retrospective study of 1,369 mothers and their prescribed and self-administered drug histories during pregnancy, Nelson and Forfar (136) found caffeine was not associated with abnormalities in offspring. In a recent survey of birth defects in humans as related to drug intake, Heinonen et al. (137) found no evidence of the teratogenic activity of caffeine. The standardized relative risk of birth defects in offspring of 12,700 mothers who consumed caffeine during pregnancy was 0.99.

Effects on reproduction: Bachman et al. (64) tested the influence of chronic exposure to caffeine on the reproductive ability of albino rats given a sweetened caffeine-containing beverage as the only liquid in the diet for as long as 3.5 years. The average dose was about 40 to 50 mg per kg per day. Mated at 100 days of age, the pairs were kept until the female produced no offspring for a period of 3 months after the last litter. No evidence of sterility, or unusual histological changes in the male testes were observed. Friedman et al. (138) reported that the feeding of 0.5 percent caffeine or theobromine (about 500 mg per kg) to immature Osborne-Mendel rats for 3 to 16 months can produce severe testicular atrophy and aspermato genesis in 85 to 100 percent of the animals. However, it is to be noted that no significant testicular atrophy or dose-related pathological effects were observed in a 2-year study of rats receiving dilutions of freshly brewed coffee as the only source of liquid; doses were equivalent to about 54, 32 and 14 mg caffeine per kg of body weight (18, 139).

Ax et al. (140-142) have studied the effects of dietary caffeine on the fertility, embryonic loss and testis of the domestic fowl. Eggs were collected for 14 days from pullets fed 0.05, 0.1, 0.5, and 1.0 percent caffeine in the diet and artificially inseminated. At the 0.5 and 1.0 percent caffeine levels egg production ceased within 3 days and eggs were soft-shelled. At the 0.1 percent caffeine level (estimated to be about 160 mg per kg per day) fertility was not changed as compared to controls but there was 38 percent
embryonic loss in the fertile eggs compared to 5 percent in controls. At the 0.05 percent caffeine level (estimated to be about 80 mg per kg per day) fertility was not impaired and embryonic losses were about 16 percent. Percentage fertility of eggs from untreated pullets inseminated with semen from males fed continuously a diet containing 0.1 percent caffeine was measured. Semen from roosters at the start of caffeine feeding produced 30.8 percent fertile eggs; from roosters after 7 days caffeine feeding, 33.5 percent; from roosters after 14 days caffeine feeding, 3.3 percent. Semen output and sperm concentration were markedly reduced after 17 to 21 days feeding and no semen could be collected from roosters that had received caffeine for 30 days. Removal of dietary caffeine resulted in resumption of semen production and return of egg fertility to normal levels.

Several investigators have reported that caffeine has no adverse reproductive effects at lower dose levels. Thayer and Kensler (123) exposed four generations of male and female mice continuously to caffeine in the drinking water at three dose levels of 4 to 5, 12 to 18, and 25 to 39 mg per kg body weight per day. No consistent, dose-related effects of caffeine on fertility, age at sexual maturity, mean litter size, weight of offspring at weaning, sex ratio or fetal abnormalities were observed. In the studies of Palm et al. (52) pregnant Sprague-Dawley rats received a daily dose of 30 mg caffeine per kg of body weight by intubation, or by providing a water solution of caffeine (equivalent to about 30 mg per kg of body weight per day) as the sole source of fluid. Neither regime interfered with normal reproductive performance as indicated by pregnancy, litter size and weight, and early and late deaths. Sex ratio was similar in both groups. Offspring which were raised to maturity had no gross abnormalities of growth or development, had normal reproductive capability and successfully raised their young to weaning. In a two-generation rat study (131) at a much higher daily dose level (125 mg per kg body weight incorporated in the diet) progressive reduction in litter size was observed; birth weights, postnatal survival and growth rates through lactation were decreased, but growth and survival subsequent to lactation were not affected.

Weathersbee et al. (143) made a retrospective survey of 489 households identified by random sampling of medical records of women who had been obstetric patients in hospitals in Utah. Approximately 75 percent of the individuals were Mormons whose use of alcohol, caffeine, and tobacco is proscribed. In 356 of the 489 households, where presumably no caffeine, alcohol, or tobacco was used there were 33 spontaneous abortions, 38 stillbirths, and 6 premature births, including 3 deaths. In 16 of the 489 households, when the woman's estimated mean daily caffeine intake was 686 mg (approximately 11 mg per kg per day) and the man's 566 mg, there were 8 spontaneous abortions, 5 stillbirths, and 2 premature births with no deaths. In 13 of the 489 households where the woman's estimated mean daily caffeine intake was less than 400 mg (about 6.7 mg per kg per day) and the man's more than 600 mg there were 4 spontaneous abortions, 2 stillbirths, and 2
premature births with 1 death. In 23 of the 489 households where mean daily caffeine intake by the man or woman was no more than 450 mg (about 7 mg per kg per day) there were no abortions, stillbirths or premature births. The authors concluded that a cause-and-effect relationship could not be established by this study but suggested that excessive intake of caffeine might be a factor in spontaneous abortion and perinatal mortality.

In a detailed review of direct and indirect influences of caffeine on reproduction, Weathersbee and Lodge (144) suggest that future studies should center on a clearer understanding of caffeine's ability to alter catecholamine, free fatty acid levels, and cyclic nucleotide content within the developing fetus and the reproductive tract of both males and females. They point out that caffeine must be considered a factor in reproductive outcome since it readily gains access to the uterine lumen and testes and because of its known association with cyclic adenosine monophosphate.

Cardiovascular effects: Riker and Kensler (145) indicate that while caffeine and coffee exercise marked dose-related action on the cardiovascular system, individual reactions in normal subjects vary, and detectable effects are negligible at usual consumption levels. Chronic effects are unclear, though protracted abuse appears responsible for arrhythmia in a small percent of the population. Injection of 30 to 50 mg of caffeine into the umbilical vein of a newborn infant may produce slight tachycardia (146). Robertson et al. (147) found a single 250 mg dose of caffeine, administered to fasted non-coffee drinkers increased mean blood pressure 14/10 mm one hour after ingestion. There was a slight fall and then a rise in heart rate. Plasma renin activity, epinephrine, and norepinephrine increased by 57, 207, and 75 percent, respectively. No other studies on the effects of caffeine per se in this regard have been found by the Select Committee. However, it is to be noted that coffee or tea drinking has been suspected and studied along with other factors such as smoking, drinking alcoholic beverages, high cholesterol diets, aspirin consumption, and exercise, as etiologically associated with myocardial infarction and other cardiovascular diseases (148-154). Kannel and Dawber (155) have concluded, in light of these and other studies, that "no relation of antecedent coffee intake to subsequent myocardial infarction, regardless of outcome, has been observed."

