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A Critical Evaluation of the Information and Data Submitted on the Safety of EGCG, Epigallocatechin Gallate (TEAVIGO™)

Introduction

The proper assessment of the safety of a food ingredient or dietary supplement involves a critical evaluation by properly qualified experts of the available information on the particular substance and on chemically related substances. Sound scientific data derived from properly designed and executed studies designed to determine the biological effects of a substance forms the basis for this assessment. These studies should at least satisfy currently accepted guidelines such as those proposed by OECD and the U.S.F.D.A. (Redbook 2) and must meet appropriate GLP guidelines. Studies that do not meet these criteria may be used as supportive or corroborative evidence of safety. Documented history of safe use (valid epidemiological data) that involves comparing the proposed new product with one or more appropriate comparators may form a critical part of the assessment of safety.

(A list of studies evaluated is attached to this report).

Characterization of the Product

TEAVIGO™, DSM , is a green tea extract containing ≥ 90% epigallocatechin gallate (EGCG), a tea polyphenol (Ro 26-7624/000). Dried green tea contains 15-20% catechins, 25-40% of which is EGCG. TEAVIGO™ is intended for use as a dietary supplement and food fortificant at a recommended dose of 100- 300 mg EGCG per person per day.

Consumption/Exposure Information

About 20% of total tea production (2.6 million tons) is green tea (0.52 million tons). It is consumed widely in Japan, China, North Africa and the Middle East. Consumption is increasing elsewhere presumably due to the purported health benefits (including decreased incidence of cancer, cardiovascular disease, diabetes and obesity) of green tea consumption (for example, Yang and Landau, 2000 and Liao, et al, 2001). The Tea Council of the USA (1998) reported that the EGCG content of a single cup of green tea ranges between 40 and 90 mg. Epidemiological data reported by Imai (1995) indicates that 23% of Japanese consume more than 10 cups of green tea per day resulting in a daily intake of 345-1095 mg EGCG and that 19% of Chinese ingest 230-730 mg EGCG per day.

Toxicity/Safety Studies
Acute Toxicity
Rodents
The acute oral toxicity of EGCG is very low. The acute oral LD_{50} in rats has been reported to be 3000- 5000 mg/kg bw (Yamane, et al, 1996) and for mice, it is 2170 mg/kg bw (Kiso, 1960). Wolz, E., at al (2001) reported an acute oral LD_{50} of TEAVIGO™ in male and female Wistar rats of between 200- 2000 mg/kg bw.

Repeated-dose Toxicity
Rats
"No significant changes are observed in body weight or blood hematological and biochemical parameters when 15 or 75 mg/kg of a green tea extract is administered orally for 28 days." (from Kao, et al, 2000, cited in Liao, et al. 2001).

Sub chronic Toxicity
Rats
Male and female Sprague-Dawley rats (20/ sex/group) received EGCG by gavage at daily doses of 0, 45, 150, or 500-mg/kg bw/day for 90 consecutive days. The reported NOELs in this NCI-sponsored study conducted at IITRI (Chicago, IL, USA) were 45-mg/kg bw/day for males (based on reduced body weight gain and decreased absolute and relative thymus weights at the mid-dose) and 150-mg/kg bw/day for females based on early deaths, suppression of body weight gain, gastrointestinal pathology and necrosis/atrophy of the thymus in both sexes at the highest dose. (McCormick, et al, 1999).

In another NCI-sponsored study conducted at IITRI (Chicago, IL, USA), male and female Sprague-Dawley rats (20/sex/group) received "a green tea polyphenol (GTP) fraction [Polyphenon E; Mitsui Norin] whose major components are epigallocatechin gallate (EGCG; 53.4%), epigallo-catechin (11.4 %), epicatechin (9.1%); gallocatechin gallate (5.1 %); and epicatechin gallate (4.9 %)" at daily oral doses of 0, 90, 300 or 1000 mg/kg bw/day by gavage. "...the NOEL of GTP in rats (both sexes) is 990 mg/kg/day. Mortality patterns in rats indicate that GTP is more toxic than would be predicted based on EGCG content alone, suggesting that polyphenols other than EGCG play a role in its toxicity." Early deaths, suppression of body weight gain, gastrointestinal pathology and pathological effects on the thymus, pancreas and liver were reported at the mid- and high doses. (Johnson, et al., 1999)

Male and female Sprague-Dawley rats (20/sex in the control and high dose groups and 10/sex in the low and mid dose groups) received TEAVIGO™ as a dietary admixture at nominal daily doses of 0, 50, 150 and 500 mg/kg bw/day for 90 consecutive days followed by a four-week recovery period. There were no consistent, dose-dependent adverse effects reported. The reported NOEL in this Roche-sponsored study conducted at IITRI (Chicago, IL, USA) was 500-mg/kg bw/day, the highest dose tested. (F. Hoffmann-LaRoche Ltd., Basle (CH). Research Report B-0172301, Pfannkuch, F., et al, 23 June 2000).

