#822

AIBMR Life Sciences, Inc.

Notice to US Food and Drug Administration of the Conclusion that the Intended Use of Curcumin is Generally Recognized as Safe

Submitted by the Notifier:

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Part 1: Signed Statements and Certification

1.1 Submission of GRAS Notice

Laurus Labs Pvt., Ltd. (the notifier) is submitting a new GRAS notice in accordance with 21 CFR part 170, subpart E, regarding the conclusion that their synthetic curcumin product (VEAMIN 99™) is Generally Recognized as Safe (GRAS) for its intended use, consistent with section 201(s) of the Federal Food, Drug and Cosmetic Act.

1.2 Name and Address of the Notifier and Agent of the Notifier

Notifier

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1.3 Name of the Substance

The appropriately descriptive term for Laurus Labs' VEAMIN 99™ product is synthetic curcumin (hereafter referred to as "curcumin").

1.4 Intended Conditions of Use

Curcumin is intended to be used as an ingredient in various food categories (for a complete list, see Part 3) at addition levels of 0.5–100 mg/100 g, depending upon the specific category. Curcumin is not intended for use in infant formula, meat, poultry, egg products, catfish, or any products that would require additional regulatory review by USDA.

1.5 Statutory Basis for GRAS Conclusion

The conclusion of GRAS status of curcumin for its intended conditions use, stated in Part 1.4 of this notice, has been made based on scientific procedures.

1.6 Not Subject to Premarket approval

We have concluded that curcumin is GRAS for its intended conditions of use, stated in Part 1.4 of this notice, and, therefore, such use of curcumin is not subject to the premarket approval requirements of the Federal Food, Drug, and Cosmetic Act.

1.7 Data and Information Availability Statement

The data and the information that serve as the basis for this GRAS conclusion will be available for review and copying during customary business hours at the office of Laurus Labs limits, DS-1, IKP Knowledge Park, Turkapally, Shameerpet, Hyderabad 500078, India or will be sent to FDA upon request.

1.8 Exemption from Disclosure under the Freedom of Information Act

None of the data and information in Parts 2 through 7 of this GRAS notice are considered exempt from disclosure under the Freedom of Information Act (FOIA) as trade secret or commercial or financial information that are privileged or confidential.

Personal privacy information is present in Part 1 of this GRAS notice.

1.9 Certification of Completion

We hereby certify that, to the best of our knowledge, this GRAS notice is a complete, representative, and balanced submission that includes unfavorable information, as well as favorable information, known to us and pertinent to the evaluation of the safety and GRAS status of the use of curcumin.

(b) (6)

September 4, 2018

Mr. Chava Krishna Chaitanya
Assistant Vice President of Corporate Development
Notifier

Part 2: Identity, Manufacture, Specifications, and Physical or Technical Effect

2.1 Identification

Laurus Labs' curcumin (VEAMIN 99™) is synthesized through a series of chemical processes to create a compound with the IUPAC chemical name of (1E, 6E)-1, 7 – di (4-hydroxy-3-methoxyphenyl)-1, 6-heptadiene-3, 5-dione, chemical formula of $C_{21}H_{20}O_6$ and molecular weight of 368.39. Its chemical abstract number (CAS) is 458-37-7 and its structural formula is shown in **Figure 1**. The VEAMIN 99™ manufacturing process is patented in India (patent IN283756).

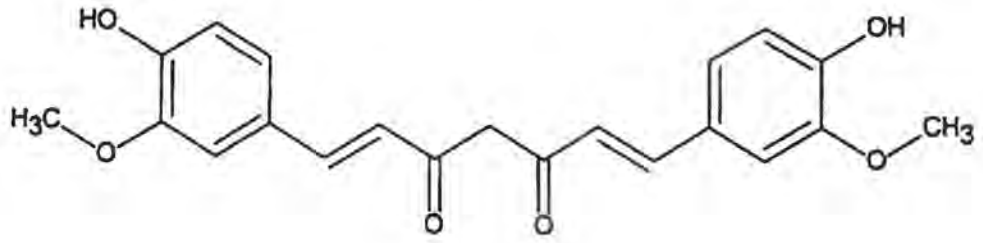

Figure 1. Structural formula for curcumin

2.2 Manufacturing

Laurus Labs' curcumin synthesis begins with a preparation of tri-n-butyl borate from n-butanol, boric acid, and toluene. Water and toluene are released from the preparation through a distillation process. Vanillin, 2,4-pentadienone, n-butyl amine, and ethyl acetate are added to the tributyl borate preparation in a condensation reaction yielding a curcumin boron complex. The curcumin boron complex combined with acetic acid and water in a hydrolysis reaction forms a crude solid of curcumin. The crude curcumin is combined with methanol and water and filtered. The residue is washed thoroughly with water and dried in a vacuum tray dryer resulting in pure curcumin (**see Figure 2**).

2.2.1 Manufacturing Overview

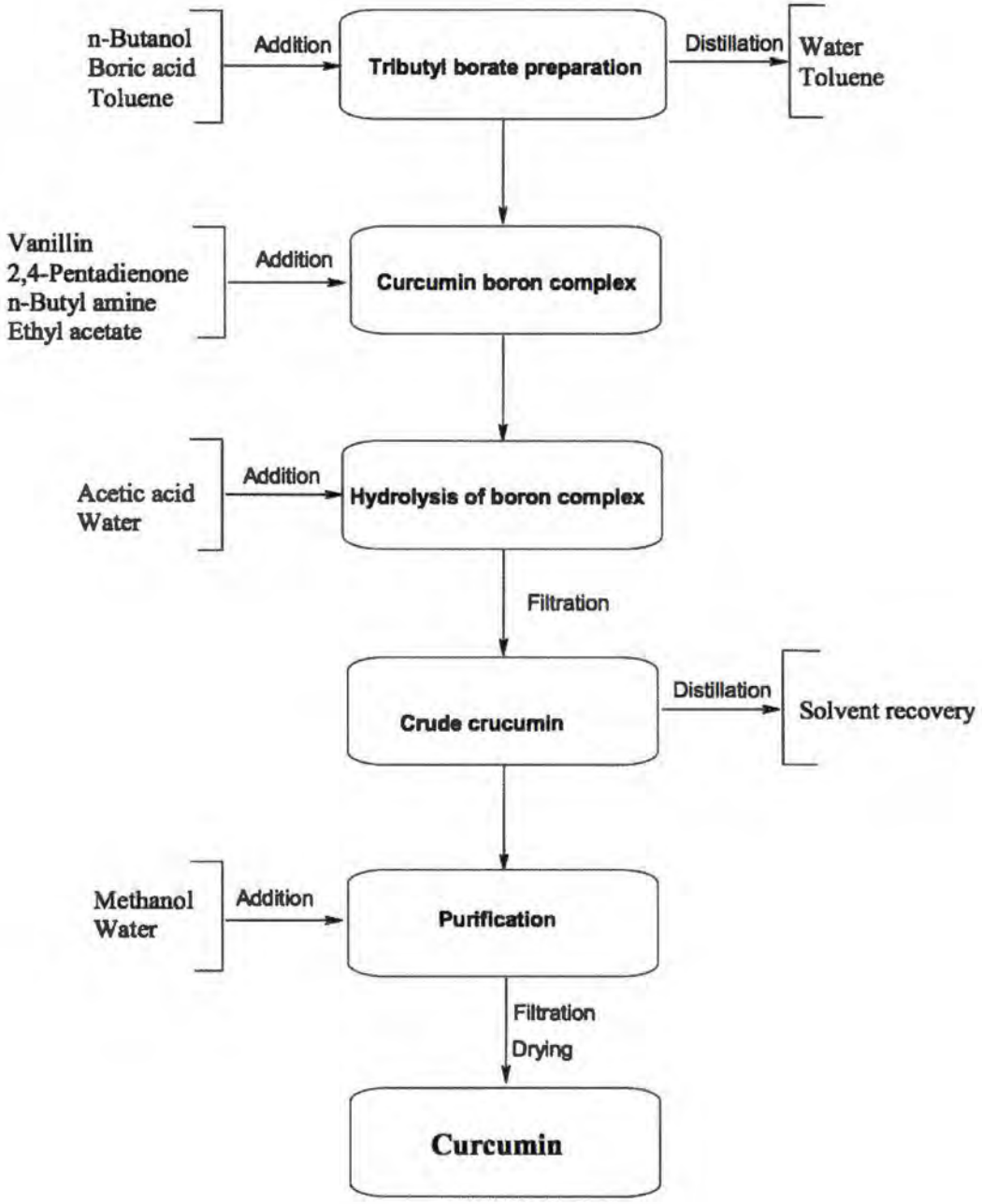

Figure 2. Manufacturing flowchart for curcumin

2.2.2 Good Manufacturing Practice

Laurus Labs Limited follows Good Manufacturing Practices as stipulated under the provisions of India's Schedule 'M' of Drug and Cosmetics Rules, 1945 for the manufacture of curcumin. No material of human or animal origin is used. Curcumin from Laurus Labs is non-GMO and not irradiated.

2.3 Specifications

The specifications for the food-grade product curcumin, along with the specification methods, are listed in **Table 1** below.

Table 1. Curcumin specifications

Test Items	Specification	Method*
Marker Compounds		
Curcumin identity	Matches/concordant with the respective standard	HPLC In-house and **IR -(USP <197 K > / Ph.Eur < 2.2.24 >)**
Physical Characteristics		
Description	Bright yellow to orange solid	USP < Reference tables >
Water content by Karl Fischer (% w/w)	NMT 0.5	USP <921> Method Ia / Ph.Eur < 2.5.12> Method A)
Purity (% area)	NLT 99.0	HPLC In-house
Melting range (°C)	175–185	USP <741> / Ph.Eur < 2.2.14>
Loss on drying (% w/w)	NMT 0.5	USP <731> / Ph. Eur. <2.2.32>
Heavy Metals		
Arsenic (ppm)	≤ 1.0	ICP-MS In-house
Cadmium (ppm)	≤ 1.0	ICP-MS In-house
Lead (ppm)	≤ 1.0	ICP-MS In-house
Mercury (ppm)	≤ 1.0	ICP-MS In-house
Microbiological Tests		
Total Aerobic Microbial (cfu/g)	≤ 1000	USP<61> and <62>
Total Yeast & Mold (cfu/g)	≤ 100	USP<61> and <62>
Salmonella	Negative	USP<61> and <62>
Staphylococcus	Negative	USP<61> and <62>
Escherichia coli	Negative	USP<61> and <62>
Pseudomonas aeruginosa	Negative	USP<61> and <62>
Residual Solvents		
Ethyl acetate (ppm)	NMT 5000	GC-HS In-house
Methanol (ppm)	NMT 3000	GC-HS In-house
Toluene (ppm)	NMT 890	GC-HS In-house
n-Butanol (ppm)	NMT 5000	GC-HS In-house

Abbreviations: cfu, colony forming units; GC-HS, gas chromatography head space; HPLC, high performance liquid chromatography; ICP-MS, inductively coupled plasma mass spectrometry; IR, infrared spectroscopy; NMT, not more than; NLT, not less than; Ph. Eur., Pharmacopoeia Europaea; ppm, parts per million; USP, United States Pharmacopeia; w/w, weight by weight.

2.3.1 Batch Analysis

Production conformity and consistency of Laurus Labs' curcumin is tested in production lots. Batch analyses of three non-consecutive lots are shown below (see **Table 2**) and are reasonably consistent and met the product specifications for physical/chemical composition, curcumin content/identity, manufacturing impurities, heavy metals, microbial analyses, and residual solvents.