Behavioral effects: Intraperitoneal injection of 25 to 50 mg caffeine per kg body weight doubled the motility of mice but motility decreased after a dose of 100 mg per kg (156). Rats given as little as 2 mg caffeine per kg intraperitonally exhibited increased spontaneous motor activity with still further increase at doses up to 32 mg per kg (157). Hirsh et al. (158) found spontaneous locomotor activity to be barely significantly increased in mice by an oral dose of 2.5 mg per kg. Hand-arm tremor increased 11 percent about 3 hours after administration of 325 mg caffeine (5 mg per kg) in
gelatin capsules to human volunteers (159) and body sway with eyes open was significantly increased 40 minutes after oral administration of 4.3 mg per kg body weight to healthy subjects (160). A series of psychological tests evaluating the performance of physical and intellectual tasks by humans, influenced by caffeine, was reviewed by Weiss and Laties (181). Among other effects, oral doses of 500 mg of caffeine (about 8 mg per kg body weight), significantly enhance performance of physically exhausting work, relieve fatigue and boredom, increase the speed of such tasks as typing, and decrease the number of errors. However, intellectual performance, as measured by simple arithmetic tests, is not improved by caffeine.

Goldstein (162), using a double-blind design in a study of several hundred medical students, found evidence that caffeine in single doses of 150 to 200 mg (about 2.5 to 3.3 mg per kg) does prolong the time required to fall asleep. Regular coffee drinkers were less affected, and some experienced headache in the morning after abstaining from coffee for 18 hours. Goldstein et al. (163) reported similar but more detailed studies of the psychotropic effects of caffeine in women. The physiological and psychological effects of a single dose of caffeine (2.5 to 5 mg per kg) in humans were different in those who were habituated and those who were abstainers.

Karacan et al. (164, 165) studied the effects of one cup of warm water, one, two, and four cups of instant regular coffee, a four-cup equivalent of decaffeinated coffee, and a four-cup equivalent of caffeine, given 30 minutes before bedtime on sleep disturbance in young (20 to 30 yr) and middle aged (35 to 49 yr) adults. Sleep evaluations were made for standard electroencephalogram-electrooculogram parameters and presleep and postsleep questionnaire responses. Neither the young nor middle-aged subjects experienced sleep disturbance after consuming decaffeinated coffee or one cup of regular coffee. All subjects experienced increasing sleep disturbance with increasing dose levels of caffeine, whether as coffee or caffeine solution, with the older subjects experiencing the greater dose-related sleep disturbance. Coffee at the four-cup dose or the equivalent in caffeine solution (estimated to be about 6 mg caffeine per kg body weight) reduced sleep time from 416 minutes to 395 minutes in the younger subjects and from 406 to 352 minutes in the older; sleep latency increased from 12 to 29 minutes in the younger subjects and from 12 to 50 minutes in the older.

Dreisbach and Pfeiffer (166) in an early study of caffeine habituation, gave 22 human subjects increasing doses of from 120 to 780 mg (about 2 to 13 mg per kg) per day in capsules for 6 or 7 days and then substituted placebos without the subject's knowledge. Withdrawal symptoms, consisting of severe headaches, characterized more than half the trials. Blood samples showed a decrease in serum calcium and a slightly elevated serum phosphorus and possibly an increase in blood volume accompanying the withdrawal headaches.
Diamond and Cole (167) in 1970 reported that 1.7 to 3.3 mg caffeine per kg body weight given as capsules to three human subjects (previously trained in the experiments to be performed) caused a dose-related decrease in visual luminance threshold as compared to placebo capsules containing calcium lactate; in other words, after caffeine ingestion, the visual pathways in these subjects became more sensitive to light. Differences between placebo and caffeine effects were small (averaging about 10 percent difference at the higher caffeine level) and no tests for significance were reported. These doses of caffeine are not known to produce perceived visual changes in most people.

Baker and Theologos (168) examined the effects of caffeine on a protracted visual monitoring task in 100 volunteers. An oral dose of 200 mg caffeine at the beginning of the second hour of the test significantly inhibited attention lapses. Effects were apparent within 1 hour following administration.

A review of many studies of behavioral effects of caffeine reveals that while oral or parenteral doses as low as 1 to 2 mg per kg elicit noticeable stimulatory effects in some tests* with mice, rats, and monkeys, levels ranging upward from about 10 mg per kg were usually required to elicit peak effects (156, 157, 169-184). Burg (18) has reviewed data on the effects of caffeine on such brain neurotransmitters as serotonin, catecholamines, and acetylcholine in adult animals. The results of these experiments usually conducted at caffeine levels of 10 to 100 mg per kg, are difficult to interpret due to the complexity of the systems involved. No similar data are available for the effects of caffeine on the neurotransmitter levels in the newborn or growing brain.

Neims and Aranda (38) treated apnea in premature infants with caffeine such that plasma levels of 5 to 18 mg per liter, and in several instances as high as 85 mg per liter, were maintained for several weeks. Careful physical examination was performed daily during therapy and for 6 to 24 months thereafter follow-up examinations were performed for growth, neurological and psychological development, physical condition and ophthalmoscopic normality. They concluded that high plasma concentrations of caffeine during treatment of apnea does not predispose to neurological or intellectual residua and that infants are not more susceptible to the effects of caffeine than adults. However, Levitt and O'Hearn (185) hold that children appear to be relatively more sensitive than adults to the excitant effects of caffeine.

Garfinkel et al. (186) administered 150 mg caffeine by capsule daily in two doses to eight hyperactive boys, aged 6 to 10, for 10 days, in a double-blind crossover study. Behavior was carefully evaluated by trained observers

*Tests included spontaneous motor activity, T-maze, Y-maze, cage jiggle, running on wheel, lever pressing.