Sub chronic Toxicity
Dogs
Male and female beagle dogs (4/sex/group) understood to be non-fasted received EGCG by capsule at daily doses of 0, 30, 100, or 300-mg/kg bw/day for 90 consecutive days. There were no consistent, dose-dependent adverse effects reported. The reported NOEL for both male and female dogs in this NCI-sponsored study conducted at IITRI (Chicago, IL, USA) was 300-mg/kg bw/day, the highest dose tested. (McCormick, et al, 1999).

Male and female beagle dogs (4/sex/group) fasted for at least four hours before dosing received TEAVIGO™ by capsule at daily doses of 0, 50, 150, or 500 mg/kg bw/day for 13 consecutive weeks. Vomiting and liquid feces were reported in all groups but were most severe at the highest dose and sporadic at low dose and control groups. There were deaths at the top dose and pathology at the high and mid doses (including gastric erosion, proximal tubular renal necrosis, liver necrosis and lymphatic atrophy). The reported NOEL was 50-mg/kg bw/day. This Roche-sponsored study was conducted at MDS PS facilities in France and Switzerland. (F. Hoffmann-LaRoche Ltd., Basle (CH). Regulatory Document RDR-1004582, Pfannkuch, F., et al, 28 May 2001).

In another study, pre-fed male and female beagle dogs (4/sex/group) received TEAVIGO™ by capsule at daily doses of 0, 50, 300, or 500-mg/kg bw/day for 13 consecutive weeks. "The daily doses were divided into two equal capsule doses of 0, 25, 150 and 250 mg/kg and were administered approximately one hour after the animals were given access to food." There were no consistent, dose-dependent treatment-related adverse effects reported. The reported NOEL was 500 mg/kg bw/day. This Roche-sponsored study was conducted at IITRI (Chicago, IL, USA). (F. Hoffmann-LaRoche Ltd., Basle (CH). Regulatory Document RDR-1009351 Pfannkuch, F, et al, 24 Jan 2003).

Long-Term Toxicity
Rats
Green tea extract (Polyphenon 70S, polyphenol content more than 70%) was "orally administered to rats (sex, strain, number not specified gavage or dietary administration not specified) for six months"..."in dose ranges of 500-2000 mg/kg." The following were reported: no inhibition of body weight gain, increased food intake, decrease in food efficiency, increased liver weight and increased levels of alkaline phosphatase and GPT in the 2000 mg/kg group (reversible after one month withdrawal period). "...the max non-toxic dose of Polyphenon 70S appears to be 1000 mg/kg bw." (Matsumotoi, et al, 1999).

Reproductive and Developmental Toxicity
Two-Generation Reproduction
Rats

Male and female Sprague-Dawley rats (F0 generation: 30/sex/group; F1 generation: 25/sex/group) received TEAVIGO™ as a dietary admixture at concentrations of 0, 1200, 3600 and 12000 ppm for two consecutive generations. The authors stated: "In conclusion, the no observable adverse effect level (NOAEL) for adult mating performance and fertility was the dietary concentration of 12000 ppm. This level corresponded to a nominal dose of 1000 mg EGCG/kg body weight/day." "The NOAEL for general toxicity in adult animals was the dietary concentration of 3600 ppm. This level corresponded to a nominal dose of 300 mg TEAVIGO™ /kg body weight/day." "The NOAEL for effects on growth and development of the offspring was considered to be 1200 ppm. This level corresponded to a nominal dose of 100 mg TEAVIGO™ /kg body weight/day." The authors suggest that this NOAEL could be increased to 200 mg TEAVIGO™ /kg body weight/day because most of the effects on growth and development of the offspring were seen during lactation when there is "higher food consumption." (Pfannkuch, F., et al, 2002 a). This Roche-sponsored study was conducted at MDS Pharma Services in France and in Switzerland.

Developmental Toxicity
Rats

Time-mated female Sprague-Dawley rats (25/group) received TEAVIGO™ as a dietary admixture at concentrations of 0, 1400, 4200 and 14000 ppm from days 6 to 20 of gestation inclusive. Females were sacrificed on gestation day 20. "Three satellite females per group were included for a toxicokinetic investigation and were given TEAVIGO™ (Ro 26-7624/000) under the same conditions as the main group females. These females were sampled for proof of absorption on days 7 and 16 of gestation and then killed without necropsy with a determination of their pregnancy status by internal inspection." "The average achieved intake of TEAVIGO™ during the treatment period was 111, 337 and 1079 mg/kg body weight/day in the 1400, 4200 and 14000 ppm groups respectively." There were no consistent dose-dependent adverse effects reported; there were no adverse effects on any parameter evaluated including morphological development.

