

Docket No. 78N-036L

BEFORE THE
UNITED STATES OF AMERICA
DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

SUBMISSION OF A REVIEW OF DATA FROM THE
NATIONAL TOXICOLOGY PROGRAM
AND RELEVANT TO THE STATUS OF
CASCARA SAGRADA INGREDIENTS
AS OVER-THE-COUNTER DRUG ACTIVE INGREDIENTS

BY THE
AMERICAN HERBAL PRODUCTS ASSOCIATION

78N-036L

SUP 15

December 19, 2002

The American Herbal Products Association (AHPA) hereby submits additional information to Docket No. 78N-036L that is relevant to the status of cascara sagrada ingredients as active ingredients in stimulant laxative over-the-counter drug products. This submission is a supplement to CP25.

This submission consists of an expert review by the Toxicology Group, LLC, a division of NSF International, of publicly available data in the form of two Technical Reports published by the National Toxicology Program (NTP) at the National Institutes of Health (NIH). The reports are Technical Report Series, No. 465 (TR-465): *Toxicology and Carcinogenesis Studies of Phenolphthalein (CAS No. 77-09-8) in F344/N Rats and B6C3F₁ Mice (Feed Studies)* and Technical Report Series, No. 493 (TR-493): *Toxicology and Carcinogenesis Studies of Emodin (CAS No. 518-82-1) in F344/N Rats and B6C3F₁ Mice (Feed Studies)*.

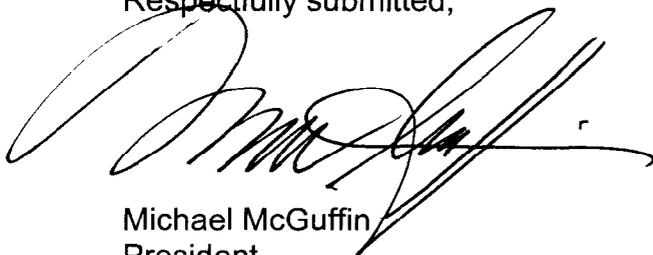
AHPA and the International Aloe Science Council (IASC) on June 10, 2002 submitted a petition to request a stay and reconsideration of the provisions of 21 C.F.R. § 310.545(a)(12)(iv)(C) and (d) regarding the status of aloe vera ingredients (aloe, aloe extract, aloe flower extract) and cascara sagrada ingredients (casanthranol, cascara fluidextract aromatic, cascara sagrada bark, cascara sagrada extract, cascara sagrada fluidextract) which were purportedly made final in a Federal Register notice published May 9, 2002 (67 Fed. Reg. 31125). The relief requested was that the Food and Drug Administration (“agency”) stay the November 5, 2002 effective date of this regulation and that the agency reconsider the regulation in light of new information not previously considered by the agency or its Advisory Review Panel on OTC Laxative,

Antidiarrheal, Emetic, and Antiemetic Drug Products or, insofar as the associations are aware, by its OTC Drug Product staff. The submission made to this docket today is part of the information that may not have been previously considered by these parties for cascara sagrada.

In a notice in the *Federal Register* of June 19, 1998 (63 FR 33592) FDA reopened the administrative record and reclassified several stimulant laxative ingredients, including those that are derived from cascara sagrada, from Category I (monograph) to Category III (more data needed). The agency stated that it had not received any mutagenicity, genotoxicity, and carcinogenicity data for cascara sagrada ingredients. AHPA believes that the information submitted here represents such data.

AHPA further believes that the information submitted here supports the Citizen Petition of June 10, 2002 insofar as it is related to cascara sagrada ingredients.

Respectfully submitted,



Michael McGuffin
President

**Response to FDA request for more information for Cascara Sagrada.**

Cascara sagrada bark has been used as a stimulant laxative ingredient since the late 19th century. Due to emerging safety concerns for other stimulant laxative ingredients, questions have been raised about the mutagenicity, genotoxicity and carcinogenicity of cascara sagrada.