- 29 -
who administered a number of visual perception, motor coordination, steadiness, and matching tests. Hyperactive behavior was not reduced by caffeine but a slight pharmacological effect (undescribed) from caffeine was noted. In a double-blind crossover study Heustis et al. (187) administered as much as 240 mg of caffeine in divided doses in capsules at 9 a.m. and noon for 3 weeks to 18 hyperactive boys and girls, aged 5 to 12, and effects were compared with d-ampheta mine, methylphenidate and placebo. Behavior was evaluated by parents, teachers, and physicians. Hyperactive behavior was reduced by amphetamine and methylphenidate but not by caffeine or placebo. No adverse effects of caffeine were reported. Reichard and Elder (188) in a double-blind study compared the effects of a single dose of 6 mg of caffeine per kg body weight on reaction time in six hyperactive children and a matched group of apparently normal children. Reaction time was improved in the hyperactive subjects but did not change in the normal subjects. No adverse effects were noted in either the hyperactive or normal subjects. Snyder (189) referred to unpublished studies of Harley who found that caffeine consumption (average of 100 mg per week) from all sources (soft drinks, chocolate milk, other chocolate foods) of 26 hyperactive males, aged 6 to 12 years, was lower than the national average consumption by subjects of similar age, suggesting that caffeine was not likely responsible for their hyperactivity.

Effects on glucose metabolism: Deakins (190) recognizing that increase in blood sugar level has been reported to occur in laboratory animals after administration of caffeine, conducted experiments in man. In a self-administered dose of about 8 mg caffeine per kg body weight with 50 g of glucose, he observed a slight depression (from 125 to 105 mg percent) in the peak of the sugar-tolerance curve, with a slightly delayed return of blood glucose to pretreatment levels. The same dose of caffeine alone did not raise the blood sugar level appreciably. Cheraskin et al. (191), however gave single oral doses of 250 mg caffeine (about 4 mg per kg body weight) to 20 healthy, fasting dental students and observed a statistically significant but slight increase in blood glucose level as compared to that of a like group of students on placebo. Blood glucose concentration 2 hours after caffeine ingestion was 93 mg per 100 ml, compared to 86 mg in the controls. Daubresse et al. (192) found no effect on human blood glucose levels within 5 hours after oral administration of 3.3 mg caffeine per kg body weight.

Strubelt et al. (69) found slightly decreased serum glucose concentration in rats given 60 mg caffeine per kg body weight per day in their drinking water for 7 months.

From the information available, the effects of caffeine ingestion on blood glucose level and glucose tolerance in normal subjects appear to be slight and transitory.
Lipotropic effects: Heppel et al. (193) fed weanling, male, Sprague-Dawley rats a low-casein, high-fat, choline-deficient diet containing 0.3 to 0.6 percent caffeine (about 170 to 340 mg per kg body weight) for up to 27 days. After sacrifice, livers were analyzed for fat content, which was 9.5 to 17 percent in rats receiving caffeine, as compared with 29 percent in rats on the basal diet, indicating caffeine's lipotropic activity.

Naismith et al. (194) fed male Sprague-Dawley rats a starch-based diet, devoid of known atherogenic agents, and supplemented variously with caffeine (about 210 mg per kg body weight, initially) or the concentrated freeze-dried residues of brewed tea or coffee (about 120 mg and 200 mg per kg body weight, respectively). Growth, food utilization and plasma lipids were measured. After 54 days, the only differences observed among experimental animals and controls were in the plasma lipid values: cholesterol level increased from 85 to about 100 mg per 100 ml, phospholipid level increased from 140 to about 170 mg per 100 ml, and triglyceride level decreased from 36 to about 30 mg per 100 ml. Changes in the plasma lipid values were proportional to the caffeine content of the diet.

Strubelt et al. (195) used male Wistar rats to investigate the possibility that caffeine exerts a hepatotoxic effect. A dose of 60 mg per kg, given either subcutaneously or intraperitoneally, doubled or tripled serum levels of free fatty acids 2 hours after injection, but no histological evidence of hepatotoxicity was found. However, in later studies in rats, Strubelt et al. (69) found no lipolytic effects of caffeine fed in doses up to 60 mg per kg body weight per day in drinking water for periods up to 7 months.

The studies of Heyden et al. (196) failed to demonstrate a relationship between the subcutaneous injection of caffeine (about 15 mg per kg body weight) and the development of ischemic heart disease in rabbits receiving atherogenic diets containing cholesterol.

Bellet et al. (197-199) tested the effects of caffeine sodium benzoate (about 8 mg per kg body weight) on free fatty acid concentrations in humans by oral and intramuscular injection and in dogs by the latter route. The results in both human and animal experiments showed consistent and significant free fatty acid mobilization, the mean serum free fatty acid levels were increased. Cola beverages given to 12 human subjects ranging in age from 14 to 42 indicated essentially the same results. Consumption of sucrose-containing cola (about 1.8 mg caffeine per kg body weight, assuming 60 kg adult) showed a slight increase 155 ± 61 μEq per liter in mean serum free fatty acid levels in 4 hours, but sugar-free cola (about 0.8 mg caffeine per kg) showed marked increase 237 ± 80 μEq per liter in serum free fatty acid levels in the same period. The difference, according to the authors, is probably due to suppression of the caffeine-induced free fatty acid mobilization by the sugar through reesterification of the released free fatty acids.
The effects of caffeine on free fatty acids and blood coagulation factors of dogs were reported by Bellet et al. (200). Caffeine sodium benzoate, 25 mg per kg body weight, was administered intravenously to dogs and several blood samples were taken over a 4-hour period. No influence of caffeine on clotting times was observed, but significant increases in the levels of serum free fatty acids were seen. Daubresse et al. (192) found plasma levels of non-esterified fatty acids in humans to increase from 550 to about 800 µEq per liter within 2 hours after oral administration of 3.3 mg of caffeine per kg body weight.

The effects of caffeine in lipid metabolism appear real, but transitory and are without evidence of hazard.
V. OPINION

Caffeine has been consumed by man for centuries in coffee and tea. This opinion is not concerned with such naturally occurring caffeine in foods. It is addressed solely to caffeine as commercially added to food commodities. Cola beverages comprise the largest and only significant source of caffeine in this latter group. Such beverages have been in use for decades.

The Select Committee's opinion on the health aspects of caffeine as a commercially-added food ingredient rests primarily upon the integrated interpretation of a cluster of eight factors. These are:

1. Levels of consumption of caffeine as a commercially-added food ingredient

Three points of reference have been used: (a) the total amount of caffeine added to foods in the United States supplies about 0.2 mg per kg per day for the population as a whole; (b) most cola drinkers consume about 0.3 mg of caffeine per kg per day from this source with a few in the 1 to 5 year age range consuming as much as 1.8 mg per kg per day; (c) the consumption of a 12-ounce container of cola beverage containing 0.01 percent caffeine represents a dose of about 0.9 mg per kg for a 40 kg child, for example, or about 0.6 mg per kg for an adult. It is to be noted that these figures represent the amount of caffeine solely from cola drinks. They, therefore, represent the minimum levels of caffeine consumption on the part of individuals consuming a range of caffeine-containing foods and beverages.