In the satellite animals, "Mean EGCG plasma concentrations showed an approximate linear dose-relationship (36.63 and 59.47 ng/ml at 1400 ppm, 112.2 and 154.6 ng/ml at 4200 ppm and 300.1 and 436.6 at 14000 ppm for days 7 and 16 of gestation, respectively..."

The authors conclude, "Within the context of this study, the dietary concentration of 14000 ppm (equivalent to a limit dose of 1000 mg/kg body weight/day) can be considered as a no observable adverse effect level (NOAEL) for both maternal and embryo-fetal toxicity in the rat." The data support this conclusion. (Pfannkuch, F. 2002 b). This Roche-sponsored study was conducted at MDS PS in France and in Switzerland.

Absorption, Metabolism, Distribution and Excretion (ADME)
Excretion balance studies were conducted in male and female Wistar rats administered ^{14}C-EGCG at doses of 50 and 500 mg/kg body weight. The data indicate that EGCG is poorly absorbed intact, that plasma levels are low due to poor absorption and to hepatic first pass metabolism where "EGCG is partly conjugated and/or methoxylated and predominantly excreted via the bile," that EGCG is metabolized by gut microflora "to 5-(3', 5'-dihydroxyphenyl)-gamma-valerolactone and structurally related metabolites..." "They are absorbed to a much larger extent than EGCG, widely distributed into the body and appear in the urine in partly conjugated forms." About 80% of the administered dose was excreted in the feces. (Goelzer, P., 2002).

The pharmacokinetics and tissue distribution studies of ^{3}H-epigallocatechin gallate (EGCG) were investigated in male beagle dogs. The authors reported, "The estimated oral bioavailability of 10 to 20 % is consistent with the excretion data and indicate that EGCG is relatively well absorbed in the beagle dog. In addition, it is likely that a large fraction of absorbed EGCG is readily metabolized by the dog based on the rapid appearance of radiolabel in the GI tract, feces and urine." (Green, C., et al, 2000).

Genotoxicity
In Vitro Studies
Ames Test
"The Ames test did not indicate a genotoxic potential (E. Gocke, B0163'294). TEAVIGO™ was tested up to 5000 micrograms/plate, the maximum dose level recommended..." against tester strains TA 1535, TA 97, TA 98, TA 100, TA 102, with and without metabolic activation (Gocke, E., 1996 and Gocke, E., et al, 2002).

Mouse lymphoma/thymidine kinase
TEAVIGO™ showed chromosomal aberrations in 2 ML/TK tests in both the absence and presence of metabolic activation. (Kirchner, S., 2000 and Gocke, E., et al, 2002).

Micronucleus Test with Chinese Hamster Ovary Cells
TEAVIGO™ was equivocally to moderately positive (showed chromosomal aberrations) in this MNT in both the absence and presence of metabolic activation. (cited in Gocke, E., et al, 2002).

In Vivo Studies
Micronucleus Test in Mice
TEAVIGO™ did not induce micronuclei in the mouse bone marrow assay following a single oral dose of 0, 500, 1000 or 2000 mg/kg bw or repeated administration at nominal doses of 0, 500, 1000, 1500 mg/kg bw/day as a dietary admixture, for 10 consecutive days). TEAVIGO™ was administered intravenously to rats at doses of 0, 10, 25, 50mg/kg bw/day for two consecutive days and it did not induce micronuclei. (Muster, W. and King, M.T., 1997; Pfannkuch, F., et al, 2001 and Gocke, E., et al, 2002).

Micronucleus Test in Rats

TEAVIGO™ "was administered intravenously to SPF-bred Wistar rats of both sexes at doses of 10, 25 and 50 mg/kg body weight/day on 2 consecutive days. It was concluded that under the experimental conditions of this study Ro 26-7624/000 (TEAVIGO™) did not show genotoxic activity in bone marrow cells." (Pfannkuch, F., et al, 2002).

The definitive tests for genotoxicity are the in vivo tests. The in vivo data indicate that TEAVIGO™ is not systemically genotoxic. The in vitro findings may be artefactual "with no relevance to the use of this compound as a dietary supplement." (Gatehouse, D.G. and Kirkland, D.J., 2002) and may be explained by the production of hydrogen peroxide by EGCG in the culture medium.