Table 2. Curcumin batch analyses

Test Items	Batch 25027-1VSP11290817	Batch 25027-1VSP11270817	Batch 25027-1VSP11350917
Marker Compounds			
Curcumin identity	Matches/concordant	Matches/concordant	Matches/concordant
Physical Characteristics			
Description	Orange solid	Bright yellow solid	Orange solid
Water content by Karl Fischer (% w/w)	0.07	0.06	0.1
Purity (% area)	99.6	99.6	99.7
Melting range (°C)	176–177	176–177	176–178
Loss on drying (% w/w)	0.05	0.1	0.06
Heavy Metals			
Arsenic (ppm)	<LOQ*	<LOQ*	<LOQ*
Cadmium (ppm)	<LOQ*	<LOQ*	<LOQ*
Lead (ppm)	<LOQ*	<LOQ*	<LOQ*
Mercury (ppm)	<LOQ*	<LOQ*	<LOQ*
Microbiological Tests			
Total Aerobic Microbial (cfu/g)	<10	<10	<10
Total Yeast & Mold (cfu/g)	<10	<10	<10
Salmonella	Negative	Negative	Negative
Staphylococcus	Negative	Negative	Negative
Escherichia coli	Negative	Negative	Negative
Pseudomonas aeruginosa	Negative	Negative	Negative
Residual Solvents			
Ethyl acetate (ppm)	720	927	770
Methanol (ppm)	11	10	8
Toluene (ppm)	363	353	123
n-Butanol (ppm)	1680	2155	1968

*LOQ, Limit of Quantification (0.5 ppm)

2.3.2 Residual Solvent Analysis

The solvents ethyl acetate, methanol, toluene, and n-butanol are utilized in manufacturing, and residual levels are tested on every batch per specifications as described above. These residual solvent specifications meet guidelines as set forth by the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use.[1] In the initial stages of curcumin

production acetic acid tests were conducted and levels were not detectable. As acetic acid appeared to be effectively removed during the water/methanol purification step, this test was discontinued.

2.3.3 Shelf–Life Stability

A three-year shelf-life from the time of manufacture has been recommended as an appropriate expiration period for curcumin. This recommendation is based upon 36-month long-term stability testing and 6-month accelerated stability testing of curcumin lot numbers 25027-1/VSP1/021/10, 25027-1/VSP1/022/10, and 25027-1/VSP1/023/10 (manufactured in August of 2010). The long-term and accelerated stability tests were conducted at 25 ± 2 °C, 60 ± 5% relative humidity and 40 ± 2 °C, 75 ± 5% relative humidity, respectively, under conditions of commercial packaging (primary pack with transparent low-density polyethylene bag with strip seal, followed by secondary pack with transparent low-density polyethylene bag with strip seal and finally kept in high density polyethylene container). At all time points, outcome measures included the same physical and chemical tests and test methodologies used for commercial batch analysis, except heavy metals and residual solvents were not included. The measures were stable and within specification throughout the tests with no significant changes occurring in the parameters assayed. Results from sample analysis at initial and final time points are summarized below for the real time (**Table 3**) and accelerated (**Table 4**) stability tests.

Table 3. Long-term stability study

Test Item	Specification	Long-Term Stability Test (25 ± 2° C, 60 ± 5% RH)					
		Batch Number					
		25027-1/VSP1/021/10		25027-1/VSP1/022/10		25027-1/VSP1/023/10	
		Initial	36 mos	Initial	36 mos	Initial	36 mos
Marker Compounds							
Curcumin identification	Concordant with IR of standard	passes*	passes	passes	passes	passes	passes
Purity by HPLC (%)	NLT 99.0	99.5	99.5	99.56	99.5	99.51	99.5
Physical Characteristics							
Description	bright yellow to orange solid	orange solid	orange solid	orange solid	orange solid	orange solid	orange solid
Loss on drying (0.5% w/w)	NMT 0.5	0.4	0.05	0.1	0.08	0.4	0.08
Microbiological Tests							

Total Aerobic Microbial (cfu/g)	≤ 1000	100	<10	10	<10	<10	<10
Total Yeast & Mold (cfu/g)	≤ 100 cfu/g	<10	<10	<10	<10	<10	<10
Salmonella	Negative	Absent	Absent	Absent	Absent	Absent	Absent
Staphylococcus	Negative	Absent	Absent	Absent	Absent	Absent	Absent
Escherichia coli	Negative	Absent	Absent	Absent	Absent	Absent	Absent
Pseudomonas aeruginosa	Negative	Absent	Absent	Absent	Absent	Absent	Absent

Abbreviations: cfu, colony forming units; IR, infrared spectroscopy; NLT, not less than; NMT, not more than; RH = Relative Humidity; w/w, weight by weight. mos=months
*passes means that the batch tested was concordant with the IR spectrum of the standard.

Table 4. Accelerated stability study

Test Item	Specification	Accelerated Stability Test (40 ± 2°C, 75 ± 5% RH)					
		Batch Number					
		25027-1/VSP1/021/10		25027-1/VSP1/022/10		25027-1/VSP1/023/10	
		Initial	6 mos	Initial	6 mos	Initial	6 mos
Marker Compounds							
Curcumin identification	Concordant with IR spectrum of standard	passes*	passes	passes	passes	passes	passes
Purity by HPLC (%)	NLT 99.0	99.5	99.5	99.56	99.5	99.51	99.5
Physical Characteristics							
Description	Bright yellow to orange solid	Orange solid	Orange solid	Orange solid	Orange solid	Orange solid	Orange solid
Loss on drying (% w/w)	NMT 0.5	0.4	0.05	0.1	0.03	0.4	0.04
Microbiological Tests							
Total Aerobic Microbial (cfu/g)	≤ 1000	100	60	10	10	<10	20
Total Yeast & Mold (cfu/g)	≤ 100	<10	<10	<10	<10	<10	<10
Salmonella	Negative	Absent	Negative	Absent	Negative	Absent	Negative
Staphylococcus	Negative	Absent	Negative	Absent	Negative	Absent	Negative
Escherichia coli	Negative	Absent	Negative	Absent	Negative	Absent	Negative
Pseudomonas aeruginosa	Negative	Absent	Negative	Absent	Negative	Absent	Negative

Abbreviations: cfu, colony forming units; IR, infrared spectroscopy; NLT, not less than; NMT, not more than; RH = Relative Humidity; w/w, weight by weight., mos=Months
*passes means that the batch tested was concordant with the IR spectrum of the standard

2.4 Physical or Technical Effect

Curcumin has no intended technical effect in food that is relevant to safety. Curcumin is an antioxidant and the intended effect in food is for human health.

Part 3: Intended Use and Dietary Exposure

Laurus Labs' curcumin, manufactured in accordance with GMP, is intended to be used an ingredient in the food categories and at the addition levels shown in **Table 5,** as standards of identity allow. The ingredient is not intended for use in infant formula, meat, poultry, egg products, catfish, or any products that would require additional regulatory review by USDA.

Table 5. Curcumin intended uses

Food Category	Maximum intended addition level (mg/100 g)
Milk, fluid, evaporated and condensed	5
Yogurt	10
Sweet dairy cream	5
Milk desserts, frozen	15
Puddings, custards, and other milk desserts	10
Finfish	10
Other seafood	10
Shellfish	5
Meat, poultry, fish in gravy or sauce or creamed	50
Sandwiches with meat, poultry, fish	10
Soups, broths, extracts from meat, poultry, fish base	5
Gravies from meat, poultry, fish base	5
Dried peas, lentils, and mixtures	20
Soups with legumes as major ingredient	5
Meat substitutes, mainly legume protein	2
Nuts	10
Bars	5
Pancakes	5
Waffles	10
French toast	10
Soups with grain product as major ingredient	5
Potato recipes	20
Dark-green vegetable soups	5
Tomato soups	5
Other cooked vegetables, cooked with sauces, batters, casseroles	20
Vegetable soups	5
White potato with meat, poultry, fish (mixtures)	5
Puerto Rican stews or soups with starchy vegetables (viandas)	5
Regular salad dressings	5
Jellies, jams, preserves	5
Ices or popsicles	15

Candies	10
Chewing gums	30
Coffee	20
Tea	20
Soft drinks, carbonated	10
Fruit drinks	10
Nutrition drinks	20
Nutrition powders	100
Other functional beverages	20
Crackers and Salty Snacks	5
Breads and Pastas	20
Beverages non-fruit, fruit and veggie juices	20
Energy and Sports Drinks	50
Cookies, cakes, pies, breakfast pastries	5
Cereals and cereal grains ready to eat and cooked	10
Cheeses	10
Flavored milk and milk drinks regular and imitation	15
Egg dishes	5
Fats and Oils	0.5
Vegetables	20
Sauces	50

Exposure to Laurus Labs' curcumin from the intended use categories was estimated for the U.S. population using food consumption data from the What We Eat in America (WWEIA) dietary component of the National Health and Nutrition Examination Surveys (NHANES). The most recent data available at the time of this writing (2013–2014) was analyzed using Creme Food Safety software 3.6 (www.cremeglobal.com). This data was obtained from 7,574 individuals that underwent two non-consecutive 24-hour dietary recall interviews (the first was collected in-person, the second by phone 3–10 days later).

WWEIA food codes that were considered most similar to the intended use categories were utilized in the assessment and were assigned the relevant intended use concentrations. Note that while some of the NHANES food codes chosen for the assessment could require USDA approval for additive ingredients, such food codes were included only to be conservative. Laurus Labs does not intend to use the ingredient in any foods that would require USDA additional approval. As an example, while some of the food codes in the food group "white potato with meat, poultry, fish (mixtures)" could contain meat levels high enough to require USDA approval, Laurus Labs intends to only use their ingredient in foods with meat levels below that which would require additional approval.

Creme software is a probabilistic modeling tool that uses high-performance computing to predict intake (including total aggregate exposure) of food groups

and/or individual food ingredients. Creme Food Safety performs calculations using large-scale food consumption data sets. It bases the calculated estimates on each individual's body weight from the survey, as opposed to averaged body weights. Calculations also incorporated the NHANES assigned sample weights for each individual in the survey, which measure the number of people in the population represented by that specific subject and help to ensure that the results statistically represent the entire U.S. population. Sample weights for NHANES participants incorporate adjustments for unequal selection probabilities and certain types of non-response, as well as an adjustment to independent estimates of population sizes for specific age, sex, and race/ethnicity categories. The data is shown for "food consumers" (which includes only data from individuals who reported consuming one or more food/beverage categories intended to contain curcumin over the two-day survey period, as opposed to the whole population). Results are given as both absolute exposure (mg/day), as well as exposure relative to body weight (mg/kg bw/day).

The relative standard error (RSE; calculated by dividing the standard error of the estimate by the estimate itself and multiplying by 100) is a statistical criterion that can be used to determine the reliability of estimates as pertains to the population (the larger the RSE the less reliable the estimate).[2] RSE values greater than 25–30% are often considered reasonable cut-offs by which to consider a value unreliable.[2, 3] For the purpose of this GRAS conclusion, an RSE value of greater than 25% was used to indicate that the estimated value was unreliable with regard to representing the population. RSE values are shown for the 90th percentile values only, as the 90th percentile values are the most pertinent for the exposure estimates. All of the values were considered reasonably reliable using the 25% cut-off.

Data estimated directly from the NHANES short 2-day survey do not necessarily adequately represent individual usual long-term intake due to the large amount of random error. This is because it may not correctly capture infrequent consumers. It assumes that subjects who consumed a product on a survey day consume it every day of the year, and it does not adjust for potential day-to-day variation in intake (i.e., intra-individual variation over time is not accounted for). Thus estimation of "usual" or "lifetime" exposure was also added to the model based on methodologies developed by Nusser et al., 1996, at Iowa State University.[4] This lifetime data is considered the most relevant data, as GRAS exposure estimates should be based on expected regular exposure over the lifespan. The technique of estimating usual/lifetime intakes relies on the ability to transform the input daily average data (from food consumers) into normality, which is tested using the Anderson-Darling test statistic within the Creme Global software. Occasionally the Creme software determines that lifetime intake estimates required warnings or were not possible due to issues with the original data set; such issues are noted with asterisks and are

explained below the table/s. If lifetime intake estimate calculations fail then they are replaced by the original daily average data results.

Because of the large number of food codes in these intended use food categories, it is nearly impossible that curcumin will be present in 100% of the food codes, or that an individual will randomly or intentionally consume a product containing Laurus Labs' curcumin every single time that he/she consumes a product from the intended use food categories daily over a lifetime. While food labels will list curcumin as an ingredient and may even highlight the ingredient in marketing, it is assumed that many consumers will not always realize that the ingredient is present in the food. In other words, it will likely be an "invisible" ingredient to many consumers, which decreases the chance that only food products that contain the ingredient will be chosen by those consumers. Additionally, there will be cost and market share limitations of adding this specialty ingredient to foods in general, making it even less likely that an individual would consume it in all proposed food categories daily.