2. History of cola consumption

Despite widespread human consumption of cola beverages over many years, the literature contains no definitive studies of possible long-term effects.

3. Mutagenicity

Caffeine causes chromosomal damage in certain microbial and other non-mammalian test systems, and caffeine has similar effects at high concentrations on mammalian cells in culture in several in vitro tests. However, in vivo tests utilizing mice and rats have failed to demonstrate mutagenic effects of caffeine.

4. Teratogenicity

Many animal tests showed that teratogenic effects are generally absent at caffeine doses up to 50 mg per kg body weight. At doses up to 75 mg per kg of body weight, teratogenic effects of caffeine are neither striking nor
consistently demonstrated. At bolus doses greater than 75 mg per kg teratogenic effects are apparent. Two retrospective studies of more than 14,000 mothers on whom caffeine consumption histories were obtained, revealed no association between caffeine intakes and abnormalities in offspring.

5. Carcinogenicity

A very recent and as yet unpublished report has indicated that rats given caffeine orally at daily doses of 150 to 250 mg per kg for 15 months develop cancer of several organs. Epidemiological studies suggest that there is no causal relationship between drinking coffee or the caffeine contained in it and cancer.

6. Long-term feeding studies

Two to four generation studies with rats intubated daily with up to 30 mg per kg body weight of caffeine or supplied the same dosage in drinking water, showed no consistent dose-related effects. Mice given 250 mg caffeine per kg body weight daily in drinking water throughout life, continued to breed satisfactorily. Fertility of eggs from pullets fed 80 mg caffeine per kg per day was not impaired but embryonic losses were about 16 percent compared to 5 percent in controls. Marked but reversible reduction in sperm output and concentration was found in roosters after 3 weeks feeding of 160 mg caffeine per kg per day.

7. Dose effects in humans

The pharmacological dose of caffeine used to stimulate central nervous system activity in humans is about 3 mg per kg and is observable at about 2 mg per kg. The acute human fatal dose of caffeine appears to be greater than 170 mg per kg. Oral administration of caffeine (4 mg per kg) has been found to increase blood pressure in fasted individuals.

8. Behavioral effects on children

Concerns with respect to behavioral effects are less for adults, particularly when the amount of caffeine consumed as cola beverages is compared to that consumed in coffee, tea or other natural sources of caffeine, than for children where there can be chronic consumption of caffeine in cola-type beverages during the period of brain growth and development. It is during this period of plasticity that the developing central nervous system is most sensitive to the effects of all aspects of the environment. The estimated levels of caffeine intake at these ages are near those levels that are known to cause central nervous system effects in adults. A few short-term human studies suggest that infants (treated neonatally with caffeine for apnea) were not more sensitive than adults to caffeine, that neonatal caffeine treatment
did not predispose to neurological or intellectual residua when the children were evaluated 2 years post-treatment, and that caffeine had no observable behavioral effects on either normal or hyperactive school aged children. Other studies indicate that children may be more sensitive than adults to the stimulant effects of caffeine. In mice, rats and monkeys noticeable behavioral effects have been elicited at dose levels as low as 1 to 2 mg of caffeine per kg, with definite effects apparent at doses upward of 10 mg per kg.

In addition to considering these eight factors, the Select Committee views with concern the continued addition of caffeine to cola-type beverages, representing as it does a unique addition to food of a pharmacologically active central nervous system stimulant. The amount of caffeine consumed as cola-type beverages borders on the dose known to produce central nervous system stimulation in animals and man. Whether such stimulation constitutes an adverse effect or whether a potential hazard may exist for the segment of the population, particularly children, that is exposed chronically to stimulating doses of caffeine, cannot be answered on the basis of the evidence now available. Despite the long history of use and absence of definitive evidence of toxicity in mammalian in vivo test systems, there is a possibility that behavioral effects in children from the consumption of caffeine from infancy through adolescence exist, even though these potential effects are neither adequately documented nor are their consequences clear.

The Select Committee is well aware that caffeine in cola-type beverages is not the only dietary source of this substance. However, based on the evidence available in May 1978, the Committee believes it is not appropriate to continue to consider caffeine as a generally recognized as safe substance for addition to cola-type beverages. A series of rigorously controlled chronic studies in appropriate species, including fetal, neonatal, and growing animals, of the immediate and ultimate behavioral and cardiovascular effects of caffeine added to the diet and given in cola-type beverages, would reduce areas of speculation in this regard. Such animal studies should include doses equivalent to the present estimated daily intakes of caffeine due to consumption of cola-type beverages containing 0.01 percent caffeine, and multiples of that dosage. In addition, appropriate pharmacokinetic studies (acute and chronic) in human subjects appear to be essential in order to establish patterns of absorption, biotransformation and excretion of caffeine. Such studies should consider caffeine as it occurs in cola-type beverages, as it occurs in natural sources, and in combinations of the two in common use by the general population, in order to study the effects of ranges of total body loads. Such data would be useful in providing a sounder basis for interpreting the possible long-term health implications of caffeine consumption.

In light of these considerations, the Select Committee concludes that:
A. While no evidence in the available information on caffeine demonstrates a hazard to the public when it is used in cola-type beverages at levels that are now current and in the manner now practiced, uncertainties exist requiring that additional studies be conducted.

B. It is inappropriate to include caffeine among the substances generally recognized as safe (GRAS). At current levels of consumption of cola-type beverages, the dose of caffeine can approximate that known to induce such pharmacological effects as central nervous system stimulation.

A minority report of Select Committee member R.G.H. Siu appears as an appendix to this report.
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May 31, 1978

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VIII. APPENDIX

Minority Opinion of Ralph G. H. Siu

I would like to go much further than my learned colleagues in expressing concern over the safety of caffeine as actually consumed in real life. I would also raise the question of prudence in promulgating an official regulatory position on the safety of caffeine as consumed in cola-type beverages alone, on the basis of the artificial scenario imposed upon this report.

Potential hazards of caffeine as a food ingredient

Caffeine is unique among ingested food ingredients. To evaluate it thoroughly over the entire realm of its physiological and psychological effects requires considerations of issues some of which have not heretofore been seriously addressed by the prevailing wisdom of toxicology. To disregard them in the case of caffeine is to assume a priori that they are hypothetical or inconsequential and hence can be ignored. In my opinion, many of them are real and important, some of which occur within the levels of caffeine consumption by a significant segment of our population. This would call for an in-depth facing up to all relevant questions before promulgating an official judgment on the safety of caffeine as a food ingredient in any of the commercially furnished commodities.