In order to identify information that might be available in the public record, we conducted, between June and October, 2002, literature reviews for cascara sagrada and several of its constituents, and specifically aloe-emodin (CAS Registry No. 481-72-1); barbaloin (1415-73-2); casanthranol 8024-48-4); cascara (8047-27-6); cascarioside (50814-04-5); chrysaloin (no CAS Registry No.); chrysophanol (481-74-3); and emodin (518-82-1). The literature search strategy employed for each compound was based on the CAS Registry Number and/or chemical name and at least one common name, and searched numerous data banks, including: ChemID Plus; Registry of Toxic Effects of Chemical Substances (RTECS); Hazardous Substances Data Bank (HSDB); GENE-TOX; Environmental Mutagen Information Center (EMIC); Developmental and Reproductive Toxicology (DART/ETIC); TOXLINE; Toxicology Literature from Special Sources (TOXLIT); CANCERLIT; Chemical Carcinogenesis Research Information System (CCRIS); Medline (via PubMed); Integrated Risk Information System (IRIS); Syracuse Research Corporation Online Toxic Substance Control Act Database (TSCATS); and Current Contents.

The reviews described here resulted in compilations of a significant amount of scientific data on cascara sagrada and its constituents in publicly available resources. These compilations were provided to the American Herbal Products Association (AHPA) on October 24, 2002 without further analysis and we have been informed that were submitted to FDA Docket No. 78N-036L on October 28, 2002.

The current document discusses two reports published by the National Toxicology Program, one of which was concerned with the toxicity of phenolphthalein and the other with the toxicity of emodin.

- **Identification of ingredient**
- **Primary Ingredient: Cascara Sagrada**

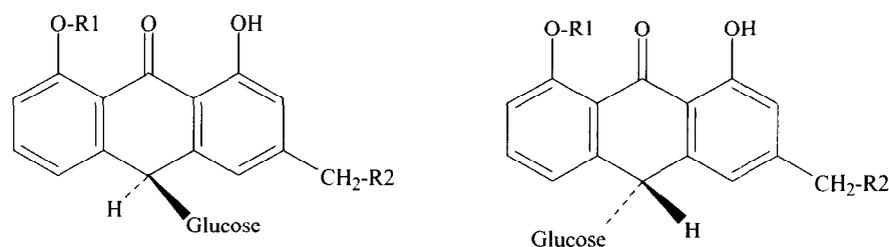
Cascara sagrada is the common name for *Rhamnus purshiana*¹ (family *Rhamnaceae*), a short (< 12 m) shrubby tree native to the Pacific Northwest of the United States. The dried bark of this tree, also called cascara sagrada, is the source of several anthraquinone laxative drugs, a class of laxatives used by many people throughout the world (van Gorkom et al., 1999).

¹ According to some taxonomists the accepted name is *Frangula purshiana*.

Other members of the *Rhamnus* genus historically used as anthraquinone laxatives include *Rhamnus frangula*² and *Rhamnus cathartica*. *Rhamnus frangula* is a shrubby tree native to Europe, Western Asia, and North Africa, and has been introduced to the eastern coast of the United States as well. *Rhamnus cathartica* is native to Europe and Asia, and has also been introduced to northern United States. The fruit of *Rhamnus cathartica* is used as the laxative agent as opposed to the bark used from the *R. purshiana* and *R. frangula* species.

▪ Individual Constituents

Cascara sagrada dried bark contains approximately 7-10% hydroxyanthraquinone glycosides (Newall et al. 1996; Wichtl and Bisset, 1994; USP 25, 2002). Hydroxyanthraquinone glycosides are hydroxyanthracene derivatives with hydroxyl groups at the C-1 and C-8 position and sugar groups at the hydroxyl groups (*O*-glycosides) or at the C-10 position (*C*-glycosides) (van Gorkom et al., 1999; van Os, 1976). Not less than 60% of the 7-10% consists of cascariosides, expressed as cascarioside A (USP 25, 2002). There are four forms of cascariosides: A, B, C and D. Cascariosides A and B are diastereoisomers, as are Cascariosides C and D (Figure 1). Additional constituents of the cascara sagrada dried bark are the diastereoisomers of barbaloin and chrysaloin.



	R1	R2		R1	R2
Cascarioside A	Glucose	OH	Cascarioside B	Glucose	OH
Cascarioside C	Glucose	H	Cascarioside D	Glucose	H
Barbaloin (L)	H	OH	Barbaloin (R)	H	OH
Chrysaloin (L)	H	H	Chrysaloin (R)	H	H

Table and figures modified from Wichtl and Bisset (1994).