Thus, to calculate a more realistic curcumin exposure estimation from the proposed food uses, an additional exposure assessment was performed that assumed a curcumin presence probability of 20% in all of the proposed food categories. The 20% presence probability factor was intended to represent an approximate 20% market share of the ingredient in each of the intended use categories, which is still considered a highly conservative assumption. The maximum addition level for each food category was utilized in both assessments. The resulting exposures using both a 100% and a 20% presence probability factor are shown in **Tables 6** and **7** below.

Table 6. Estimated exposure to curcumin, 100% presence probability

Total Population (ages 2+)	Food Consumers							
			Daily Average					Lifetime
	n	% Total	Mean	Mean SE	90th	90th SE	90th % RSE	90th %
Curcumin absolute (mg/day)	7066	99.9	255.2	3.5	424.9	5.6	1.3	411.4*
Curcumin relative to body weight (mg/kg bw/day)			3.94	0.05	7.0	0.14	2.0	6.79*

Creme #283, SE = standard error; RSE = relative standard error (<25% is considered reliable).
*Creme Warning -2048, "Number of days per person should be constant for a foods calculation" (data may still be used)

Table 7. Estimated exposure to curcumin, 20% presence probability

Total Population (ages 2+)	Food Consumers							
			Daily Average					Lifetime
	n	% Total	Mean	Mean SE	90th	90th SE	90th % RSE	90th %
Curcumin absolute (mg/day)	6787	95.9	52.5	1.1	112.9	3.4	3.0	77.7*
Curcumin relative to body weight (mg/kg bw/day)			0.81	0.02	1.78	0.05	5.6	1.32*

Creme #287, SE = standard error; RSE = relative standard error (<25% is considered reliable).
*Creme Warning -2048, "Number of days per person should be constant for a foods calculation" (data may still be used)

According to the estimates above, nearly 100% of the U.S. total population (ages 2 and above) was identified as potential consumers of curcumin from the proposed food uses when using the 100% presence probability factor. This is obviously an extremely conservative assumption. The lifetime 90th percentile estimated exposure to curcumin using the 100% presence probability factor was 411.4 mg/day (6.79 mg/kg bw/day). Using the 20% presence probability assumption, the identified consumers still made up 96% of the population, which is also considered extremely conservative. The lifetime 90th percentile estimated exposure to curcumin using the 20% presence probability factor was 77.7 mg/day (1.32 mg/kg bw/day).

As AIBMR was not able to locate background dietary exposure levels to curcumin for the U.S. population, potential background levels are discussed using the 2010 and 2014 EFSA Scientific Opinions on the re-evaluation of curcumin (E 100) as a food additive, in which exposure estimates for the E.U. are discussed.[5, 6] The Opinions also re-evaluated the safety of curcumin, including a review of the JECFA-allocated ADI of 0–3 mg/kg bw/day. In both Opinions the Panel concluded that the data available supported the ADI of 3 mg/kg bw/day based on an estimated NOAEL of 250–320 mg/kg bw/day from a reproductive toxicity study.

The EFSA 2014 Opinion estimated exposure to curcumin at the 95th percentile from natural dietary sources as follows (mg/kg bw/day, min–max across surveys): 0, toddlers; 0–9.2 x 10^{-6}, children 3–9 years; 0–5.9 x 10^{-6}, adolescents 10–17 years; 0–0.1 x 10^{-3}, adults 18–64 years; 0–4.1 x 10^{-6}, adults ≥65 years. According to the aggregate lifetime estimates above for the 90th percentile using the 20% presence probability factor, exposure to curcumin from Laurus Labs' product is estimated at approximately 1.32 mg/kg bw/day; addition of that amount to the estimated dietary exposures for all age categories in the EFSA report would result in an exposure level well within the JECFA ADI of 3 mg/kg bw/day.

Part 4: Self-limiting Levels of Use

There are no known inherent self-limiting levels of use for Laurus Labs' curcumin related to taste or smell. Addition levels are potentially limited by the low solubility of the ingredient, although this can usually be addressed by utilizing appropriate delivery systems for different applications.

Part 5: Experience Based on Common Use in Food Prior to 1958

The GRAS conclusion for this synthetic curcumin is based on scientific procedures, and thus, experience based on common use in food prior to 1958 is not considered pivotal information. To the best of our knowledge, synthetic curcumin was not commonly used in foods prior to 1958.

Part 6: Narrative

6.1 Pharmacokinetics

6.1.1 Human Studies

Absorption and bioavailability studies on curcumin (a hydrophobic polyphenol) in humans have reported very low (ng/mL) or undetectable serum/plasma and tissue levels even after doses of 1000 to 12,000 mg/day.[7-15] This is attributed to poor absorption, rapid systemic elimination and the rapid first-pass biotransformation of curcumin in the intestinal lining and/or liver, producing the following conjugates and metabolites: curcumin glucuronide, curcumin sulfate, hexahydrocurcumin, and octahydrocurcumin[12-19] In a clinical trial utilizing single doses of 500–12,000 mg of 95% curcuminoids, blood levels of curcumin were undetectable in the 500–8000 mg test groups. Curcumin was detectable in one subject each in the 10,000 and 12,000 mg groups at ng/mL levels at 1, 2, and 4 hours post administration.[9]

Vareed et al. (2008) investigated the human pharmacokinetics of curcumin and its conjugates using fourteen different measurement points 0–72 hours after single-dose administration of 10,000 mg or 12,000 mg of curcumin.[13] Free curcumin was detected in only one subject (limit of detection was 50 ng/mL); however, curcumin sulfate and glucuronide conjugates which appeared ~0.68 h post-dose, were detected in all subjects. After single doses of 10,000 mg and 12,000 mg, the derived pharmacokinetic variables were as shown in **Table 8**; additionally, the absorption constant was 1.05 ± 0.26/hour, the elimination constant was 0.08 ± 0.0050/hour, and the bioavailability/volume was 3.54 ± 0.41 (no units given).[13] The values for the 10,000 mg dose group were higher than that of the 12,000 mg dose group, perhaps due to a saturable process. Results from other human pharmacokinetic studies are also summarized in **Table 8**.

Table 8. Summary of selected pharmacokinetic results in orally dosed curcumin studies in humans

Study	Dose and type of curcumin	C_{max}	T_{max}	AUC	$T_{1/2}$ (elim)	Cl
Shoba et al. 1998[7]	2 g/kg* curcumin pure powder	0.006 ± 0.005 µg/mL	1 hour	0.004 µg/h/mL	-	-**
Jäger et al. 2014	1800 mg curcuminoids single dose	5.2 ± 0.2 ng/mL	9.5 ± 0.2 h	39.6 ±1.5 ng/mL.h (0–12 h)	-	-
Antony et al. 2008[10]	2 g/day of curcumin*	149.8 ng/g	2 h and undetectable by 4.5 h	461.86 (0–infinity)	2.63 h	K_e 0.296 h

Cheng et al. 2001[11]	4000 mg synthetic curcumin 99.3% pure	0.51 ± 0.11 µM	1.67 ±0.58 h	2.55 ±1.76 nMol.h/mL	-	-
	6000 mg	0.64 ± 0.06 µM	2.00 ± 1.73 h	4.80 ±4.49 nMol.h/mL		
	8000 mg	1.77 ± 1.87 µM	1.75 ± 0.35 h	13.74 ± 5.63 nMol.h/mL		
Vareed et al. 2008[13]	10,000 mg C3 complex containing 75% curcumin	2.30 ±0.26	3.29 ± 0.43 h	35.33 ± 3.78 µg.h/mL	6.77 ± 0.83 h	-
	12,000 mg	1.73 ± 0.196 µg/mL	3.29 ± 0.43 h	26.57 ± 2.97 µg.h/mL	6.77 ± 0.83 h	

Results given mean ± standard deviation
Abbreviations: "-", measure not provided; AUC, area under the curve; Cl, total clearance; Cmax, concentration maximum; Elim, elimination; h, hours; T ½, half-life; Tmax, time to maximum concentration.
*Purity of curcumin was not provided
**Cl was not calculated because serum levels were too low to make the calculation.

Garcea et al. studied plasma levels and the colorectal and hepatic tissue content of curcumin after doses of 450, 1800, or 3600 mg/day for 7 days in subjects with colorectal cancer.[14, 15] Trace amounts of curcumin and its metabolites were found in the hepatic tissue and portal circulation while levels in the normal and malignant colorectal tissues ranged from 7–20 nmol/g tissue (normal tissue contained higher levels than malignant tissue). Curcumin was detectable in the plasma, but its conjugates were not. Curcumin conjugate levels were present in colorectal tissue at concentrations of about 1 pmol/g tissue.[14, 15] Results of an in vitro study using caco-2 cells also suggest that curcumin is almost completely lost by first-pass metabolism and chemical degradation during intestinal absorption and only minute amounts of unconjugated curcumin and very small amounts of its conjugates reach the portal blood.[16]

Elimination of curcumin and its metabolites is primarily through the feces; however, Shoba et al. were unable to calculate a V_d or clearance rate due to undetectable serum levels at most time points in most subjects.[7, 8] One study provided an elimination constant of 0.296/h.[10] In a Phase I clinical trial in patients with adenocarcinoma of the colon or rectum, Sharma et al. (2004) detected the following amounts of curcumin and its conjugates in all urine samples from six patients taking 3.6 g of curcumin daily: 0.1–1.3 µmol/L of curcumin, 19–45 nmol/L of curcumin sulfate, and 210–510 nmol/L of curcumin glucuronide.[12] Abundant amounts of curcumin were recovered in the feces from all dose-level groups with curcumin levels in the fecal samples of the 3.6 g/day group between 25 and 116 nmol/g dried feces and trace amounts of curcumin sulfate in only several of those patients.[12]

6.1.2 Animal Studies

Absorption in rats is quantitatively generally higher than that of humans, with results varying from 3.88–60% absorption of the administered dose detected in the blood of rats;[20-23] however, qualitatively the metabolites in rats and humans are very similar.[7, 13, 17, 18, 21] Ireson et al. reported in an in vitro and in situ study comparing absorption in humans and rats, that the extent of sulfation of curcumin in the cytosol of human intestinal tissue was four times that in the rat intestine, whereas sulfation in human liver cytosol was only one fifth of that observed in rat liver cytosol.[18] These results suggest that tissue enzyme content varies considerably by species and that experiments in rats may greatly underestimate the extent of intestinal metabolism which occurs in humans. [18] Results for orally dosed pharmacokinetic studies on rats, are reported in **Table 9**.

Table 9. Summary of selected pharmacokinetic results in orally dosed curcumin studies in rats

Study	Dose and type of curcumin	C_{max}	T_{max}	AUC	$T_{1/2}$ (elimination)	V_d	Cl
Shoba et al., 1998[7]	2g/kg curcumin* "pure powder"	1.35 ± 0.23 µg/mL	0.83 ± 0.05 hours	2.36 ± 0.28 µg/h/mL	1.70 ± 0.58 hours	1366.00 ± 248.70 L/kg	713.00 ± 12.00 L/h
Yang et al., 2007[24]	500 mg/kg curcumin (910325-01 1)	0.06 ± 0.01 µg/mL	41.7 ± 5.4 minutes	3.6 ± 0.6 min µg/mL	44.5 ± 7.5 minutes	-	-
Suresh & Srinivasan, 2010[20]	500 mg/kg curcumin*	83.8 µg/mL	6 hours	2470.4 µg/mL.h	12.83 hours	-	-

Results given mean ± standard deviation
Abbreviations: "-", measure not provided; AUC, area under the curve; Cl, total clearance; Cmax, concentration maximum; Elim, elimination; h, hours; T ½, half-life; Tmax, time to maximum concentration; Vd, volume of distribution
*Purity of curcumin not provided in these studies

Intact curcumin has been detected in microgram and trace amounts in the serum, blood, liver, kidney, intestine (small, large, and cecum), and stomach tissues of rats after 400 mg (approximately 2000 mg/kg bw), 500 mg/kg bw, and 1000 mg/kg bw dosing.[20, 23, 25] Intact curcumin is eliminated primarily in the feces (~36–40% or 65–85% of the administered dose), with either low urinary excretion or only conjugated curcumin detected in urine after doses ranging from 10 mg to 1 g/kg.[20, 22, 23, 25]

Approaches that have been described in the literature to improve bioavailability include use of 1) adjuvants such as piperine that interfere with glucuronidation; 2) liposomal curcumin; 3) curcumin nanoparticles; 4) curcumin phospholipid complex; and 5) structural analogues of curcumin (e.g., EF-24).[19, 26, 27] Study results show increased bioavailability for the curcumin preparations and no serious adverse effects. Because of the biochemical differences in these preparations as compared to Laurus Labs' curcumin, such studies are not considered directly relevant for the GRAS assessment, although they lend general corroborative evidence of safety.