From a survey of these ranging effects, it would appear premature to conclude that "no evidence in the available information demonstrates a hazard to the public." Illustrative apprehensions are discussed in the ensuing paragraphs. As points of reference for the dosages mentioned, a 12-oz cola beverage is assumed to contain about 50 to 80 mg caffeine, a cup of coffee about 75 to 150 mg, a No-Doz tablet 100 mg, and a Vivarin tablet 200 mg.

1. Caffeine is the only drug freely consumed in food by human beings at pharmacologically active levels practically over their entire life span, generation after generation.

The compound crosses the placental barrier from the pregnant mother to the fetus (A-47) and enters the infant with the breast milk (A-60). With an interruption of only a few years, the child is again exposed to caffeine in soft drinks and chocolate, followed by coffee, tea, and/or other caffeine-containing foodstuffs in the subsequent years.

The consumption of caffeine-containing beverages has been on the rise for the last several decades. About a fourth of the coffee drinkers average 5 cups or more per day (A-101). Habituation to caffeine occurs, as shown
by observations on both animals (A-129) and human beings (A-33, A-46). A pathological dependence has been given the name of caffeinism, which has been reported in a number of clinical patients, such as one consuming 15 to 18 cups of brewed coffee a day (A-112) and another consuming 60 cups (A-92). Dysphoric withdrawal symptoms, including nervousness, irritability, and headache, are exhibited by heavy drinkers (A-33, A-54).

There is also an apparent trend toward greater use of psychoactive drugs, as well as a widening of their use in all socio-economic classes in America (A-39). Whether or not such a movement has already or will ever traverse the hazardous threshold from the standpoint of health considerations for the public at large and whether caffeine in foods plays a significant interactive role with respect to cravings for other psychoactive supports stand unresolved. Positive correlations have been published between coffee consumption and smoking habits and between coffee consumption and alcohol intake (A-43, A-111).

2. Caffeine participates in metabolic processes in a broad and central sense in its influence on the equilibrium content of adenosine 3', 5' cyclic monophosphate (cyclic-AMP) in the tissues. The latter high-energy compound is present in virtually all cells of the human body (A-136). Through the inhibition of the enzyme phosphodiesterase (A-4), which inactivates cyclic-AMP, caffeine may increase the concentration of cyclic-AMP in the cell over its normal value.

The significance of this readjustment of equilibrium concentration of cyclic-AMP rests on the wide array of metabolic catalytic processes in which the molecule acts as a mediator or messenger. Examples of these experimentally verified reactions are the following: protein kinase, phosphorylase, lipolysis (A-20), gluconeogenesis, steroidogenesis, calcium resorption by bone, glycogen synthetase, proliferation of thymocytes, protein synthesis by liver, discharge frequency by Purkinje's cells, secretion of insulin, action of adrenocorticotropic hormones, platelet plug formation in the control of bleeding (A-138), and cell division (A-1) or growth (A-13).

Biochemical equilibrium within the human body is buffered by homeostatic mechanisms and metabolic bypasses. For this reason a moderate disturbance of one or a relatively few processes on the part of a food ingredient may be viewed without much toxicological uneasiness. This may not be warranted, however, when the ingredient in question may perturb natural equilibria in a basic and pervasive manner throughout the body (A-19), thereby externally imposing, as it were, a generalized regulatory influence (A-120). The associated polemic may be too nebulous to be dissipated by the diffuse light of our present knowledge. Nevertheless, it remains an important point of departure with respect to the potential health hazard of caffeine as a food ingredient.
3. Positive findings have been made empirically on the effect of caffeine in a broad array of biochemical and physiological processes. The following are typical:

A dose-dependent rise in plasma lipid in rats occurs beginning at intakes somewhere below 4.8 mg caffeine per 100 g of diet (A-95). Oral administration of 3.2 mg caffeine per kg body weight raises free fatty acids in human plasma (A-26). Prolonged elevation of blood glucose results from a one-week replacement of drinking water by coffee in mice with hereditary obese hyperglycemic syndrome (A-75). Two hundred and twenty mg of caffeine taken as coffee stimulates the urinary secretion of catecholamines in human subjects (A-10) and 3 cups of coffee does the same for urinary adrenaline (A-80). In a double-blind, randomized, cross-over protocol, a single oral dose of 250 mg caffeine to healthy non-coffee drinkers increased plasma epinephrine by 207 percent (A-117). Secretion in the stomach increases following the ingestion of caffeine (A-118) and a striking net secretion in the jejunum occurs in human subjects given 75 to 300 mg caffeine (A-131).

A greater desensitization of muscle postjunctional membrane receptors is induced by caffeine (A-24). There is a relaxation of the lower esophageal sphincter (A-27). A stimulation of the myocardium is elicited (A-32).

Caffeine reduces the blood-brain barrier permeability to the alkaloid harmine in rats (A-7) and sensitizes the mammalian respiratory center to carbon dioxide (A-114). It potentiates the effects of low doses of dopamine injected into the neostriatum or the nucleus accumbens (A-3) and inhibits the cholinesterase activity in rat brain homogenate and mitochondrial fractions (A-29). Fifty mg per kg, intraperitoneally, lowers the brain stem norepinephrine in guinea pigs (A-12) and 100 mg per kg raises serotonin and 5-hydroxyindoleacetic acid in rat brain (A-11). The intraperitoneal administration of 5 mg caffeine per kg body weight results in an increase in contralateral circling in the opiate withdrawal of rodents (A-56).

An enhancement of the hepatic microsomal enzyme activity in rats is brought about by the administration of 30 mg per kg twice daily (A-91) or of 150 mg per kg for 3 days (A-2). Caffeine depresses antibody formation in mouse spleen cells in vitro after antigenic stimulation (A-77) and reduces the number of splenic germinal centers and total spleen cellularity, as well as the number of plaque forming cells, in mice immunized with sheep erythrocytes (A-79). Severe reactions may result from the interactions between caffeine in high doses and such drugs as propoxyphene and monoamine oxidase inhibitors (A-86).

When singly assessed, most of these changes may with some justification be looked upon as innocuous. Some may even be seen as beneficial for specific purposes, such as sharpening the sense of smell in dogs (A-94)
and decreasing the visual threshold in human beings consuming 1.7 to 3.3 mg caffeine per kg body weight (A-28). Yet the uncertainty keeps gnawing away at the safety assurances that can be offered in the face of potential synergistic concatenations of alterations, one or more of which may initiate an unhealthy cascade.

