

Toxic Solvent Found in Curcumin Extract

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In this article I wish to illustrate 4 major points:

- 1) the absolute need for clinicians to ascertain that their supplement manufacturers/suppliers are vigilant in contamination screening and actually go beyond the US Food and Drug Administration (FDA) Dietary Supplement current Good Manufacturing Practices (cGMPs)—you will see the reason why I say they need to go beyond cGMPs as you read this article;
- 2) the importance of the concept that “You only find what you look (test) for”;
- 3) that some amount (maybe a large amount) of the worldwide curcumin (*Curcumin longa*) extract supply may be tainted with a Class 1 (the highest level) toxic solvent, and clinicians—as well as some manufacturers—have no awareness of this possibility; and
- 4) the importance of total daily dose and duration of treatment when evaluating patient toxicity load and exposure.

Also in this article, I decided to say as little as possible and let the information and data I have collected speak for itself.

FDA Requirements for Contamination Testing

FDA Dietary Supplement cGMPs say the following regarding contaminant testing (taken from Section 111.70 of the *Final Rule*; author emphasis/bold added)^{1(p771)}:

In regard to components, aka raw materials (111.70 [b]):

- (2) You [the manufacturer] must establish component specifications that are necessary to ensure that specifications for the purity, strength and composition of dietary supplements manufactured using the components are met; and
- (3) You [the manufacturer] must establish limits on those types of contamination that may adulterate or may lead to adulteration of the finished batch of the dietary supplement to ensure the quality of the dietary supplement.

In regard to in-process production/manufacturing (111.70 [c]):

- (2) You [the manufacturer] must provide adequate documentation of your basis for why meeting the in-

process specifications, in combination with meeting component specifications, will help ensure that the specifications are met for the identity, purity, strength, and composition of the dietary supplements and for limits on those types of contamination that may adulterate or may lead to adulteration of the finished batch of the dietary supplement.

In regard to finished product (111.70 [e]):

For each dietary supplement that you manufacture you must establish product specifications for the identity, purity, strength, and composition of the finished batch of the dietary supplement, and for limits on those types of contamination that may adulterate, or that may lead to adulteration of, the finished batch of the dietary supplement to ensure the quality of the dietary supplement.

Essentially, what this language says is that a manufacturer has to set contamination specifications (limits) on those types of contamination that may adulterate or may lead to adulteration for raw materials, in-process materials, and finished products; and the manufacturer has to provide documentation (test results, etc) that it met those specifications.

Unfortunately, there are several weaknesses in the FDA rules:

1. To make the point pertinent to this article: If a supplier sells a manufacturer a raw material such as curcumin extract and the certificate of analysis (COA) says it was extracted with acetone, but, in reality, it was extracted with 1,2-dichloroethane (aka ethylene dichloride [EDC]), how is the manufacturer supposed to know? Unless it does independent testing, it doesn't know, and then EDC becomes part of the final product sold to patients. That is to say, in the words of the above ruling, the manufacturer would not know EDC is a “type of contamination” because it was not listed as one (and prior to this article, it was not generally known that it has been used as one).
2. In my experience, I have found that it is common place for many suppliers to omit solvent residue data—either a complete omission or a partial omission (where they list 1 solvent but not another)—from the COA, as above. I know this because I have discovered unlisted contaminants during my own testing.
3. I have been told unofficially that the FDA expects manufacturers to know what contamination is possible in a

material and then, in accordance with the quoted rules, to test for it and establish acceptable limits. If the manufacturer doesn't know, however, there is no system of checks and balances—again, it becomes part of the final product sold to patients.

4. Nowhere in the FDA cGMPs is there a mandate that manufacturers test for solvent residue—in fact, solvents are mentioned 5 times in the cGMPs but never once is it mandated that they be tested as a contaminant. Fortunately, this oversight is mitigated by US Pharmacopeia (USP) requirements for solvent residue testing, but there is a question if FDA enforces this particular rule since their own provisions are less stringent. (For more information on FDA's relationship with USP, please see the sidebar.)