6.2 Toxicology Studies

Laurus Labs sponsored the independent investigation of the potential in vitro and in vivo mutagenic activity and 14- and 90-day subchronic repeated-dose oral toxicity of its curcumin in rats.[28] No additional published toxicological studies were identified in a literature search for synthetic curcumin and/or VEAMIN 99™; however, toxicological studies on other curcumin preparations were located and are discussed in sections 6.2.6 and 6.3 below.

All three genetic toxicology studies and the 90-day study performed on Laurus Labs' curcumin were conducted in Good Laboratory Practice (GLP) certified facilities (Vimta Labs Limited, Pre-Clinical Division, India) and in compliance with GLP according to OECD Principles of GLP for the testing of Chemicals as Specified by International [C(97)186/Final] Legislation. The lab is GLP certified by the National Good Laboratory Practice Compliance Monitoring Authority (NGCMA) of the Department of Science and Technology of the Government of India. The Institutional Animal Ethics Committee (IAEC) of Vimta Labs approved the study protocol. Care and use of study animals was in accordance with the Committee for the Purpose of Control and Supervision of Experiments on Animals (CPCSEA) guidelines regulating animal care. The studies are published in a peer-reviewed academic journal that specializes in toxicology—*Journal of Toxicology*[28]—and are described in the summaries below.

6.2.1 Bacterial Reverse Mutation Assay

A bacterial reverse mutation (Ames) test was conducted in compliance with the internationally accepted guideline OECD Guidelines for Testing of Chemicals, No. 471 (adopted 21 July 1997).

Purpose: To evaluate the mutagenic potential of curcumin (VEAMIN 99™).

Methods: Five strains of *Salmonella typhimurium* (TA98, TA100, TA102, TA1535, and TA1537) were used in the presence and absence of rat liver S9 metabolic activation with appropriate positive and negative controls. The study

included a preliminary solubility test, and two independent experiments (a preliminary cytotoxicity test and a mutagenic assay), both of which were carried out in triplicate. Concentrations of curcumin used for the mutagenicity assay were: 5.0, 16.0, 50.0, 160.0, 500.0, and 1600.0 µg/plate.

Results: Spontaneous revertant colony numbers of the vehicle control agreed with historical control data, and positive controls induced the expected responses. Sterility controls were negative for colony forming units and tester strain genotypes were confirmed. Due to heavy precipitation in the 5000 µg/plate levels in the preliminary cytotoxicity test, the high dose was determined to be 1600 µg/plate for the mutagenicity assay. There were no increases in the mean number of revertant colonies in any of the test article plates compared to vehicle control. All results were unequivocally negative according to the study criteria for positive responses.

Conclusions: Under the experimental conditions applied, curcumin failed to induce gene mutations by base pair changes or frameshifts in the genome of the strains used at concentrations up to the maximum recommended test concentration of 1600 µg/plate.

6.2.2 Chromosomal Aberration Study

A chromosomal aberration test was conducted in compliance with the internationally accepted guideline OECD Guidelines for Testing of Chemicals, No. 473 (2014).

Purpose: To evaluate the clastogenic potential of curcumin.

Methods: On the basis of preliminary cytotoxic investigations curcumin was suspended in dimethyl sulfoxide (DMSO), and test article concentrations for each experiment were determined. The chromosomal aberration assays were conducted in two independent experiments (each in duplicate) using human peripheral blood lymphocytes. The cells were exposed to the negative control or each test article concentration with and without metabolic activation using rat liver microsome preparations (S9-mix). Groups of cells were also exposed to the respective positive controls for use with or without S9-mix. Exposure times, harvest times and test article concentrations were as follows:

- Short term exposure: 4h treatment without S9-mix/~22h harvest time. Concentrations were: 10.0, 20.0, and 40.0 µg/mL.
- Short term exposure: 4h treatment with S9-mix/~22h harvest time. Concentrations were: 6.3, 12.5, and 25.0 µg/mL.
- Continuous exposure: 22h treatment without S9-mix/~22h harvest time. Concentrations were: 6.3, 12.5, and 25.0 µg/mL.

Cells were exposed to selection agent, colchicine (0.2 µg/mL), 2.5 hours prior to harvesting and fixing for slide preparation. Chromosome aberration frequencies were then scored blind for at least 300 well-spread metaphase cells per test concentration (150 from each duplicate culture). The following were recorded and/or calculated: number of cells with aberrations, including and excluding gaps, percent polyploidy and endoreduplication. A minimum of 1000 cells was randomly screened per culture from which the number of metaphases was counted, and mitotic index was then calculated.

Results: The short term and continuous exposure experiments without metabolic activation, were negative for inducing significant structural chromosomal aberrations. However, the short-term exposure experiment with metabolic activation did show a dose dependent increase in the frequency of aberrant cells with the 25.0 µg/mL treated cells statistically significantly increased compared to vehicle control.

Conclusions: Based on these results, curcumin is clastogenic in this test system.

6.2.3 Micronucleus Study

An in vivo mammalian erythrocyte micronucleus test was conducted in compliance with the following internationally accepted guidelines OECD Guidelines for Testing of Chemicals, No. 474 (2014).

Purpose: To evaluate the genotoxic potential of curcumin.

Methods: Curcumin was administered by gavage to male and female Swiss Albino mice at test concentrations of 0 (vehicle-control), 500, 1000, 2000 mg/kg bw/day. The negative control/vehicle was 0.5% w/v carboxymethylcellulose sodium salt (CMC). The positive control, cyclophosphamide 30 mg/kg bw, was administered by oral gavage.

The test article and vehicle control were administered in a split dose (twice daily about 1–2 hours apart) for two consecutive days at a uniform volume of 10 mL/kg bw per dose. The positive control was administered in a single dose, 24 hours prior to sacrifice. Each group consisted of 10 animals (5 animals/sex/group).

Group designation:

Dose (mg/kg bw)		males/females
Negative Control	0	5/5
Low–dose	500	5/5
Mid–dose	1000	5/5
High–dose	2000	5/5
Cyclophosphamide	30	5/5

All animals were observed for clinical signs immediately following dosing and at regular intervals until sacrifice for mortality, signs of toxicity, or adverse reactions to treatment.

Bone marrow samples were collected from both femurs of each animal, 24 hours after the last dose. Slides were prepared in triplicate, blind coded, and assessed for incidence of micronucleated cells. At least four thousand polychromatic erythrocytes (PCEs) were scored per animal from which the frequency of micronucleated cells was determined. The proportion of PCE to total erythrocytes was determined by the number of mature cells encountered while counting at least 500 erythrocytes.

Results: No mortality, clinical signs of toxicity, or adverse reactions to treatment were observed in any animals during the study. No significant differences were observed in frequency of MPCE or proportion of PCE to mature erythrocytes between the three dose groups compared to the negative control, and all results were within the laboratory's historical control range. As expected, a large, statistically significant increase in MPCE frequency was observed in the positive control group compared to negative control.

Conclusions: Curcumin, at concentrations up to the limit dose of 2000 mg/kg bw, was negative for producing micronuclei in this in vivo mouse micronucleus test.

6.2.4 Fourteen-day Repeated-Dose Oral Toxicity Study

An unpublished, 14-day repeated-dose, oral toxicity non-GLP study was conducted according to Schedule Y: Drugs and Cosmetics (2nd amendment) Rules, Ministry of Health and Family Welfare, Department of Health, New Delhi, 2005.

Purpose: To evaluate the potential health hazards, including identification of toxic effects and target organs, of repeated oral exposure to curcumin in male and female rats for 14 days, and to provide data for dose selection for a 90-day oral toxicity study.

Methods: Six Wistar rats/sex/group were administered curcumin (formulated in 0.5% w/v CMC vehicle) at concentrations to provide for uniform administration by gavage of a dose volume of 10 mL/kg bw. Four groups were administered doses of 0 (vehicle-control), 500, 1000, or 2000 mg/kg bw/day (in split doses, 250, 500 and 1000 mg/kg bw twice daily (bid)), for 14 days.

Group designation:

Dose (mg/kg bw/day)		Males/Females
Control	0	6/6
Low–dose	500	6/6
Mid–dose	1000	6/6
High–dose	2000	6/6

All tests and examinations were conducted according to study protocols and in accordance with above stated guidelines:

- Observations of mortality and clinical signs, measurements of food intake and body weight, examination, urinalysis (macro and micro), and evaluation of hematology, coagulation, and clinical chemistry parameters were conducted.
- Measurement of organ weights (absolute and relative) and gross pathological examinations were conducted on all animals at necropsy.
- Full histopathological examinations were conducted on the preserved organs and tissues of all control and high-dose animals.
- Histopathological examinations of organs in which gross lesions or other abnormalities were observed in animals of the lower dose groups were also conducted.
- All quantitative data was subjected to statistical analysis.

Results: On clinical examination, yellow colored feces were observed in all test article groups, in the low- and mid-dose groups from Day 3–15 and in the high dose group from Day 2–15. None of the following were affected by test article administration: mortality, detailed clinical examination, body weight or body weight gain changes, changes in mean daily food consumption, pathologic changes in the evaluated hematological, coagulation, or blood chemistry parameters, specific macroscopic changes in the gross pathology findings, changes in absolute or relative organ weights, or histopathological lesions.

Conclusions: Oral administration of curcumin at doses up to 2000 mg/kg bw/day for 14 days did not cause signs of toxicity in male or female Wistar rats. Based on these results, the no observed adverse effect level (NOAEL) was determined to be 2000 mg/kg bw/day; the highest dose tested.

6.2.5 Ninety-day Repeated-Dose Oral Toxicity Study

A 90-day repeated-dose oral toxicity study in rats was performed and followed the test procedure recommendations of the OECD Guidelines for the Testing of Chemicals, No. 408 (adopted 21 September 1998).

Purpose: To evaluate the potential health hazards, including identification of toxic effects and target organs, of repeated oral exposure to curcumin in male and female rats for 90 days, and to determine a NOAEL.

Methods: Twenty Wistar rats/sex/group were administered curcumin dissolved in 0.5% w/v CMC (vehicle) at concentrations to provide for uniform administration by gavage of a dose volume of 10 mL/kg bw. Four groups were administered doses of 0 (vehicle-control), 250, 500 and 1000 mg/kg bw/day (125, 250 and 500 mg/kg bw bid) for 90-days. A reference group received curcumin powder, a mixture of natural curcuminoids containing 95% curcumin, in the same vehicle, at the same dose and dosing schedule as the high-dose test article group. This group was included for purposes of comparing the toxicological profiles of synthetic curcumin with the natural curcumin.

Group designation:

Dose (mg/kg bw/day)		Males/Females
Control	0	20/20
Low–dose	250	20/20
Mid–dose	500	20/20
High–dose	1000	20/20
Reference	1000	20/20

All tests and examinations were conducted according to study protocols and in compliance with above stated guidelines:

- Observations of mortality and clinical signs, measurements of food intake and body weight, ophthalmological examination, and evaluation of urinary, hematology, coagulation, and clinical chemistry parameters were conducted.
- A functional observation battery (FOB) consisting of home cage, handling, open field, and neuromotor observation was conducted during the final exposure week.
- Measurement of organ weights (absolute and relative) and gross pathological examinations were conducted on all animals at necropsy.
- Full histopathological examinations were conducted on the preserved organs and tissues of all control and high-dose animals.

- Histopathological examinations of organs in which gross lesions or other abnormalities were observed in animals of the lower dose groups were also conducted.
- All quantitative data was subjected to statistical analysis.