4. Caffeine is a central nervous system stimulant. It acts on the cerebral cortex and the medulary centers at the lower doses and may even affect the spinal cord at very high concentrations. Children appear relatively more sensitive than adults to the excitant effects (A-81).

At a dose of 150 to 250 mg, the cortex shows an EEG of arousal (A-74). There is a shift to a higher frequency (A-41). An intake of 300 mg caffeine citrate in water results in a rise in the negative shift of vertex EEG, which occurs prior to an expected stimulus (A-6). At extremely high doses clonic convulsions can be precipitated (A-49).

A hundred and fifty to 300 mg caffeine delays the onset of sleep for young adults (A-48). The soundness of sleep is also disrupted, as well as the quality. Four cups of coffee or caffeine equivalent produce a dose-related change in the electroencephalogram-electrooculogram sleep parameters (A-67). The rapid eye movement sleep shifted to the early part of the night and stages 3 and 4 to the latter part.

Fatigue is counteracted at moderate doses (A-44). Vigilance in monitoring is improved (A-8). Locomotor activity in mice is doubled after an injection of 25 mg caffeine per kg body weight (A-132). Three hundred mg caffeine in a cup of coffee speeded up the completion of cognitive tests among college students (A-82). Five hundred mg caffeine citrate led to a consistent increase in work output (A-116).

Less desirable impacts on operational effectiveness also appear. The ability to hold the arm steady in a given position is lessened; tremor is intensified at 300 mg caffeine citrate (A-63). The body sway of healthy persons with eyes open was increased with 300 mg caffeine (A-38). The reaction times of human subjects are modified; it is lengthened at lower ingestions of 60 to 240 mg but shortened at higher doses of 300 to 360 mg (A-59). Accuracy in tracking moving targets is compromised at daily doses of 3 to 4 mg per kg (A-61).

This sampling of the effects of caffeine on the central nervous system suffices to show that while certain manifestations may be considered as desirable for circumscribed purposes, such an increased wakefulness, others may not be, such as decreased accuracy in tracking moving targets. Whether the potential impairment of operational effectiveness, associated with increased jeopardy of occupational safety, falls within the elasticity of the definition of
"health hazards" of food ingredients merits some analysis, with particular reference to socially acceptable occupational safety decrements. Furthermore, what may be regarded as harmless, or even as beneficial, on a short-term basis may not turn out to be so on a continuing basis. The anti-fatiguing stimulation may be a case in point. The short-term desirability is obvious. Yet stimulation of this sort may also be looked upon as an override of a physiological deficit, thereby postponing the natural need for rest and/or repair. If continued over a long period of time on an unnaturally demanding level of activity, without conscious intent on the part of the individual, the physiological mortgage delays the ever-accruing ultimate payment. In some persons, this might be negligible relative to their recuperative capacity. In others, it may be significant and the final lump-sum toll may be physiologically bankrupting. To what degree this conjecture holds validly for caffeine remains an open issue.

5. Caffeine is the most widely consumed of the psychotrophic drugs (A-43). The following are representative reactions.

Spontaneous motor activity is exhibited by mice given 2.5 mg caffeine per kg body weight by mouth (A-58) and in rats given 2 mg caffeine per kg body weight intraperitoneally (A-65). Copulation by male rats is stimulated by 20 mg per kg, given intraperitoneally (A-141).

Caffeine produces a U-shaped curve for novelty preference in rats with concentration (A-62). When injected into mice, it leads to a dose-dependent disruption of performance during retention testing in an appetitive maze, apparently by interfering with the retention of the initial training (A-124). The compound also diminishes the latency of the avoidance response in a signaled-avoidance paradigm at low doses and heightens it at high doses (A-9) and raises the rate of punished responding (A-93).

Massive doses of caffeine given to rats lead to high aggressiveness and attacks upon other animals (A-104). Caffeine-intoxicated rats exhibit psychotic-like behavior (A-89), biting and mutilating their own feet and tails until they hemorrhage to death (A-17). This occurs at doses of 185 mg per kg (A-105). When the rats are starved, doses of 100 mg per kg suffice (A-108).

As far as human beings are concerned, an alteration in their patterns of body consciousness may be induced with the ingestion of 325 mg of caffeine citrate (A-21). There is a positive correlation between the degree of arousal and the subject's focus of attention upon the outer and right sides of their own body as compared to the inner and left sides. The verbal performance of introverts under time pressure orally administered 200 mg caffeine fell by 0.63 standard deviations and that of extroverts by 0.44 (A-113). High coffee ingestion produces symptoms indistinguishable from anxiety neurosis (A-50). Psychiatric patients consuming large amounts of coffee tend to exhibit more state anxiety than those consuming low amounts (A-137).
The way in which a child interacts with other human beings is crucial in the development of his or her personality. It is to be noted that caffeine gives rise to significantly higher lethality, motor activity, and rectal temperature in grouped than in isolated mice (A-51). Whether the continuing consumption of psychoactive drugs, which alter the behavioral characteristics of human beings as discussed above, during their developmental periods is undesirable engenders complex psychiatric controversies that go beyond the pale of conventional assessments of the safety of food ingredients. One may contend that such effects as the modification of copulation frequency, body consciousness, and curiosity, are a-health in nature and as such should not be of concern. It is doubtful, however, that he or she would speak with the same degree of indifference about anxiety, aggressiveness, and interference with the retention of learning. There are no scientific criteria for validly grappling with "safety thresholds" in this psychological and psychosocial sense. They need thorough airing. Not to do so is to come down arbitrarily on the side that they are "harmless" as far as caffeine is concerned.

6. Caffeine continues to be embroiled in a number of disagreements over its potential contributions to clinical disorders. None of them has so far been definitively established as far as singularly causal relationships for the average consumer is concerned. Yet none of them can be written off as being noncontributing as far as the high consumers of caffeine are concerned.

A philosophical dilemma poses itself. If a probable risk in a single clinically untoward manifestation constitutes sufficient grounds for questioning the safety of a food ingredient, does a less probable but nonetheless more than possible risk for several or more clinically untoward manifestations, as seems to be the case with caffeine (A-43), constitute comparably sufficient grounds? Many of the enhancing effects of caffeine on mutagenicity, chromosome-damage, carcinogenicity, and teratogenicity of other agents, for example, arise at levels of consumption only 6 to 10 times that of heavy coffee drinkers (A-70). When does the total of several or more separately minor fractions of the population, each specially sensitive to one particular effect of a given food ingredient, constitute a significant fraction of the public at large in the aggregate? These matters require resolution in the case of caffeine, especially in view of observed variations of toxicity with respect to age and sex of rats (A-107), the level of starvation (A-103), and the kind of diet (A-106) and suspected genetic differences in its influence on escape-avoidance (A-121), as well as individual human differences with respect to such manifestations as wakefulness, psychomotor coordination, and mood (A-45).