Figure 1. Chemical structures of cascara sagrada constituents cascarioside, barbaloin and chrysaloin.

The fresh bark of cascara sagrada contains mono-anthrone-*O*-glycosides, dianthrone, *C*-glycosides, aloe-emodin-*O*-glycoside and free anthrones. Of those free anthrones 80-90% are

² According to some taxonomists the accepted name is *Frangula alnus*.

bound as *C*-glycosides and 10-20% are bound as *O*-monoanthrone glycosides (van Os, 1976). During the preparation of the cascara sagrada bark, it is dried for one year or at very high temperatures for several hours. This is done to oxidize the mono-anthrone and their *O*-glycosides to dianthrone- and anthraquinone-*O*-glycosides. The mono-anthrone and their *O*-glycosides cause unwanted emetic effects whereas the other forms do not.

Other constituents of cascara sagrada include: *O*-glycosides of emodin, emodin oxanthrone, aloe-emodin, and chrysophanol, dianthrone (a combination of two mono-anthrone), anthraquinone with H₂ at C-10, and free anthraquinones such as aloe-emodin and chrysophanol (Figure 2). Linoleic, myristic and syringic acids can also be found in the bark of cascara sagrada (Newall et al., 1996).

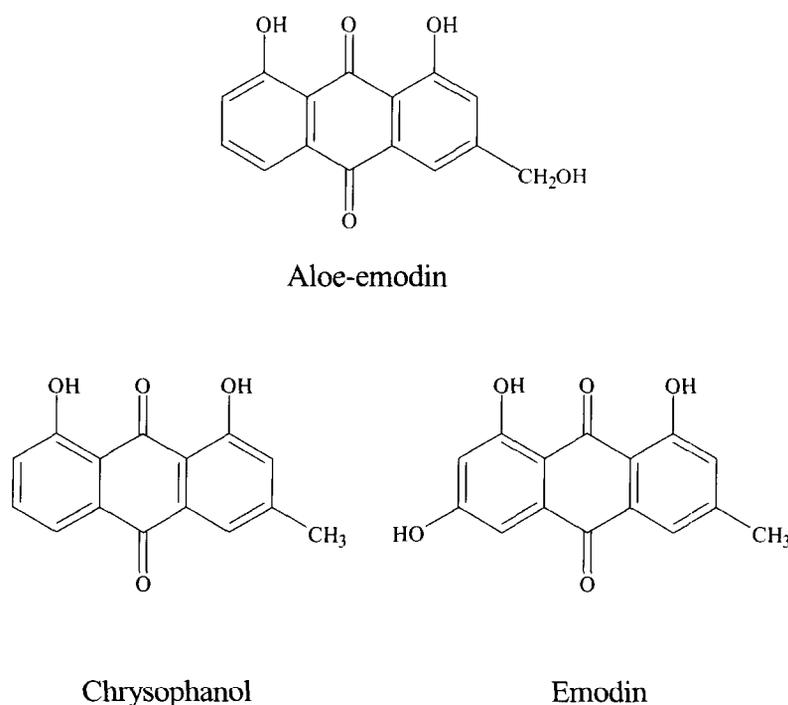


Figure 2. Chemical structures of cascara sagrada constituents aloe-emodin, chrysophanol and emodin.

▪ Description of Cascara Sagrada Preparations

The current United States Pharmacopeia (USP 25, 2002) lists five ingredients related to cascara sagrada, including cascara sagrada bark and four preparations derived from the bark. The subject of this document is limited to only cascara sagrada bark. The other four preparations are:

- *Casanthranol* is a purified mixture of anthranol glycosides extracted from cascara sagrada (Robbers et al., 1996). It contains not less than 20% total hydroxyanthracene

derivatives, calculated as cascarioside A, of which not less than 80% consists of cascariosides (USP 25, 2002; Robbers et al., 1996).