Results

There were no mortalities in any of the groups throughout this 90-day study. General cage-side, detailed clinical, and functional observations were normal except for the yellow discoloration of the feces, fur, and tails in males and females of the test article and reference item groups which was observed near the end of the first two weeks of the treatment period and persisted through the end of the treatment period. The yellow discoloration of the feces was attributed to the test article; discoloration of fur and tails resulted from contact with the feces. There were no abnormalities observed in any of the groups during any of the functional observation tests. There were no treatment related abnormalities on ophthalmologic examination of the vehicle control, high-dose or reference group; hence, low- and mid- dose animals did not receive the examination.

There were no statistically significant changes compared to control in body weight in the test article groups or reference group; additionally, there were no statistically significant differences between the high-dose and reference item groups. There were statistically significant differences in feed consumption compared to control in males and females sporadically throughout the study in the various test article groups and in reference group males (see **Table 10**). These changes were minimal and did not affect the body weight of the animals; thus, the changes were not considered toxicologically significant. Statistically significant increases in feed consumption observed in high-dose males compared to the reference item group were considered of no toxicological significance. High-dose and reference item group females' food consumption was similar throughout the study.

Table 10. Summary of feed consumption, 90-day study curcumin

Group (n=20) mg/kg bw/day		Feed Consumption (g) /day/animal													
	Days	1–2	8–9	15–16	22–23	29–30	36–37	43–44	50–51	57–58	64–65	71–72	78–79	85–86	89–90
Males															
Vehicle 0	Mean	20.55	21.86	21.96	21.89	23.15	22.40	21.58	21.49	21.07	21.46	21.89	22.36	22.60	21.17
	SD	2.25	1.47	2.55	2.07	3.46	1.43	1.45	1.37	1.48	1.59	1.51	1.09	1.64	0.68
250	Mean	19.92	22.19	21.57	21.03	23.97	21.28	21.67	19.56^{*-}	22.19	21.30	20.42	21.03	21.20	20.88
	SD	1.92	1.45	1.52	1.20	3.49	1.32	1.39	1.01	0.65	1.35	1.50	1.08	1.13	0.95
500	Mean	40.80^{*+}	23.70	22.80	21.50	26.28^{*+}	22.37	22.33	21.05	21.99	21.75	21.30	21.18	21.63	21.14
	SD	2.52	2.42	1.28	0.96	4.32	1.04	0.85	0.91	0.96	1.67	1.00	1.71	1.37	0.70
1000	Mean	19.99	23.71$^{*+\uparrow}$	22.68	23.24$^{\uparrow}$	24.06$^{\uparrow}$	23.47$^{\uparrow}$	22.72$^{\uparrow}$	21.64	20.22	21.35$^{\uparrow}$	21.59$^{\uparrow}$	21.58	22.48	21.13
	SD	1.17	2.44	1.24	1.26	3.36	1.33	1.44	1.13	1.37	1.55	1.25	1.06	1.28	1.23
Ref Item 1000	Mean	17.30^{*-}	21.27	21.54	21.51	20.76	21.16	20.19	21.34	19.77	19.83	19.91^{*-}	20.80^{*-}	21.27	21.85
	SD	3.80	1.96	1.82	1.42	1.56	1.37	1.17	2.06	1.75	1.39	1.74	1.12	1.60	0.76
Females															
Vehicle 0	Mean	15.07	15.04	16.23	16.18	16.66	17.89	14.65	16.82	16.42	17.08	16.23	16.08	14.81	16.59
	SD	2.54	1.08	1.28	1.30	1.18	0.55	0.79	1.31	1.02	0.94	0.79	0.66	0.44	1.53
250	Mean	15.51	13.92	16.71	16.45	17.75	14.62^{**-}	15.75^{*-}	17.10	15.51	16.28	15.23	16.58	15.36	15.92
	SD	1.29	1.15	1.07	1.72	1.40	1.64	0.97	1.81	2.02	1.96	2.18	1.13	1.75	1.27
500	Mean	12.76^{*-}	14.03	15.85	15.98	16.46	16.32^{*-}	15.17	17.44	14.43^{**-}	15.38^{*-}	16.03	16.26	14.75	15.26
	SD	1.05	1.77	1.47	1.77	1.45	1.92	1.75	0.46	1.11	1.46	1.57	1.08	1.03	1.23
1000	Mean	15.46	15.11	16.31	16.61	16.92	18.80	16.21^{**+}	17.18	16.45	17.19	16.81	16.54	16.45$^{**\uparrow}$	16.31
	SD	1.30	1.85	2.08	1.90	1.81	1.17	1.08	1.37	0.71	0.76	0.98	1.28	1.93	1.33
Ref Item 1000	Mean	15.75	15.51	15.47	16.64	17.17	18.49	16.02	16.12	17.31	16.76	16.37	16.31	16.01	16.22
	SD	2.26	2.00	2.97	2.64	2.60	2.43	2.94	0.64	2.39	1.23	1.13	1.19	2.34	1.33

Key: N= No. of animals, $^{*+/*-}$ = Statistically significant increase/decrease as compared to vehicle control ($p<0.05$), $^{**+/**-}$ = Statistically significant increase/decrease as compared to vehicle control ($p<0.01$), ↑/↓ = Statistically significant increase/decrease as compared to the reference item group ($p<0.05$); Ref, reference. Table borrowed from Damarla, et al (2018)[28].

There were several statistically significant changes compared to control in hematology measures for males and females of the test article groups, and in reference group males (see **Table 11**). In males, the changes in hemoglobin, mean corpuscular volume, mean corpuscular hemoglobin concentration, reticulocyte distribution width, mean platelet volume, white blood cells (WBC), and lymphocytes lacked dose dependency and were within historical control values; thus, they were considered neither test article related nor of toxicological significance. While changes in red blood cells, mean corpuscular hemoglobin, neutrophils, and monocytes in males did show some dose dependency, the results were within the normal historical ranges. Thus, the changes were not considered toxicologically relevant. The statistically significant changes in the female test article groups were in the low- and mid-dose groups only and were considered incidental and not toxicologically significant. Hematology measures in the high-dose groups compared to the reference item were comparable except for an increase in WBC and lymphocytes in the male high-dose group and a decrease in reticulocytes in the female high-dose group. While there were statistically significant changes in the high-dose group compared to control, these differences were considered incidental as the values were within historical control ranges.

There were also statistically significant changes in clinical chemistry measures in the male and female test article groups (see **Table 12**). In males, the statistically significant changes occurred without dose-dependency; values were also within or marginal to historical control ranges, thus not considered test article related. Phosphorus and chloride were statistically significantly increased in the high-dose group compared to control and showed apparent dose-dependency; however, the values were within historical control ranges, were present without correlating findings in gross pathology and histology, and thus, were not considered toxicologically relevant. Phosphorus and chloride in high-dose males were significantly elevated compared to the reference group. These changes were considered incidental as values were within historical control ranges. Statistically significant changes in clinical chemistry results were also observed among the female groups. However, the changes lacked dose-dependency and values were within or marginal to the historical reference ranges and/or were considered non-adverse.

There were statistically significant changes in several coagulation parameters in males and females of the test article groups and the reference groups (see **Table 13**). The values remained within normal biological range, showed no dose-relationship, were not of biological consequence, and there was no corresponding change in platelets. Therefore, the changes were considered within the range of normal variation and non-adverse.

Table 11. Summary of hematology results, 90-day study curcumin

Group n=20 mg/kg bw/day		RBC (10^6 cells/µL)	HGB (g/dL)	MCV (fL)	MCH (pg)	MCHC (g/dL)	RDW (%)	Retic ($x10^9$ cells/L)	MPV (fL)	WBC (10^3 cells/µL)	Neu (10^3cells/ µL)	Lymp (10^3 cells/µL)	Mono (10^3 cells/µL)	Mono (%)
Males														
Vehicle 0	Mean	9.12	15.65	54.02	17.17	31.80	12.55	110.20	9.01	7.07	1.74	5.00	0.17	2.42
	SD	0.26	0.41	1.74	0.70	0.56	0.63	20.54	0.37	1.39	0.78	1.02	0.08	0.71
250	Mean	8.84$^{**\downarrow}$	15.50	55.18	17.55	31.81	12.95$^{**\uparrow}$	116.79	8.76$^{*\downarrow}$	6.35	1.40	4.67	0.13$^{\downarrow}$	1.94$^{*\downarrow}$
	SD	0.33	0.49	1.28	0.49	0.71	0.35	16.55	0.61	1.15	0.50	0.93	0.05	0.56
500	Mean	8.76$^{**\downarrow}$	15.43$^{**\downarrow}$	56.37$^{**\uparrow}$	17.63	31.27$^{*\downarrow}$	13.05$^{**\uparrow}$	104.27	8.76$^{*\downarrow}$	5.37$^{**\downarrow}$	1.22$^{**\downarrow}$	3.91$^{**\downarrow}$	0.12$^{**\downarrow}$	2.42
	SD	0.71	1.22	2.15	0.78	0.58	0.58	32.83	0.21	1.12	0.44	0.79	0.09	2.23
1000	Mean	8.67$^{**\downarrow}$	15.43$^{*\downarrow}$	55.57$^{**\uparrow}$	17.84$^{**\uparrow}$	32.09	12.57	111.90	9.56$^{**\uparrow}$	6.10$^{*\downarrow\downarrow}$	1.19$^{\downarrow}$	4.65$^{\uparrow\uparrow}$	0.10$^{**\downarrow}$	1.60$^{**\downarrow\uparrow}$
	SD	0.47	0.39	2.40	0.80	0.54	0.57	21.42	0.55	1.20	0.42	0.96	0.03	0.30
Ref Item 1000	Mean	8.75$^{**\downarrow}$	15.71$^{**\uparrow}$	55.69$^{**\uparrow}$	17.97$^{**\uparrow}$	32.26	12.65	98.60	9.34$^{**\uparrow}$	5.35$^{**\downarrow}$	1.18**	3.93$^{**\downarrow}$	0.10$^{**\downarrow}$	1.87*
	SD	0.40	0.52	1.90	0.69	0.62	0.34	25.64	0.38	0.76	0.37	0.68	0.03	0.42
Historical Range		7.67–9.45	13.00–16.00	46.00–54.80	14.30–17.90	30.60–34.60	11.90–14.30	40.70–164.30	6.7–11.6	3.72–10.81	0.84–2.94	2.45–8.85	0.07–0.27	1.30–2.70
Females														
0	Mean	8.15	14.92	57.17	18.30	32.04	11.56	116.71	7.63	4.96	1.20	3.53	0.11	2.05
	SD	0.29	0.56	1.75	0.62	0.48	0.44	27.68	0.43	1.99	0.92	1.09	0.08	0.81
250	Mean	8.09	15.39$^{**\uparrow}$	57.94	19.04$^{**\uparrow}$	32.86$^{**\uparrow}$	11.13*	145.26$^{*\uparrow}$	8.59$^{**\uparrow}$	5.11	1.02	3.84	0.10	1.94
	SD	0.29	0.52	1.76	0.59	0.49	0.39	35.77	0.63	1.05	0.39	0.95	0.03	0.39
500	Mean	8.11	15.08	56.63	18.61	32.84$^{**\uparrow}$	11.25	116.62	8.62$^{**\uparrow}$	3.58$^{**\downarrow}$	0.68$^{**\downarrow}$	2.73$^{\downarrow}$	0.06$^{\downarrow}$	1.67
	SD	0.29	0.31	1.31	0.46	0.68	0.46	27.41	0.46	0.89	0.24	0.68	0.02	0.49
1000	Mean	8.22	15.13	57.17	18.44	32.26	11.38	98.44$^{\downarrow}$	7.47	4.29	0.97	3.11	0.08	1.98
	SD	0.35	0.49	1.55	0.59	0.65	0.44	28.90	0.35	1.11	0.36	1.00	0.03	0.59
Ref item 1000	Mean	8.01	14.92	57.36	18.65	32.51	11.56	117.96	7.41	4.54	1.05	3.24	0.09	1.90
	SD	0.31	0.48	2.11	0.73	0.78	0.59	31.28	0.61	1.08	0.43	0.90	0.04	0.65
Historical Range		6.64–8.87	12.00–15.20	49.70–58.20	16.10–18.60	31.10–35.40	10.60–14.30	72.40–221.30	6.5–11.5	3.14–10.03	0.60–2.24	1.24–7.07	0.05–0.25	1.10–3.60