Some of the more prominent disputations are summarized below.

Heart ailments. The most vigorous of the debates concerns the association of caffeine consumption with heart ailments.
The introduction of 30 to 50 mg of a 50:50 mixture of sodium benzoate and caffeine into the umbilical vein of a newborn infant may produce tachycardia (A-25). A positive relationship between the amount of caffeine-containing beverages consumed and ventricular premature beats (VPB) has been observed (A-109). Ectopic impulse formation regresses with the suppression of coffee drinking (A-87). Although VPB is found in apparently healthy individuals, epidemiologic surveys have connected it with higher risks of sudden deaths (A-15, A-22, A-57). It may not be an independent causal factor (A-31).

As far as interpretations of epidemiologic studies on caffeine consumption and coronary attacks are concerned, professional opinion is divided. One prospective analysis in California involving first myocardial infarctions in 464 patients concluded that coffee drinking is not an established risk factor (A-71). Another prospective analysis of 7705 Japanese men in Hawaii showed a positive association between coffee drinking and coronary risk but the authors claim it to be statistically insignificant when cigarette smoking was taken into account (A-139).

In contrast, a multicenter Boston collaborative retrospective study of 276 patients found that those with myocardial infarction consumed more coffee than matched controls (A-16). The Boston study was extended to over 12,000 patients with the same result (A-64), which could not be explained away by such factors as sugar intake, past coronary disease, obesity, diabetes, smoking, and occupation. The risk of acute myocardial infarction in patients drinking 1 to 5 cups of coffee a day was 60 percent higher than those drinking 0 cups and that in those drinking 6 or more cups was 120 percent higher. The conclusion was supported by a prospective study in Chicago (A-102).

It appears that cardiovascular reactions to moderate caffeine ingestion is negligible for the majority of the population (A-115). What is not clear is the size of the minority that is susceptible to the effects of the equivalent of more than several cups of coffee a day. In the meantime, even physicians who do not subscribe to the connection of caffeine consumption to cardiovascular illnesses are quick to recommend against their liberal imbibiing on the part of those more prone to dysrhythmias (A-66). They invariably prescribe restrictions in caffeine consumption for patients actually suffering from heart disease. Furthermore, recent studies (A-117) with human subjects reported an increase of 14/10 mmHg in mean blood pressure after an intake of 250 mg caffeine. This change is of obvious clinical concern for borderline individuals.

**Ulcerogenesis.** Most physicians are less concerned over caffeine as a potential cause of peptic ulcers in the healthy average caffeine consumer. Nevertheless, they usually recommend a suppression of caffeine intake by patients already suffering from peptic ulcers.
Ulcerogenic effects of caffeine have been noted in guinea pigs (A-90). Intramuscular injections of 55 to 85 mg caffeine per kg body weight every day or so produced bleeding erosions or ulcers in the stomach of cats (A-119) but 250 mg did not give rise to ulcers in dogs (A-118). The effective concentrations in cats are so high that the finding is not regarded as strong evidence of directly implicating caffeine as a cause of peptic ulcers in the average person. Nevertheless, oral administration of 250 mg caffeine gave 324 percent stimulation of gastric secretion as the free acid in human subjects (A-118).

Although one epidemiologic analysis (A-40) did not implicate coffee drinking in peptic ulcers, another (A-99) did find an increased likelihood of 1.8-fold in the development of peptic ulcers in later life for college students drinking 2 or more cups of coffee a day over their classmates drinking none.

Mutagenicity. A fairly large number of tests has been recorded on the potential mutagenicity of caffeine. Many different methods have been employed. Some of the data indicate potential mutagenic activity; others do not.

Illustrative of results suggesting mutagenicity of caffeine are the following: higher mutagenic effect of ultraviolet light in T1 phage (A-53), hamster cell systems (A-37), and human cell systems (A-85), increased mutagenicity of cyclophosphamide in bone marrow cells of hamster (A-68), isoloocus chromosome breakage in HeLa cells in culture in proportion to caffeine concentration (A-98), cytostatic activity in human lymphocytes (A-128), damage in metaphase chromosomes of human lymphocytes in culture (A-134), and chromosome breaks in human lymphocytes in culture (A-78).

Illustrative of the larger group of observations suggesting non-mutagenicity are the following: no significant aberration in metaphase chromosomes in rats (A-83), nonmutagenic data in dominant lethal assay with rats or host mediated assay involving S. cerevisiae with mice (A-83), nonsynergistic effect on known mutagens in male rats based on fetal examination after mating (A-35), nonmutagenic reactions in Salmonella microsome tests (A-88), no incidence of chromatid breaks in HeLa cells in culture over 9 weeks (A-125), no chromosome breaks in human lymphocytes in vivo (A-135), and no significant aberration in anaphase chromosomes of human embryonic lung cells in culture (A-83).

There has been some tendency in the discussion over mutagenicity to juxtapose one set of results against another. Since no single one or cluster of these screening tests has gained authoritative consensus as reliably predicting the human situation, the exercise is not entirely convincing. Some attempts have been made to resolve the discrepancies by analyzing the character of the various tests. It has been shown, for example, that the mutagenic action of caffeine on E. coli is of the frameshift type (A-23), which
would not be expected to be detected in tests involving base-pair substitutions. Other workers (A-76) have hypothesized that caffeine may produce cumulative "premutations" in the germ cells thereby increasing the mutational risk. So far, preliminary examination of human populations has not confirmed this possibility (A-130). Most workers seem to be of the opinion that the mutagenicity of caffeine has not been established "as being either of great concern or as being dismissible" (A-127).

Teratogenicity. No fetal anomalies have been observed in 4 generations of rats given caffeine in drinking water equivalent to 20 to 31 cups of coffee a day for a 70-kg person (A-126). Two surveys of birth defects associated with drugs administered during pregnancy (A-55, A-96) showed no increase in malformed children from mothers exposed to various drug forms of caffeine. The baseline for caffeine-containing beverages, however, was not clear.

On the other hand, other animal tests (A-14, A-52, A-72, A-84, A-100) suggest that caffeine ingestion of between 30 to 50 mg per kg in single doses may significantly increase the hazard of birth defects. Intraperitoneal injections of 4 to 16 mg caffeine per day throughout pregnancy resulted in significant fetal resorptions and decreased birth rates in rats (A-42).