Human Studies

In a single ascending dose (SAD) study, 8 healthy male subjects received 50 mg, 100 mg, 200 mg, 400 mg, 800 mg or 1600 mg of TEAVIGO™ and 10 subjects received placebo. EGCG was rapidly absorbed. The authors concluded "The mean $t_{1/2}$ values were seen between 1.9 and 4.6 h. Single oral doses of EGCG up to 1600 mg were safe and well tolerated." (Ullmann, U., et al, 2003). In a multiple ascending dose (MAD) tolerance study, 36 Caucasian healthy males were divided into three groups of twelve, nine received TEAVIGO™ and three received placebo. The daily doses of TEAVIGO™ were 200 mg, 400 mg and 800 mg/day for 10 consecutive days. The authors concluded "In this present study TEAVIGO™ in the dose range 200 mg, 400 mg and 800 mg administered orally once daily in the morning (fasting) for 10 subsequent days to healthy male volunteers was safe and well tolerated. Neither serious or unexpected adverse events nor any other kind of clinically relevant adverse events occurred," and "It could be concluded, that EGCG excretion is a dose-dependent, capacity-limited process which was saturated at least after repeated dosing with 800 mg TEAVIGO™ ." (Ullmann, U., et al, 2003). The effect of TEAVIGO™ on non-heme iron absorption in women with low iron stores was evaluated in a randomized, placebo-controlled, double-blind, balanced three-way cross-over study in 30 healthy female volunteers. "The three treatments were consumed at breakfast and comprised placebo and TEAVIGO™ given at a daily dose of 300 mg or 150 mg. The study consisted of three study periods, each lasting eight subsequent study days." It was reported that "All participants completed the study and showed no signs or symptoms of adverse effects due to or related to the study substance. No clinically relevant laboratory pre-study, in study (haemoglobin) and post-study check up results were reported. No serious adverse events were reported," and "The results showed that a daily dose of 150 mg of TEAVIGO™ reduced fractional non-haem iron absorption by 14% as compared to the control, which effect was not statistically significant. A daily dose of 300 mg TEAVIGO™ significantly reduced fractional non-haem iron absorption by 27 % as compared to the control. The effect of TEAVIGO™ on iron absorption was linearly related to the TEAVIGO™ -dose." (Bakker, G.C.M., et al, 2003).

Discussion

The data from the available toxicological studies are adequate for proper safety assessment of TEAVIGO™ . A safe dose for humans can be estimated from the animal data and supported by limited studies in humans. A safe daily dose for humans, sometimes referred to as an Acceptable Daily Intake (ADI), can be established by considering the NOAEL from properly designed and executed studies in appropriate species and the use of an appropriate safety/uncertainty factor (SF/UF). A SF/UF of 100 is usually applied to a lifetime study. For studies of shorter duration, and an additional factor of 10 may be included because of the shorter duration of exposure. However, the USFDA now accepts 100 as an appropriate factor for definitive sub chronic studies but it should be applied to the lowest NOAEL unless there are scientific reasons for not considering it.

The NOAEL from the beagle dog studies will be used since the bioavailability is greater in the dog than the rat making it a worse case situation. The NOAELs for the dog studies are 300 and 500 mg/kg bw/day. Since there were no adverse effects at the highest dose tested in the earlier study, namely 300mg/kg bw/day, it is appropriate to consider 500 as the NOAEL. Applying a 100-fold SF/UF, the ADI would be 5 mg/kg bw. For a 60 kg human, this would be 300 mg/day. In the rat studies, the NOAELs were 45 and 150-mg/kg bw/day for males and females, respectively. However, TEAVIGO™ was administered by gavage which is a much more severe route of administration than as a dietary admixture which is the preferred route for evaluating the safety of food ingredients and dietary supplements. When TEAVIGO™ was administered in the diet, the NOAEL was 500mg/kg bw/day, the same value obtained in the beagle dog.

In the two-generation reproduction study in rats, the NOAEL was 100mg/kg bw/day. The effects on growth and development of offspring were apparently due to lactation. Following lactation, the pups began to thrive. The NOAEL in the developmental toxicity study was 1079 mg/kg bw/day, the highest dose tested.

There were several properly designed and executed studies in humans. It was reported that humans can tolerate (no adverse effects) a single oral dose of 1600 mg TEAVIGO™ /day and 800 mg TEAVIGO™ /day for ten consecutive days. These data suggest that the proposed ADI from the dog data is conservative.

Based on evidence of gastrointestinal irritation in the dog, it is recommended that the daily dose be divided and, further, that it not be taken on an empty stomach.

Conclusion

A critical evaluation of the available toxicological data supports a conservative safe daily dose of 300 mg of TEAVIGO™ .

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