- *Cascara sagrada extract* is a dry extract prepared by maceration and percolation of dried cascara sagrada bark powder in boiling water. Cascara sagrada extract contains 10-12% hydroxyanthracene derivatives, of which not less than 50% consists of cascariosides, both calculated as cascarioside A (USP 25, 2002).
- *Cascara sagrada fluidextract* is an aqueous extract of dried cascara sagrada bark powder. The extract is prepared with boiling water, partially evaporated, and preserved with 20% alcohol. Each ml of the extract represents 1 gram of the dried bark (USP 25, 2002).
- *Aromatic cascara fluidextract* is an aqueous extract of dried cascara sagrada bark powder and magnesium oxide. The extract is prepared with boiling water, partially evaporated, flavored with "suitable" sweetening agents, essential oils and flavoring agents, and preserved with 20% alcohol. Each ml of the extract represents 1 gram of the dried bark (USP 25, 2002).

▪ **Dosage and Duration of Use**

Federal Register notices on January 15, 1985 and October 1, 1986 published proposed rules for several over-the-counter (OTC) drugs, including laxative drugs. Absent a final rule in the intervening years, the 1985 and 1986 documents have established the *de facto* dosage and labeling of OTC laxative drugs, including those that contain cascara sagrada bark and preparations thereof.

Based on the information in these *Federal Register* notices and on the discussion above regarding cascara sagrada's constituents, the daily dosage of cascara sagrada bark, and the related daily consumption of constituents of cascara sagrada are shown in Table 1.

Table 1. Daily doses of cascara sagrada bark and constituents based on standard OTC doses.

	drug	total hydroxyanthracene derivatives	
	daily dose	%	daily dose
children (age 2-12)	150-500 mg	7-10%	10.5-50 mg
adults	300-1000 mg	7-10%	21-100 mg

Based on the data in this Table 1 and assuming standard average weights for adults and for children, the average daily dose of total hydroxyanthracene derivatives can be calculated. These calculations are presented in Table 2, based on adult weight (70 kg) and child weight (10 kg)³.

Table 2. Calculation of daily consumption of total hydroxyanthracene derivatives per kilogram bodyweight.

children 2-12 years; (10 kg)		adults; (70 kg)	
total daily hydroxyanthracenes	daily dose per kg bodyweight	total daily hydroxyanthracenes	daily dose per kg bodyweight
10.5-50 mg	1.05-5 mg	21-100 mg	0.3-1.43 mg

Long-term use of stimulant laxatives, including cascara sagrada, is not recommended due to potential dependence and loss of electrolytes, especially potassium (Robbers et al., 1996; Wichtl and Bisset, 1994). Labeling required by the U.S. Food and Drug Administration (FDA) for all laxative drug products includes a statement that the product “should not be used for a period longer than one week unless directed by a doctor.”

▪ **Mode of Action**

Cascara sagrada is considered a prodrug. Six to eight hours after ingestion the drug begins to take effect (Rosengren and Aberg, 1975). The primary constituents, anthraquinone glycosides, do not act directly on the intestinal system. Once ingested the sugar moiety confers hydrophilic characteristics to the anthraquinone glycoside allowing it pass through to the colon. Once in the colon, gut flora enzymes hydrolyze the glucosidic linkage freeing the anthraquinone molecule. The exact mechanism of action at this point is still unclear (Sendelbach, 1989). Possible mechanisms that have been proposed include inhibition of Na⁺ absorption, a nonspecific metabolic effect on the epithelial cells, or inhibition of Na⁺/K⁺ ATPase.

³ The average weight of child 2-12 years old can range between 12-13 kg for a two year to 42-40 kg respectively for girls and boys (<http://www.cdc.gov/growthcharts>). The body weight of 10 kg used for calculation purposes is conservative and results in the worse case dose calculations which is only representative of a two year old child in the first weight-for-age percentile.

■ Toxicity Information

2.1 FDA and NTP Actions on Laxative Ingredients

In a *Federal Register* notice of September 2, 1997, FDA presented new information on phenolphthalein and proposed that phenolphthalein and another laxative ingredient, danthron, be reclassified as “not generally recognized as safe and effective or misbranded.” The new information on phenolphthalein identified several studies that had been undertaken through the National Toxicology Program (NTP), including 14 day, 13 week and 2 year feeding studies in rats and in mice, as well as several genetic toxicology studies. The agency provided information about which of these studies had produced positive results that led to conclusions that phenolphthalein exhibits some mutagenic activity in certain tests and that there is clear evidence of carcinogenic activity of phenolphthalein in rodents. These studies were published in November 1996 as NTP’s Technical Report Series, No. 465 (TR-465): *Toxicology and Carcinogenesis Studies of Phenolphthalein (CAS No. 77-09-8) in F344/N Rats and B6C3F₁ Mice (Feed Studies)*.