Remember, in medicine and in dietary supplement quality assurance, you only find what you look (test) for. I found the information presented in the rest of this article because I believe that manufacturers should test and look comprehensively to ensure quality. It was test results that led me to search and dig deeper to uncover what I present here.

Curcumin Contamination

A number of years ago, I discovered what I considered to be a big problem while trying to buy curcumin extract. I brought a batch from a supplier that imports from India. Routine contamination tests were performed: heavy metals, aflatoxins, herbicides and pesticides, and solvent residues. When I was reviewing the results of these tests, it was the solvent residue data that caught my eye. I saw something I had never seen before, which led me on a bit of a quest. The solvent residue test showed positive for EDC, with a result of 6 parts per million (ppm). A seemingly low level—or so I thought at the time.

I scrutinized the supplier's COA and, lo and behold, 1,2-dichloroethane was listed as the extraction solvent at 5 ppm. Since I'd gotten 6 ppm, I repeated the test—only to get a similar result. While the solvent residue test was being repeated, I researched the effects of EDC. I did not like what I found: 1,2-dichloroethane is a Class 1 solvent, a category that the USP has labeled as "solvents to be avoided [because they are] known human carcinogens, strongly suspected human carcinogens, and/or environmental hazards."²

Hence, although 6 ppm may not sound like a lot, in reality it is; the USP limit for use in pharmaceuticals and dietary supplements is 5 ppm. (Again, you can see more information about USP requirements in the sidebar.) This is what the USP says about Class 1 solvents (emphasis added): "Class 1 residual solvents . . . should not be employed in the manufacture of drug substances, excipients, and drug products because of the unacceptable toxicities or deleterious environmental effects of these residual solvents. However, if their use to produce a medicinal product is unavoidable, their levels should be restricted," and, "When Class 1 solvents are used . . . these solvents should be identified and quantified."²

The USP has an official monograph for curcumin, *Curcumin*

Collaboration Between the USP and the FDA

I want to bring to the fore information about the relationship between the US Pharmacopeia (USP) and the US Food and Drug Administration (FDA). I feel it is important to know this as most clinicians have no idea how these 2 organizations collaborate.

The USP, an independent, not-for-profit, standards-setting organization, was founded in 1820³ by practitioners in an effort to standardize the composition and nomenclature of medicinal preparations in that era. The preparations were made by apothecaries through a process now called compounding. These pioneers understood the importance of their motto, "Good pharmaceutical care for all,"³ long before our modern concepts of pharmaceutical manufacturing materialized.

The USP maintains an important relationship with the FDA—which, itself, has a complicated history, being first established as part of the US Division of Chemistry in 1862, which later became the Bureau of Chemistry. Ultimately, the FDA was established as part of the Department of Agriculture, effective July 1, 1930, by the Agricultural Appropriation Act (46 Stat. 422) on May 27, 1930.⁴

In general, the USP's role in setting public standards begins after the FDA has given its approval to a product. Working with pharmaceutical manufacturers, the USP develops a public standard; ie, monographs delineating appropriate tests, procedures, and acceptance criteria (the specifications) for the product. USP's relationship with FDA dates back to when it was the Bureau of Chemistry. At that time, legal recognition of USP's standards for strength, quality, and purity was included in the Federal Food and Drug Act of 1906.⁵

USP helps to maintain public health by publishing public standards in 2 compendia, the *United States Pharmacopeia (USP)* and the *National Formulary (NF)*. Both the *USP* and the *NF* were cited as official compendia of the United States in the Federal Food, Drug, and Cosmetic Act of 1938.⁶ Since this time, the public standards published in *USP-NF* are legally enforceable by FDA. *USP-NF* contains official public standards for prescription and over-the-counter drug substances and dosage forms, biologicals, dietary supplements, some medical devices, and excipients. The USP continues to collaborate with the FDA to establish public standards supporting testing. USP also publishes compounding monographs, remaining true to its founders' intentions.