Several reports of co-teratogenetic effects of caffeine have been published. In one study (A-140), a single dose of 25 mg caffeine per kg body weight given intraperitoneally to pregnant mice 3 hours before X-ray treatment doubled the incidence of cleft palate over that of the controls. In another study (A-97), 5 doses of 50 mg caffeine per kg body weight given at 6-hour intervals following X-ray treatment increased the incidence of cleft palate, tail anomaly, and oligodactyly. The no-adverse-effect threshold as a co-teratogen appears to fall below 25 mg per kg. This estimate from animal tests is in line with the suggestion (A-133) that intakes of caffeine exceeding 7 mg per kg per day might contribute to spontaneous abortion and perinatal mortality in human beings.

The general thinking among the experts today is that caffeine-containing beverages as "normally consumed" offers little danger as a teratogen (A-127). Yet the 15 to 30 mg per kg dose as representing the no-adverse-threshold provides only a 5-fold margin of safety for a person consuming the equivalent of 2 cups of strong coffee at one sitting. This margin of safety would be even less, if one chooses to extrapolate from animal to human values on the basis of metabolic body weight instead of total body weight (A-43). For this and other reasons, various specialists (A-69) have seen fit to caution against heavy caffeine intake during the early stages of pregnancy.
Carcinogenicity. Data on the possible carcinogenic effects of caffeine are rather limited. Whatever there are are not susceptible of confident interpretation with respect to causal relationships in the human situation.

A higher incidence of bladder cancer has been detected among coffee-drinking men (1.24:1) and women (2.58:1) than among matched controls (A-122) and a correlation was perceived between coffee consumption and national mortality rates for renal cancer (A-123). But other investigators (A-5) were unable to find any conjunction between coffee drinking and either adrenocarcinoma of the renal parenchyma or carcinoma of the renal pelvis.

A recent announcement (A-36) disclosed significant increases of cancers in the pituitary, thyroid, mammary glands, and uterus of rats given doses of 150 to 250 mg caffeine per kg per day in drinking water for 15 months. There has not been sufficient time as yet for others to repeat the tests. As far as co-carcinogenic action is concerned, one study (A-30) concluded that caffeine enhances the transformation frequency induced by benzo(α)pyrene, N-acetoxy-2-fluorenylacetamide, and N-methyl-N'-nitro-N-nitrosoguanidine in cultured Syrian hamster cells. The compound also inhibits the post-replication repair of DNA in mammalian cells (A-34) and the dark repair of lethal ultraviolet lesions in the DNA of mouse L cells (A-110). There are suggestions (A-73) that mutagens, which bind DNA in such a way that DNA repair is inhibited, are also carcinogenic. Whether or not this holds for caffeine is not known.

Need for a re-evaluation with appropriate citizen participation

The Select Committee had been instructed to evaluate caffeine consumption only from cola-type beverages. Having gone through the exercise, I am now convinced that restricting the question in this fashion constitutes such an artificially bounded abstraction that the resulting conclusions can only be of limited, and even misleading, operational meaningfulness in real life. After all, such beverages account for only a fourth of the total caffeine consumed from foodstuffs (A-18) and covers less than a fifth of the principal exposure time over an individual's life span. Furthermore, seldom does a consumer ingest caffeine solely from cola-type beverages over any sustained period of time. Children eat caffeine-containing chocolate; adults drink coffee and tea.

In addition, to pass judgment on cola-type beverages alone at this time may be prejudicial to coffee and other caffeine-containing foodstuffs, representatives of which had not been explicitly forewarned of the implications and who, as a consequence, had not come forward with their own data and opinions. How this may come about is simple to see.
The safety of caffeine in cola-type beverages may be examined as (a) a hypothetical sole source of caffeine for the consumer over his or her life span, (b) the principal source of caffeine over part of the consumer's life span, followed by other caffeine-containing foodstuffs for the rest of his or her life span, and/or (c) only one source of caffeine in addition to the other commodities. Under conditions "a" and "b", to say that caffeine in cola-type beverages alone is not safe is to assert, in effect, that other caffeine-containing foodstuffs, which are taken in larger quantities and over longer periods of time, are also unsafe. Under condition "c", to say that caffeine in cola-type beverages is safe is to assert, in effect, that the total body burden of caffeine is also safe, including all other caffeine-containing foodstuffs. This last question has not, in accordance with FDA instructions to the Select Committee, been entertained in this report.

The Select Committee had been requested to confine itself to caffeine in cola-type beverages, inasmuch as the other foodstuffs do not lie within the province of GRAS substances. With benefit of hindsight, I am forced to conclude that it is the better part of prudence at this time to fall out and regroup. It now seems to me that patchwork on the present draft, commendable though the exercise may be in itself, will not do in terms of scientific completeness, real-life extrapolation, and genuine public participation.

No complete literature monograph on all caffeine-containing foodstuffs has been prepared. Up to date detailed consumer distribution data involving all of them in the American population are not available to the Select Committee. Basic fundamental issues underpinning safety criteria, which are somewhat unique to caffeine as an added food ingredient of commerce, have not been satisfactorily clarified by the scientific community at large. The views and data from the industrial, scientific, and public sectors concerned with caffeine-containing foodstuffs beyond soft drinks have not been incorporated in the process of completing this report. It is also fair to state that some of the questions raised in this minority opinion had not been presented in its tentative draft; even spokesmen for the soft-drink interests had not therefore been given a chance to react to them. The economic, political and social implications of coffee, tea, and other caffeine-containing foodstuffs are so great that their safety should not be subjected to evaluation through indirection by way of soft drinks. It should be met openly and thoroughly.

Conclusions

Based on the data furnished the Select Committee and in response to the instructions of restricting caffeine consumption to that in cola-type beverages alone, I conclude that:
1. The evidence on caffeine in cola-type beverages is insufficient to determine that the adverse effects reported are not deleterious to the public health when it is used at levels that are now current and in the manner now practiced.

At the same time, I beg leave to point out that this conclusion is tantamount to prejudging the safety hazard of caffeine in coffee and other foodstuffs without benefit of a complete literature survey of the relevant information and without providing opportunity for the interested parties to submit their views and data, which might have swayed my judgment. I would have preferred not to have been boxed into such a double bind by the turn of events. But the situation can still be rectified by deferring an official regulatory pronouncement based on this report until a complete airing of the total picture is completed. I would therefore recommend that:

2. Official reevaluation of the potential health hazard of caffeine in cola-type beverages alone should be kept open until an assessment of the safety of its consumption in all foodstuffs, individually and collectively, is completed with appropriate participation by all interested parties.
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