Key: n= No. of animals, $^{*+/*-}$= Statistically significant increase/decrease as compared to vehicle control ($p<0.05$), $^{**+/**-}$= Statistically significant increase/decrease as compared to vehicle control ($p<0.01$), ↑/↓= Statistically significant increase/decrease as compared to the reference item group ($p<0.05$), ↑↑ = Statistically significant increase as compared to the reference item group ($p<0.01$); Ref, reference. Table borrowed from Damarla et. al. (2018)[28]

Table 12. Summary of clinical chemistry results, 90-day study curcumin

Group n=20 mg/kg bw/day		Glu (mg/dL)	Glob (g/dL)	Tg (mg/dL)	TC (mg/dL)	AST (U/L)	BUN (mg/dL)	Na (mmol/L)	K (mmol/L)	Cl (mmol/L)	Ca (mmol/L)	P (mg/dL)
						Males						
Vehicle 0	Mean	99.45	2.83	79.70	69.60	89.20	15.95	150.10	4.61	110.25	10.46	6.00
	SD	12.82	0.15	29.79	11.54	8.28	2.33	1.65	0.22	1.62	0.28	0.55
250	Mean	89.45	2.74	60.35	55.75^{**-}	101.50^{**+}	17.00	151.75^{**+}	4.64	110.15	10.46	6.20
	SD	20.84	0.14	12.25	12.84	15.04	2.70	1.68	0.46	1.39	0.31	0.54
500	Mean	86.90^{**-}	2.78	80.35	62.30	87.80	17.85^{*+}	150.75	4.39^{**-}	109.90	10.72^{**+}	6.27
	SD	12.60	0.12	41.86	15.51	11.37	1.70	1.33	0.22	1.71	0.27	0.61
1000	Mean	87.85^{**-}	2.73^{*-}	77.60	72.60	98.45	16.11	149.90	4.44^{*-}	110.60$^{\uparrow\uparrow}$	10.39	6.57$^{**+\uparrow\uparrow}$
	SD	11.82	0.11	23.79	11.57	17.61	2.17	1.45	0.21	1.50	0.25	0.48
Ref Item 1000	Mean	97.40	2.78	74.85	74.45	91.50	15.46	149.00	4.53	109.20	10.49	5.96
	SD	27.52	0.12	26.62	16.22	13.65	1.74	1.72	0.28	1.67	0.20	0.43
Historical Ranges		65–115	2.76–3.40	43–125	56–92	91–217	12.60–25.10	140–149	3.80–5.50	100–132	9.60–10.54	5.29–7.65
						Females						
Vehicle 0	Mean	74.50	2.63	68.85	67.50	119.40	20.13	149.10	4.15	107.55	10.72	5.04
	SD	12.03	0.13	21.97	13.99	20.74	3.27	1.45	0.27	1.85	0.24	0.58
250	Mean	84.10^{*+}	2.62	51.20**	51.15^{**-}	86.65^{**-}	22.02	150.05^{*+}	4.14	110.00^{**+}	10.89	5.06
	SD	9.59	0.13	13.00	13.47	13.35	3.65	1.47	0.27	1.03	0.23	0.47
500	Mean	85.05^{*+}	2.64	41.30^{**-}	54.30^{**-}	81.80^{**-}	22.00	151.60^{**+}	4.09	112.40^{**+}	10.91	5.09
	SD	12.05	0.09	9.69	15.65	15.42	3.59	1.57	0.27	2.23	0.33	0.48
1000	Mean	73.45	2.65	48.90^{**-}	66.75	102.30^{**-}	20.31	147.80$^{**-\uparrow\uparrow}$	4.27	107.85$^{\uparrow}$	10.76	5.52
	SD	9.69	0.15	9.16	14.14	43.00	2.62	1.51	0.36	2.32	0.32	1.41
Ref Item 1000	Mean	78.65	2.60	53.90*-	62.85	96.40^{**-}	22.41	145.65**	4.37	105.90^{*-}	10.78	5.49
	SD	12.54	0.15	15.00	18.87	29.69	2.53	2.62	1.14	2.53	0.31	0.85
Historical Ranges		60–99	2.77–3.38	30–80	45–86	68–177	14.50–26.80	142–149	3.20–4.80	100–132	9.90–11.54	4.61–8.00

Key: N= No. of animals, $^{*+/*-}$= Statistically significant increase/decrease as compared to vehicle control ($p<0.05$), $^{**+/**-}$= Statistically significant increase/decrease as compared to vehicle control ($p<0.01$), ↑= Statistically significant increase/decrease as compared to the reference item group ($p<0.05$), ↑↑= Statistically significant increase/decrease as compared to the reference item group ($p<0.01$)

Abbreviations: Ca, calcium; Cl, chloride; Glob, globulin; Glu, glucose, K, potassium; P, phosphorus; Na, sodium; TC, total cholesterol; Tg, triglycerides Table borrowed from Damarla, et al. (2018)[28]

Table 13. Summary of coagulation results, 90-day study curcumin

Group n=20 mg/kg bw/day		PT (Sec)	APTT (Sec)	Fibrinogen (mg/dL)
		Males		
Vehicle 0	Mean	17.42	16.53	431.05
	SD	3.34	5.86	117.12
250	Mean	17.29	19.03	336.03**
	SD	5.08	5.16	70.20
500	Mean	14.84**	14.67	407.63
	SD	1.99	3.13	55.83
1000	Mean	14.84**↓	13.73	355.00**
	SD	1.64	2.37	62.36
Reference Item 1000	Mean	16.30	13.48*	392.72
	SD	1.91	4.35	57.90
Historical Range		14.90–21.00	10.00–19.60	145.30–985.40
		Females		
Vehicle 0	Mean	15.08	16.32	268.18
	SD	0.75	2.83	63.57
250	Mean	18.45**	14.47	264.64
	SD	1.34	3.19	188.79
500	Mean	17.55**	12.72**	241.01
	SD	2.51	2.38	50.99
1000	Mean	14.83*	17.97	324.30
	SD	0.66	3.50	263.26
Reference Item 1000	Mean	19.20**	16.87	246.29
	SD	1.69	3.71	44.00
Historical Range		14.50–21.90	7.40–21.00	243.50–758.10

Key: N= No. of animals, */*- = Statistically significant increase/decrease as compared to vehicle control ($p<0.05$), **/** = Statistically significant increase/decrease as compared to vehicle control ($p<0.01$), ↓ = Statistically significant decrease as compared to the reference item group ($p<0.05$) Table borrowed from Damarla, et al. (2018)[28]

Urinalysis results showed no statistically significant changes compared to controls (data not included).

Absolute organ weight measurements were statistically significantly increased in the heart, brain, kidneys, testes and epididymides in the mid-dose group and decreased for spleen weight in reference group males (see **Table 14**). There was a statistically significant decrease in liver weight in mid-dose females and increase in adrenal gland weight in high-dose females. The changes were not dose-related and there were no associated histopathological findings; thus, the changes were considered incidental. Relative organ weights of the kidneys were increased in the low-, mid-dose and reference group males and were increased in the livers of high-dose and reference item males (see **Table 15**). The change in relative organ weights of the kidneys were considered incidental as there were no correlating histological changes and correlating gross pathological lesions were only found in one animal in the low-dose group and one in the mid-dose group. The relative organ weight change for the liver occurred without related clinical chemistry or gross pathological findings and a histological change was observed in a single high-dose male; thus, the change was not considered toxicologically relevant. Relative weights of the lungs and spleen were increased in low-dose females. As there was no dose-relationship and the changes occurred in the low-dose group only, the findings were considered incidental.

Gross pathological findings were observed in several individual males in the vehicle control group and in test article groups (see **Table 16**). Reference group males presented with findings in the lungs only. Several histopathological lesions were present in individual animals of the control group, high-dose or reference groups (see **Table 17**), some of which occurred at the same or higher frequency in the control group. Macroscopic and microscopic findings in the lungs of test article and reference item groups (infiltration of foamy macrophages, chronic inflammatory foci, chronic inflammation and interstitial fibrosis, foreign body granuloma and osseous metaplasia) were consistent with findings observed with oral gavage error, spontaneous lesions, and/or aspiration of the test and reference solutions.[29, 30] Macroscopic kidney changes were observed in few animals and lacked associated histopathological or urinalysis findings; therefore, the findings (cyst and nephrosis) were considered incidental.[29] The remaining histopathological findings were sporadic, occurred with greater or equal frequency in the vehicle control group and/or occurred in individual animals only; thus, they were considered incidental and unrelated to the test article.

Table 14. Summary of absolute organ weights results, 90-day study curcumin

Group n=20 mg/kg bw/d		Absolute Organ Weights (g)							
		Adrenal glands	Heart	Brain	Liver	Kidneys	Spleen	Testes/ Ovaries	Epididymides/Uterus
					Males				
Vehicle 0	Mean	0.056	1.028	2.104	10.577	2.293	0.665	3.661	1.451
	SD	0.007	0.070	0.119	1.290	0.252	0.082	0.366	0.141
250	Mean	0.059	1.028	2.174	10.378	2.332	0.614	3.776	1.497
	SD	0.007	0.080	0.090	1.118	0.247	0.104	0.218	0.103
500	Mean	0.062	1.101^{*+}	2.222^{*+}	11.452	2.605^{**+}	0.723	3.898^{*+}	1.546^{*+}
	SD	0.007	0.097	0.124	0.874	0.578	0.140	0.492	0.134
1000	Mean	0.056	1.049	2.126	11.217	2.398	0.665	3.736	1.516
	SD	0.011	0.079	0.161	1.263	0.176	0.106	0.416	0.117
Ref Item 1000	Mean	0.060	1.005	2.110	10.904	2.334	0.608^{*-}	3.755	1.498
	SD	0.010	0.082	0.132	1.064	0.186	0.137	0.257	0.103
					Females				
Vehicle 0	Mean	0.071	0.751	2.044	6.662	1.805	0.445	0.171	0.696
	SD	0.008	0.066	0.068	0.705	1.186	0.049	0.032	0.177
250	Mean	0.072	0.668	2.010	6.536	1.506	0.500	0.163	0.593
	SD	0.009	0.207	0.121	0.591	0.103	0.098	0.015	0.101
500	Mean	0.070	0.729	2.036	6.263^{*-}	1.498	0.457	0.173	0.625
	SD	0.012	0.079	0.119	0.664	0.152	0.065	0.022	0.109
1000	Mean	0.077^{*+}	0.779	2.091	7.074	1.607	0.474	0.179	0.637
	SD	0.011	0.054	0.116	0.681	0.154	0.056	0.031	0.159
Ref Item 1000	Mean	0.078	0.764	2.066	7.023	1.541	0.481	0.178	0.710
	SD	0.016	0.076	0.132	0.950	0.173	0.077	0.038	0.223

Key: N= No. of animals, $^{*+/*-}$= Statistically significant increase/decrease as compared to vehicle control ($p<0.05$), $^{**+/**-}$= Statistically significant increase/decrease as compared to vehicle control ($p<0.01$); Ref, reference. Table borrowed from Damarla, et al. (2018)[28]

Table 15. Summary of relative organ weight relative to body weight results, 90-day study curcumin

Group n=20 (mg/kg bw/day)		Fasted Body wt. (g)	Relative Organ Weights (%)			
			Lungs	Liver	Kidneys	Spleen
			Males			
Vehicle 0	Mean	380.079	0.506	2.783	0.604	0.176
	SD	36.908	0.096	0.201	0.039	0.027
250	Mean	365.490	0.529	2.843	0.640*+	0.167
	SD	34.259	0.114	0.205	0.055	0.020
500	Mean	394.160	0.571	2.913	0.661*+	0.184
	SD	28.692	0.161	0.222	0.135	0.033
1000	Mean	380.596	0.471	2.946*+	0.631	0.175
	SD	25.771	0.106	0.267	0.043	0.024
Ref Item 1000	Mean	364.692	0.549	3.003**+	0.643*+	0.167
	SD	34.131	0.160	0.305	0.051	0.036
			Females			
0	Mean	222.861	0.656	2.988	0.810	0.200
	SD	16.701	0.147	0.215	0.527	0.025
250	Mean	216.313	0.777*+	3.029	0.697	0.231**+
	SD	14.168	0.218	0.286	0.041	0.039
500	Mean	213.676	0.699	2.931	0.701	0.214
	SD	15.403	0.147	0.226	0.046	0.027
1000	Mean	228.603	0.762	3.100	0.705	0.208
	SD	21.479	0.221	0.201	0.047	0.021
Ref Item 1000	Mean	221.654	0.687	3.167	0.695	0.217
	SD	19.352	0.129	0.295	0.043	0.031