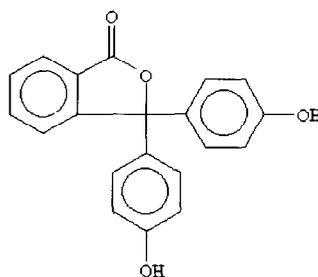


Figure 3. Chemical structure of phenolphthalein

In a subsequent *Federal Register* notice of June 19, 1998, FDA proposed to amend their previously proposed rule for several OTC laxative drug products, including cascara sagrada preparations. The agency stated that this new proposal was being made after considering data and information on four other ingredients: bisacodyl, senna, danthron and phenolphthalein. With regard to cascara sagrada preparations, the agency identified a need for mutagenicity, genotoxicity, and carcinogenicity data and specified that such data should be developed “using tests similar to those used and found positive for phenolphthalein” (FR 63 at 33593). While this information is not currently available for cascara sagrada, it is available for a closely related compound emodin, which is a constituent of cascara sagrada and is in the same chemical class as the other constituents of cascara sagrada. Studies were undertaken by NTP and published in June 2001 as NTP’s Technical Report Series, No. 493 (TR-493): *Toxicology and Carcinogenesis Studies of Emodin (CAS No. 518-82-1) in F344/N Rats and B6C3F₁ Mice (Feed Studies)*. A comparison of the outcomes of studies completed by NTP is summarized in Table 3.

The studies undertaken by NTP for evaluating toxicity of phenolphthalein and emodin and identified above were similar in design. For example, both conducted genetic toxicology studies in *Salmonella typhimurium*, cultured Chinese hamster ovary cells and mouse peripheral blood erythrocytes. Additional studies were conducted for genetic toxicity of emodin in rat and mouse bone marrow cells. Also, similarities existed in the rodent feeding

studies. Both used the same test animals (male and female F344/N rats and B6C3F₁ mice). Both conducted short-term (14 days for phenolphthalein; 16 days for emodin), medium-term (13 week for phenolphthalein; 14 week for emodin) and long-term (2 years for both) feeding studies. The same number of animals was used in each of the studies, except that only 50 animals of each gender and species were used in the 2 year study of phenolphthalein; while 65 of each rat gender and 60 of each mouse gender were studied in the 2 year emodin study. The most significant difference in the feeding studies was that larger maximum doses were given to the test animals in all of the phenolphthalein studies as compared to the emodin studies.

2.2 Relevance of NTP-465 and NTP-493 to Cascara Sagrada Toxicity.

FDA has requested data on the mutagenicity, genotoxicity, and carcinogenicity of cascara sagrada and specified that such data should be developed “using tests similar to those used and found positive for phenolphthalein.”

The chemical structures of the constituents of cascara sagrada and phenolphthalein are well characterized. The constituents of cascara sagrada (Figures 1 and 2) are hydroxyanthracene compounds while phenolphthalein (Figure 3) would be classified as either an isobenzofuranone or phthalide. As can be seen in Figures 1 and 2, the chemical structures of the other hydroxyanthracene constituents of cascara sagrada are very similar in structure to emodin. The structure of phenolphthalein and those of cascara sagrada’s constituents are significantly dissimilar so that there is little reason to think that toxicity concerns for phenolphthalein should be extrapolated for cascara sagrada preparations. This lack of similarity of the toxicity between of phenolphthalein and cascara sagrada is supported by the significantly different findings in the two studies that have been performed by the NTP as described in Table 3. This table identifies the relative outcomes of the NTP TR-465, for phenolphthalein, and NTP TR-493, for emodin, for each of those test outcomes in NTP TR-465 for which a positive outcome was recorded

Table 3. Relative outcomes of NTP TR-465 (phenolphthalein) and TR-493 (emodin).