Note above that it says USP standards are legally enforceable by FDA, and *USP-NF* contains official public standards for dietary supplements.

Collaboration Between the USP and the FDA, cont.

Responses to Frequently Asked Questions

In relation to this article, the following are USP responses to frequently asked questions about solvent residue testing.⁷

- "The USP General Notices require all products to meet the residual solvents requirements in General Chapter <467> by July 1, 2008. The purpose of the chapter is to limit the amount of solvents that patients receive."
- "If the product or substance is covered by a USP or NF monograph, the monograph standards and the General Notices apply, whether or not it is labeled 'USP' or 'NF'; that is to say, 'the General Notices requirement that the substance or product comply with General Chapter <467> applies to all substances and products covered by USP and NF monographs.'"
- The chapter states that "no testing is required if you [the manufacturer of the finished product] know that solvents are not present." I would to add a comment on this, however: It is not defined how a manufacturer "knows." Hence, there is quite a lot of wiggle room with this word, as, if solvents are found, it could come back on the manufacturer that it didn't know. Hence, according to the USP, "it is always prudent to evaluate [test for solvents]... starting materials and finished product."
- "It is up to the manufacturer to determine whether or not to test. The decision may depend on the confidence and the relationship between the manufacturer and supplier. The manufacturer may choose to audit the vendor."
- Manufacturers are instructed to "Use good science and prudent behavior in a GMP environment to demonstrate the absence of solvent. If the presence or absence can't be demonstrated, test the product." It should be noted that this is the position of the USP, but it isn't the position of the FDA, which only requires that the manufacturer must establish limits on those types of contamination that may adulterate or may lead to adulteration of the finished batch of the dietary supplement to ensure the quality of the dietary supplement. Thus, it is an USP but not an FDA mandate.
- "The bottom line," says the USP, is that it's up to manufacturers "to assure the material that is going out to patients does not harm them."
- "It's up to the manufacturer to make sure the product complies with the limits for solvents."

Capsules and Tablets. In the monograph it says that manufacturers of the raw material and manufacturers of the finished product must comply with and meet various quality parameters and standards, including solvent residue limits set by the USP. All of the

limits set forth in the USP are legally enforceable by the FDA.

Is the use of 1,2-dichloroethane "unavoidable" in creating curcumin extract? Hardly. The most commonly used solvents for extracting curcuminoids from turmeric root are acetone, ethyl acetate, or ethanol—all Class 3 solvents, ie, much less toxic. However, after much investigation and sleuthing, I learned that using a toxic chemical such as EDC is more effective and much cheaper than using these Class 3 solvents. Now we know the reason many manufacturers choose to use it.

To give the benefit of the doubt, let's say, to the supplier's mind, 1,2-dichloroethane was the only option. Even then, according to the USP rules cited above, "When Class 1 solvents are used, these solvents should be identified and quantified."

Identification and quantification simply has not been my experience. Except for that first supplier's COA, which tipped me off to this, all other curcumin extract COAs stated that acetone or some other solvent was used to extract the product. There was absolutely no mention that 1,2-dichloroethane was used in the extraction process—despite what is specified by the USP and despite that it was found in a subsequent analysis.

At best, the suppliers and distributors are either misinformed or covering up the truth; at worst, they are covering up a potential toxic nightmare that clinicians and end users have a right to know about.

What are the Health Effects of 1,2-Dichloroethane?

Short-term effects: The Department of Health and Human Services, Public Health Service Agency for Toxic Substances and Disease Registry, has found the following potential health effects when people are exposed to this toxin at levels above the maximum concentration level for relatively short periods of time: central nervous system disorders; adverse liver, kidney, and lung effects; and heart failure.⁸

Long-term effects: A probable human carcinogen.⁸

A note on children: According to the US Department of Health and Human Services,

Because 1,2-dichloroethane has been detected in human milk, it is possible that young children could be exposed to 1,2-dichloroethane from breast-feeding mothers who had been exposed to sources of 1,2-dichloroethane. . . . One study broadly suggests that heart problems could occur in the human fetus from mothers being exposed to 1,2-dichloroethane along with some other chemicals, but the information is not reliable enough for us to be sure whether 1,2-dichloroethane is responsible for the defects.⁸

Getting back to that very first supplier, needless to say, I did not purchase the curcumin raw material. But I know others have since this is a popular supplier.