Key: N= No. of animals, *+/*-= Statistically significant increase/decrease as compared to vehicle control ($p<0.05$), **+/**-= Statistically significant increase/decrease as compared to vehicle control ($p<0.01$)
Table borrowed from Damarla, et al. (2018)[28]

Table 16. Summary of gross pathology results, 90-day study, curcumin

Gross Pathology observation (s)	Number of animals with or without lesion (s)/ Numbers of animals observed				
	Vehicle 0	250	500	1000	Ref Item 1000
Males					
No abnormalities detected	19/20	18/20	18/20	19/20	13/20
Lungs- Discoloration, yellow	0/20	1/20	1/20	1/20	7/20
Testes- Small sized, unilateral/ bilateral	1/20	0/20	1/20	0/20	0/20
Epididymides- Small sized, unilateral	1/20	0/20	0/20	0/20	0/20
Epididymides- Foci, white	0/20	0/20	1/20	0/20	0/20
Kidneys- Hydronephrosis, unilateral	0/20	1/20	0/20	0/20	0/20
Kidneys- Cystic, unilateral	0/20	0/20	1/20	0/20	0/20
Females					
No abnormalities detected	19/20	19/20	20/20	18/20	19/20
Lungs- Discoloration, yellow	0/20	1/20	0/20	2/20	1/20
Kidneys- Cystic, unilateral	1/20	0/20	0/20	0/20	0/20

Table borrowed from Damarla, et al. (2018)[28]

Table 17. Summary of histopathology findings, 90-day study on curcumin

Organs/ Histopathology	lesions / no. of tissues examined				
	vehicle 0	250*	500*	1000	ref item 1000
Males					
Kidneys					
Basophilic tubules	0/20	--	--	1/20	1/20
Lungs					
Infiltration, foamy macrophages, alveolar	8/20	7/20	11/20	4/20	11/20
Inflammatory foci, chronic	4/20	1/20	1/20	0/20	0/20
Inflammation chronic and fibrosis, interstitial	0/20	1/20	7/20	3/20	11/20
Granuloma, foreign body	0/20	1/20	5/20	1/20	11/20
Osseous metaplasia	2/20	0/20	0/20	0/20	1/20
Stomach					
Erosion, mucosa, glandular, focal	1/20	--	--	0/20	1/20
Spleen					
Increased extramedullary hematopoiesis	0/20	--	--	1/20	1/20
Thymus					
Hyperplasia, epithelial	2/20	--	--	0/20	1/20
Testes					
Atrophy/ degeneration, seminiferous tubules, unilateral/ bilateral	2/20	--	--	1/20	0/20
Epididymides					
Vacuolation, epithelial	2/20	--	--	1/20	1/20
Sperm granuloma	2/20	--	--	2/20	1/20
Oligospermia	2/20	--	--	1/20	0/20
Prostate					
Infiltration, mononuclear cells, interstitial	1/20	--	--	1/20	2/20
Females					
Liver					
Vacuolation, cytoplasmic, periportal	0/20	--	--	1/20	2/20
Lungs					
Infiltration, foamy macrophages, alveolar	12/20	11/20	10/20	11/20	6/20
Inflammatory foci, chronic	1/20	4/20	1/20	0/20	2/20
Inflammation chronic and fibrosis, interstitial	0/20	4/20	1/20	8/20	4/20
Granuloma, foreign body	0/20	3/20	1/20	2/20	3/20
Infiltration, polymorphonuclear cells, alveolar	0/20	2/20	0/20	2/20	0/20
Osseous metaplasia	1/20	0/20	1/20	0/20	0/20
Ovaries					
Cyst, luteal	1/20	--	--	1/20	0/20
Uterus with cervix and vagina					
Increased mucification, epithelium, cervix and vagina	0/20	--	--	1/20	1/20
Urinary bladder					
Infiltration, mononuclear cells, submucosa	0/20	--	--	1/20	1/20

[f]findings that occurred only in the vehicle control group or only in one animal are not included.
*only target organs were processed for these groups
Table borrowed from Damarla, et al. (2018)[28]

Conclusions: Repeated administration by gavage of 250, 500, or 1000 mg/kg bw/day of curcumin for 90 days did not cause adverse effects or signs of toxicity in male or female SPF Crl:(WI)BR Wistar rats; the NOAEL was determined to be 1000 mg/kg bw/day; the highest dose tested.

As demonstrated in the study summaries above, curcumin showed no mutagenic effect in the bacterial reverse mutation or micronucleus assays. An acute/subacute/subchronic/chronic toxicity study on curcumin showed no toxic effects up to 1000 mg/kg bw, the highest dose tested.

Natural curcumin has been shown to induce chromosomal aberrations in cells at various stages of cell division at levels of 5–10 μg or more[31-37]; additionally, natural curcumin has been shown to have negative results in chromosomal aberration tests.[38-41] Indeed, some study results support the antigenotoxic and anticarcinogenic effects of curcumin.[40, 42, 43] Suggested potential mechanisms for positive chromosomal aberration results include curcumin's potential to generate and/or promote hydroxyl radical formation under chromosomal aberration test conditions as well as the ability of curcumin, a polyphenol, to act as a radical scavenger at high doses or a radical promoter when present at low doses.[31, 44, 45] Araujo et al. suggest that curcumin may act by inhibiting chromosomal damage repair, thus exacerbating chromosomal damage.[33, 34] Most importantly, in the context of the results of the current bacterial reverse mutation test and in vivo micronucleus test which suggest no genotoxic effect from this curcumin, the chromosomal aberration test results are not considered of mutagenic concern. Additionally, the results of the 14- and 90-day repeated oral dose studies that include a NOAEL of 1000 mg/kg bw/day (the highest dose tested) suggest that Laurus Labs' synthetic curcumin is of no toxicological concern.[28] More broadly, the totality of the evidence suggests that curcumin is not of toxicological concern.[37]

6.2.6 Additional Toxicological Studies

In 2007, Ganiger et al. published an OECD 416 compliant, two-generation reproductive toxicity study on a naturally extracted curcumin (turmeric yellow) of 95% purity in which four groups of 30 rats/sex/group were administered 0, 1500, 3000, or 10,000 ppm curcumin in their feed.[46] Ganiger et al. estimated NOAELs of 847 and 959 mg/kg bw/day for male rats and 1043 and 1076 mg/kg bw/day for female rats for the F0 and F1 generations, respectively. JECFA reviewed this study and determined the NOAEL to be 250–320 mg/kg/bw/day (see below).

The National Toxicology Program (NTP) performed a series of two-year long feeding studies in rats and mice using a turmeric oleoresin containing 79–85% curcumin, and concluded the following:[37]

- No evidence of carcinogenic activity in male rats administered up to the highest dose of 50,000 ppm in the diet (~2000 mg/kg bw/day);
- "Equivocal evidence of carcinogenic activity" in female rats based on increased incidences of clitoral gland adenoma in all exposed groups (up to 50,000 ppm (~2400 mg/kg bw/day));
- "Equivocal evidence of carcinogenic activity" in male mice based on a marginally increased incidence of hepatocellular adenoma at the middle dose of 10,000 ppm (~520 mg/kg bw/day) level and the occurrence of carcinomas of the small intestine in the low and middle dose groups 2,000 ppm (~220 mg/kg bw/day) and 10,000 ppm (~520 mg/kg bw/day) groups, and;
- "Equivocal evidence of carcinogenic activity" in female mice based on an increased incidence of hepatocellular adenomas in the middle dose group of 10,000 ppm (~1620 mg/kg bw/day) group.

6.3 Additional Scientific Studies

6.3.1 Human Studies

While human studies have not yet been performed on Laurus Labs' curcumin, one clinical trial on another synthetic curcumin as well as other clinical trials investigating various uses of other curcumin or curcumin-containing products were located (see **Table 18**). Four of the nine studies specifically reported the absence of side effects, but did not include a formal safety assessment, while two studies made no mention of side effects. The three remaining studies reported the occurrence of mild adverse events as summarized below.

Table 18. Summary of corroborative clinical trials

	Dose & Description	Duration	n	Condition	Comments (results)
Baum et al., 2008[47]	0, 1 or 4 g/day packet or capsule of curcumin RCT	6 months p.o.	27	Alzheimer Disease	No significant difference in plasma curcuminoid levels between test groups; plasma curcumin was 250 ± 80 nmol; curcumin did not seem to cause side effects in this group of subjects; AE occurred in all groups, including controls, with the 4 g group having the fewest
Cheng et al., 2001[11]	Phase I dose-escalation clinical trial, starting p.o. dose was 500 mg/day. If no toxicity ≥ grade II then dose was escalated to the next level (1000,	3 months p.o.	25	Recently resected urinary bladder cancer; Bowen's disease; CIN; oral leukoplakia;	No treatment related toxicity up to 8000 mg/day; doses higher than 8000 mg/day were unacceptable to patients because of the bulky volume of the test article

	2000, 4000, 8000, 12,000 mg/day) synthetic curcumin 99.3% purity			intestinal metaplasia of stomach	
Garcea et al., 2004[15]	450, 1800, or 3600 mg/day p.o. of curcumin	1 week	12	Hepatic metastatic disease from primary colorectal adeno-carcinomas	No mention of AE
Garcea et al., 2005[14]	450, 1800, or 3600 mg/day p.o. of curcumin	1 week	12	Colorectal carcinoma, Dukes stages A, B, or C	No mention of AE
Kanai et al., 2012[26]	Single dose of 150 mg, then two weeks later a single dose of 210 mg of nanoparticle curcumin	Two single-doses, one week apart	6	Healthy volunteers	One subject reported grade 1 diarrhea after intake of 150 mg of test article; no other toxicities were observed
Jäger et al. 2014[27]	376 mg of total curcuminoids in 3 different curcumin formulations (phytosome, rhizome, and combination of hydrophilic carrier, cellulosic derivatives and natural antioxidants) compared to a standardized curcumin mixture; randomized, double-blind, crossover trial	Single doses, 7 days apart	12	Volunteers with no history of gastrointestinal issues, non-diabetic, no use of blood thinners, proton pump inhibitors or H2 blockers	All treatments were tolerated well; no AE reported
Lao et al., 2006[9]	Dose escalation study of single doses of a standardized curcumin powder, starting at 500 mg, then 1000, 2000, 4000, 6000, 10,000 and 12,000 mg	Dosing about 3 days apart	24	Male and female volunteers with normal organ function	Single high-doses of curcumin are tolerated well; a total of seven grade 1 toxicity incidents (headache, diarrhea, rash, yellow stool) were spread among all dose levels except 500 and 6000 mg; no toxicity appeared to be dose related
Sharma et al. 2004[12]	Phase I dose-escalation, clinical trial of oral curcumin doses of 450, 900, 1800, or 3600 mg/day of curcumin	Up to 4 months	15	Adeno-carcinoma of the colon or rectum	Test article was tolerable at all dose levels; no dose-limiting toxicity was observed
Vareed et al. 2008[13]	Single oral dose of 10,000 mg or 12,000 mg curcumin	Single doses	12	Healthy volunteers	AE were all grade 1, two cases of yellow, loose stool which were treatment related

Abbreviations: AE, adverse effects; CIN, uterine cervical intra-epithelial neoplasm; n, number of subjects in the study; RCT, randomized, double-blind, placebo-controlled; p.o., by mouth.