- *Chinese hamster ovary cells.*
 - Phenolphthalein: Significant increases in chromosomal aberrations in presence of S9.
 - Emodin: Chromosomal aberrations were induced with and without S9.
- *Micronucleus assay.*
 - Phenolphthalein: Frequency of micronucleated erythrocytes were increased in peripheral blood samples from male and female mice after 13 weeks feeding.
 - Emodin: Peripheral blood micronucleus test in mice was negative in males and weakly positive in females after 14 weeks feeding.

(Table 3, cont.)

- *2 year study/ male F344/N rats.*
 - Phenolphthalein: Clear evidence of carcinogenic activity based on markedly increased incidences of benign pheochromocytoma of the adrenal medulla and renal tubule adenomas or adenomas and carcinomas.
 - Emodin: No evidence of carcinogenicity at any of the exposure levels.
- *2 year study/ female F344/N rats.*
 - Phenolphthalein: Some evidence of carcinogenic activity based on increased incidences of benign or benign and malignant pheochromocytoma of the adrenal medulla.
 - Emodin: Equivocal evidence of carcinogenicity based on a marginal increase in the incidence of Zymbal's gland carcinoma in 3 females at the highest dosage level.
- *2 year study/ male B6C3F₁ mice.*
 - Phenolphthalein: Clear evidence of carcinogenic activity based on increased incidences of histiocytic sarcomas and of malignant lymphomas of thymic origin.
 - Emodin: Equivocal evidence of carcinogenicity based on low incidence (1 mouse in each of the two highest dose groups) of uncommon renal tubule neoplasms.
- *2 year study/ female B6C3F₁ mice.*
 - Phenolphthalein: Clear evidence of carcinogenic activity based on increased incidences of histiocytic sarcomas, malignant lymphomas of all types, lymphomas of thymic origin, and benign sex-cord stromal tumors of the ovary.
 - Emodin: No evidence of carcinogenicity at any of the exposure levels.

2.3 Margin of Safety for Cascara Based on the Short-term Studies for Emodin.

When evaluating the risk of a chemical, greater weight should be put on an *in vivo* study compared to an *in vitro* study. Studies by the same route and duration should match the anticipated route and duration of exposure from the chemical or substance of concern. The data available and conclusions drawn for emodin in the NTP TR-493 studies on emodin therefore have significant relevance for cascara sagrada and can be used to address the toxicity concerns of cascara sagrada consumption. For purposes of this analysis, the evidence provided in these studies will be evaluated on an assumption that all of the hydroxyanthracene derivatives in cascara sagrada are equivalent to the toxicity of emodin. All of the NTP TR-493 oral feeding studies were of durations which exceed the duration of human exposure that would be encountered based upon the required OTC labeling for cascara sagrada, which includes a statement that the product "should not be used for a period longer than one week

unless directed by a doctor.” In addition, the route of exposure in these feed studies is the appropriate route for comparison. The studies that are nearest to a one week exposure among the NTP emodin studies are the 16 day studies in B6C3F₁ mice and F344/N rats.

As noted in Table 2 above, the range of daily doses of total hydroxyanthracene derivatives per kilogram bodyweight is 1.05 – 5 mg for children aged 2 to 12 and 0.3 – 1.43 mg for adults. By comparison, the most conservative no adverse effect level (NOAEL) reported for the 16 day studies is 160 mg/kg in female rats and 400 mg/kg in male mice.

The margin of safety between the actual exposure to total hydroxyanthracene derivatives in cascara sagrada bark at the dosages established by the proposed OTC monographs for this ingredient and the lowest NOAEL (160 mg/kg) recorded in the NTP TR-493 16 day rat and mouse studies for emodin is at least 32 (160 / 5 mg/kg) when the comparison is made for children and 112 (160 / 1.43 mg/kg) when the same comparison is made for adults⁴.

Based on these calculations and assuming a standard conservative 100-fold margin of safety, it can be concluded that cascara sagrada bark is within this conservative margin of safety at current OTC dosages for adults but not for children⁵.