6.4 Authoritative Safety Opinions

6.4.1 Institute of Medicine

In its *Herbs at a Glance* section, The National Center for Complementary and Integrative Health of the National Institute of Health states that turmeric, in amounts tested for health purposes, is generally considered safe when taken by mouth or applied to skin; however, high doses or long-term use of turmeric may cause gastrointestinal problems.[48]

6.4.2 World Health Organization

In 2004, the Joint FAO/WHO Expert Committee on Food Additives (JECFA) evaluated the toxicity of curcumin and determined an ADI of 0–3 mg/kg bw/day based on previous data and an unpublished (at the time) multigenerational toxicity study conducted by Ganiger in 2002.[49] (The Ganiger et al. study was published in 2007 and is described above in section 6.2.6.)

6.4.3 European Food Safety Authority (EFSA)

In 2010, EFSA issued a Scientific Opinion on the re-evaluation of curcumin (E 100) as a food additive.[5] EFSA's 2010 Panel reviewed current data and noted that all statistically significant effects in the NTP long-term carcinogenicity study in rats and mice were benign neoplastic lesions (adenomas) and the incidences for malignant neoplastic lesions (carcinomas) did not reach statistical significance. They also noted that the effects observed were not dose-dependent, were in line with historical control values and were not consistent across sexes and/or species. The Panel agreed with JECFA that curcumin is not carcinogenic, and that an ADI of 3 mg/kg bw/day was supported based on a NOAEL of 250–320 mg/kg bw/day from a reproductive toxicity study[46] based on a decreased body weight gain in the F2 generation observed at the highest dose level (960–1100 mg/kg bw/day), and an uncertainty factor of 100.

6.5 Allergenicity

Curcumin does not contain or have added, and is manufactured in a facility free of, all eight major food allergens (milk, egg, fish, Crustacean shellfish, tree nuts, wheat, peanuts, and soybeans) identified, and required to be disclosed in labeling, in the Food Allergen Labeling and Consumer Protection Act (FALCPA). Additionally, Product Name™® does not contain gluten, iodine, lactose, carbohydrate, casein, PVC, natural flavorings (fruits/berries), sulfur and sulfites or any derivatives or products of the aforementioned.

No reports of allergic reactions to curcumin were found in our investigations.

6.6 History of Consumption

Turmeric has been a part of the human diet and herbal medicines for thousands of years in India and for hundreds of years in many other areas of the world.[50, 51] Most of the world's turmeric is grown in India and about 80% of it is consumed there. Turmeric has been used as a coloring agent in foods (cakes, yogurt, biscuits, sweets, etc.) and cosmetics, and is an ingredient that is ubiquitous in curries. Turmeric has been used safely as a spice and household remedy for centuries.[50, 52]

6.7 Reported Adverse Events

No FDA letters regarding concern for safety to companies that market products containing curcumin were located. A search of MedWatch, FDA's adverse event reporting program, and FDA's Recalls, Market Withdrawals, & Safety Alerts search engine did not uncover any mention of orally ingested curcumin products (accessed on June 19, 2018). On MedWatch, two serious adverse events were reported after i.v. infusions of curcumin: one death and one hypersensitivity reaction.[53] FDA reviewed and analyzed both cases and determined that both patients suffered from immediate hypersensitivity reactions to a component of the infusion of curcumin: polyethylene glycol (PEG) 40 castor oil (that was an ungraded, inactive ingredient in the infusion), diethylene glycol (an impurity that can be found in the PEG 40 castor oil), or to the curcumin.

A search of the Center for Food Safety and Applied Nutrition (CFSAN) Adverse Event Reporting System (CAERS) database (accessed on June 18, 2018), found that out of the 92,232 adverse reactions reported during the time between January 2004 to September 2017, 60 adverse events were reported for products containing curcumin (0.06%).[54] Of these 60 adverse event reports (AERs), 54 were categorized as serious adverse events (SAEs) by the reporter of the event. Twenty of the AERs were considered concomitant (the reporter consumed multiple products) of which three were non-serious. Forty of the AERs reported the product as suspect (meaning the reporter suspected the named product caused the adverse event); three of these 40 were considered non-serious events. The type of product consumed in all reports were from the vitamin/mineral/protein/unconventional diet category with the exception of one report of curcumin as a color additive in food/drug/cosmetics. Twenty AERs involved hospitalization. One death was reported after taking an unspecified curcumin product; the product was classified as suspect. Seventeen of the products were listed simply as curcumin. The identifiable products (i.e., name and brand were provided) contain naturally derived and/or standardized forms of curcumin and several of the products contain additional ingredients (e.g., piperine). Importantly, AERs can only be considered associations as reported products may or may not be causally related to the adverse event. Additionally, CFSAN notes that the reports in CAERS represent only events that are reported, the reports do not

represent a conclusion by FDA about causality of the events, and the information contained in the reports has not been verified as to a cause and effect relationship; therefore, the data cannot be used to estimate incidence or to estimate risk.[54]

6.8 Similar Product in the Marketplace

A general internet search as well as searches of the National Institutes of Health (NIH) Dietary Supplements Label Database and several large distributors of dietary supplements resulted in a number of findings of curcumin-containing products, illustrating that this ingredient is widely available in the US. Despite this prevalence, we are unaware of any adverse events attributed to curcumin. Examples of products containing curcumin are listed in **Table 19**:

Table 19. U.S. products containing curcumin

Company	Product Name	Serving Size(s)
Ayush Herbs	Curcumin 97%	250 mg pure curcuminoids
Dr. Mercola	Curcumin Advanced	500 mg curcumin root extract (25% curcuminoids)
Doctor's Best	High Absorption Curcumin	1000 mg (>95% curcuminoids)
Jarrow Formulas	Jarrow Formulas Curcumin 95	500 mg (95% total curcuminoids)
America's Finest	Super Curcumin C3 complex with BioPerine	1000 mg C3 complex
Genestra Brands	Curcumin Complex	400.0 mg curcumin
Source Naturals	Turmeric with Meriva(R)	500 mg Meriva Turmeric complex
Kyolic	Curcumin	1000.0 mg Meriva Turmeric complex
Natural Factors	CurcuminRich Double Strength Theracurmin	60.0 mg Theracurmin Curcumin extract
NutriGold	Turmeric Curcumin Gold	500.0 mg (70–80% curcumin)
BIOVEA	Curcumin BCM-95	900 mg (BCM-Bio-Curcumin, 95% total curcuminoids)

6.9 Current Regulatory Status

A thorough search for the current regulatory status of curcumin, relevant to its use in food in the United States, was conducted. Searched entities included curcumin and curcuminoids. Summaries of the pertinent search results are shown below:

- Two FDA GRAS notices (GRN No. 460 and 686) were found in the FDA GRAS Notice Inventory database for curcuminoids and curcumin, respectively. GRN No. 460 (on curcuminoids purified from turmeric, with a purity of >95% curcuminoids and 75–81% curcumin) received FDA's no objection letter in August of 2013 indicating no current challenge to the safety of the ingredient and its intended use is as a flavor, flavor enhancer, or an ingredient in baked goods, soups, snack foods, imitation dairy products and seasoning, at levels up to 20 mg per serving.[55] GRN No. 686 (on

curcumin from turmeric, with a purity of >95% curcuminoids complex and >65% curcumin) received FDA's no objection letter in July of 2017 indicating no challenge to the safety of the ingredient and its intended use is as a nutrient supplement in yogurt, nutrition bars, smoothies and medical foods at levels intended to provide up to 60 mg of curcumin per serving.[56]

6.10 Basis for the GRAS Conclusion

The scientific procedures establishing the safety of curcumin comprise the technical element of the GRAS standard. The common knowledge element is comprised of the general availability and general acceptance, throughout the scientific community of qualified experts, of the technical element. Together, the technical element and the common knowledge element form the basis for Laurus Labs' conclusion of GRAS status of curcumin for its intended use.

6.10.1 Technical Element

Laurus Labs' VEAMIN 99™ synthetic curcumin has been the subject of a thorough safety assessment as described above. The totality of evidence supporting the safety of curcumin is comprised of data and information that establish the safety of curcumin under the conditions of its intended use (the technical element) and data and information that is corroborative of safety. The scientific data, information, and methods forming the technical element of this conclusion are:

- The establishment of identity, demonstrating the consistency and ≥99% purity of this synthetic curcumin;
- The method of manufacture and specifications, demonstrating the safe production and the high-quality control standards of curcumin;
- The bacterial reverse mutation test and in vivo mammalian micronucleus test, establishing the lack of genotoxic potential of Laurus Labs' curcumin; and
- The ninety-day repeated-dose oral toxicity study in rats and dietary exposure estimate, establishing the lack of adverse health effects and/or target organs of repeated exposure to curcumin in rats, and establishing an adequate margin of safety (MOS) for the intended conditions of use by humans of curcumin as food, as discussed below.

In the ninety-day repeated dose oral toxicity study in rats, the NOAEL for Laurus Labs' curcumin was 1000 mg/kg bw/day in male and female Wistar rats, which was the highest level tested. Based on exposure estimates from the intended use of the ingredient in a variety of foods at addition levels of 0.5–100 mg/100g, depending on the food category, the NOAEL allows for an adequate MOS (NOAEL/Exposure)

as shown in **Table 20** below. The margin of safety results are greater than the usual expected margin of safety for a food ingredient of 100 per 21 CFR 170.22, and support a conclusion that the intended use of curcumin is reasonably certain to be safe.

Table 20. Margin of safety calculations for curcumin based 90-day study NOAEL of 1000 mg/kg bw/day

90th Percentile Lifetime Exposure to Curcumin (based on Intended uses)	Curcumin: Margin of Safety (NOAEL/EDI)
6.79 mg/kg bw/day (based on 100% Presence Probability, see Table 6)	147.3
1.32 mg/kg bw/day (based on 20% Presence Probability, see Table 7)	757.6

The safety of curcumin is corroborated by a fourteen-day repeated-dose oral toxicity study in rats and the lack of serious adverse events reported in clinical trials using curcumin at daily dosages up to 8000 mg and durations up to 3 months.

6.10.2 Common Knowledge Element

The scientific data, information, and methods herein reported, that provide the basis of this GRAS conclusion by scientific procedures are published and available in the public domain. Part 7 of this GRAS notice contains the citations for the published studies. This publicly available data and information fulfills the requirement for general availability of the scientific data, information, and methods relied on to establish the technical element of the GRAS standard. The peer-review of the published studies and lack of Letters to the Editor or other dissenting opinions provides ample evidence of consensus among qualified experts that there is reasonable certainty that consumption of curcumin for its intended use is not harmful. The general availability and acceptance of this scientific data, information, and methods satisfies the common knowledge element of this GRAS conclusion.

6.11 Data and Information that is Inconsistent with the GRAS Conclusion

We have reviewed the available data and information and are not aware of any data and information that are, or may appear to be, inconsistent with our conclusion of GRAS status.

6.12 Information that is Exempt from Disclosure under FOIA

None of the data and information in this GRAS notice are considered exempt from disclosure under FOIA as trade secret or commercial or financial information that are privileged or confidential.

The signatures in the cover letter (agent of the notifier) and in Part 1 of this notice (notifier), are personal privacy information. This personal privacy information has no bearing on the safety of curcumin.

Part 7: Supporting Data and Information

7.1 Data and Information that are *not* Generally Available

The 14-day study in rats described in Subpart 6.2.4 of this report and the sales and adverse event report data provided in Subpart 6.7 are not generally available. However, this information is merely corroborative to the other data and information described in this report, and the safety conclusion can still be made even if qualified experts throughout the scientific community do not generally have access to this information.

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Bonnette, Richard

From: John Endres <john@aibmr.com>
Sent: Tuesday, December 04, 2018 12:57 PM
To: Bonnette, Richard
Subject: Re: Submission to FDA GRAS notification program - synthetic curcumin - quick question
Attachments: image002.jpg

Hi Richard,

That statement on page 5 refers only to the signature on page 6. I hope that helps with your inquiry. Let me know if you have any additional questions.

Best Regards,
John

John R. Endres, ND
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On Tue, Dec 4, 2018 at 4:18 PM Bonnette, Richard <Richard.Bonnette@fda.hhs.gov> wrote:

Hello John,

We've been looking through your most recent synthetic curcumin submission as part of the prefiling review and just had a quick question. Page 5 (1.8) notes that, "Personal privacy information is present in Part 1 of this GRAS notice." Just wanted to quickly check in with you to see what this might be.

Thanks,

Richard

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