2.4 Evaluation of Carcinogenicity of Cascara Based on the 2-year Studies for Emodin.

One of the areas in which FDA requested information on cascara sagrada was on carcinogenicity. Under the conditions of the 2-year feed studies conducted under NTP TR-493, there was no evidence of carcinogenic activity of emodin in male F344/N rats or female B6C3F₁ mice at any of the exposure levels studied. There was equivocal evidence of carcinogenicity, defined as “a marginal increase in neoplasm that may be chemically related,” in female F344/N rats based on a marginal increase in the incidence of Zymbal’s gland carcinoma. This concern is clearly not relevant to humans because humans do not have a Zymbal’s gland and there was no additional data on which the finding of equivocal evidence was made. There was also equivocal evidence of carcinogenic activity of emodin in male B6C3F₁ mice based on a single occurrence of uncommon renal tubule neoplasm in each of the two highest doses (i.e., at 35 and at 70 mg/kg bodyweight) but not in the low dose. This last finding is of questionable relevance when evaluating cascara sagrada, as the duration of the chronic study does not match the short-term duration of exposure expected for cascara sagrada when used as a laxative.

3.0 Summary

FDA has proposed to remove cascara sagrada bark and all other cascara sagrada preparations from the OTC monograph for laxatives and has requested data on the mutagenicity, genotoxicity and carcinogenicity of cascara sagrada.

⁴ These calculations are made at the highest dose levels and highest concentration of hydroxyanthracene compounds in cascara sagrada, and thus the highest calculated daily amount of these compounds per kilogram bodyweight. It should be noted that the range of daily consumption per kilogram bodyweight is nearly 5-fold in both children (1.05-5 mg) and adult (0.3-1.43).

⁵ Any review of the continued use of cascara sagrada by children should consider either reducing the dosage, especially at the high end of the current dosage range, or limiting use to children in the older age range (e.g. 6-12 years).

The National Toxicology Program published studies on the toxicity of emodin, a constituent of cascara sagrada, in June 2001. The toxicity of emodin is relevant to the toxicity of cascara sagrada since the chemical structures of the other hydroxyanthracene derivatives of cascara sagrada are very similar to emodin.

A more appropriate approach to FDA's proposal to remove cascara sagrada from the OTC monograph for laxatives, based on the above and taking into account a conservative analysis of NTP's studies on emodin, would be to maintain the current inclusion of at least cascara sagrada bark in this monograph, for adults. Use by children at the current recommended dose should be reconsidered. No recommendation for other cascara sagrada preparations is made at this time.



Clif McLellan

Director of Toxicology

References

National Toxicology Program. 1996. Toxicology and carcinogenesis studies of Phenolphthalein (CAS No. 77-09-8) in F344/N rats and B6C3F1 mice (feed studies). TA:National Toxicology Program Technical Report Series. PG:348 p VI:465.

National Toxicology Program. 2001. Toxicology and carcinogenesis studies of Emodin in F344/N rats and B6C3F1 mice (feed studies). TA:National Toxicology Program Technical Report Series. PG:278 p VI:493.

Newall, C.A, Anderson L.A, and J.D. Phillipson. 1996. *Herbal Medicines. A Guide for Health Care Professionals*. London: The Pharmaceutical Press.

Rosengren, J.E. and T. Aberg. 1975. Cleansing of the colon without enemas. *Radiologie*. 15(11): 421-426.

Robbers, JE, Speedie, MK, and Tyler, VE. 1996. *Pharmacognosy and Pharmacobiotechnology*. Baltimore: Williams & Wilkins.

Sendelbach, L.E. 1989. A review of the toxicity and carcinogenicity of anthraquinone derivatives. *Toxicology*. 57: 227-240.

USP 25 / NF 20 – *The United States Pharmacopeia; The National Formulary*. 2002. Rockville, MD: The United States Pharmacopeial Convention, Inc.

van Gorkom, B.A.P., Vries, E.G.E, Karrenbeld, A., and Kleibeuker, J.H. 1999. Review article: anthranoid laxatives and their potential carcinogenic effects. *Aliment Pharmacological Therapeutics*. 13: 443-452.

van Os, F.H. 1976. Anthraquinone derivatives in vegetable laxatives. *Pharmacology*.14(Suppl 1): 7-17.

Wichtl, M. and N.G. Bisset (Eds.) 1994. Rhamni purshiani cortex – Cascara bark (English translation by N.G. Bisset). *Herbal Drugs and Phytopharmaceuticals*. Stuttgart: CRC Press.