My questions to all clinicians are: Are you prescribing a curcumin extract to some of your patients? Does it have this toxic solvent in it? Would you know? How comfortable can you be when central nervous system disorders; adverse liver, kidney, and lung effects; and heart failures are a distinct possibility? What if

you are unaware of the contamination and you prescribed curcumin to a cancer patient at very high levels—say 8 to 10 g/d or higher (which as we all know is not uncommon). This would end up being a fairly high daily toxic load, taxing an already ill patient. What if you caused that patient harm because the product had 1,2-dichloroethane in it? How would that make you feel?

As background for such questioning: Of your professional product manufacturers, how many do you know with absolute certainty test every batch of raw material for a comprehensive panel of chemical solvents and reject batches of material that exceed rational or allowable limits? You'll only know if you ask your suppliers/manufacturers. It's really that simple.

Lab Results for EDC Contamination

As I mentioned, after finding that first incidence of 1,2-dichloroethane, I began a search for a curcumin extract that contained 0 ppm or <5 ppm of 1,2-dichloroethane. Listed in Table 1 are results for the solvent residue testing I performed over a period of years. I tested a variety of suppliers and some of them I tested more than once in an attempt to see if various lots contained less or more EDC.

The test method used by the lab that performed the solvent residue tests on curcumin extract is the USP <467> Residual Solvents Method. The lab used gas chromatography-mass spectrometry. As the name implies, it is actually 2 techniques that are combined to form a single method of analyzing mixtures of chemicals. Gas chromatography separates the components of a mixture, and mass spectroscopy characterizes each of the components individually and determines the quantities (concentrations) of each of the components.

The lab I used has done a lot of work on this method to allow it to detect EDC <2 ppm. This is useful because another lab may have a detection limit of 2 ppm and, if a curcumin extract sample really had 1.5 ppm of EDC, the lab would report it as <2 ppm. Hence, there would be no way to know if the 1,2-dichloroethane was truly 0 ppm or some greater number below 2 ppm. Although both limits are acceptable by USP standards, the least amount is always the best amount.

For reference, the USP allowable solvent limits are: 1,2-dichloroethane: 5 ppm; acetone: 5000 ppm; ethyl acetate: 5000 ppm.

It is possible to find a supplier that will make curcumin extract without using EDC, but, in my experience, this is something that has to be specifically requested and negotiated because curcumin extract with an EDC amount <5 ppm is not easily found.

Total Load and Toxic Burden of EDC

A very important piece of this article is realizing that, with the ppm listed in Table 1, anyone who would take these supplements in a concentrated form over time would ingest a serious amount of toxic solvent. For example, let's assume you have a patient with a need for curcumin extract at 6 g/d. California's Proposition 65 limit on 1,2-dichloroethane is 10 µg per day.⁹

If we use this as a starting point for an upper limit, let's calculate the µg of EDC that the patient would ingest at various levels of EDC per dose of curcumin extract. If a particular chosen dose was

Table 1. Curcumin Extract Solvent Residue Test Results

Product	Date Tested	Levels of 1,2-Dichloroethane, ppm; USP acceptable limit = 5 ppm	Other Solvents Found, ppm
Curcumin extract 90% from various suppliers: raw material	8-30-07	49.6	
	4-9-08	46.3	Acetone 965
	4-9-08	2760.0	
	4-17-08	83.9	Acetone 1300
	4-28-08	6.78	Ethyl Acetate 2610
	5-19-08	18.0	Ethyl Acetate 3330
	5-30-08	18.5	Acetone 497
	7-24-08	3270.0	
	7-24-08	32.4	
	7-24-08	2760.0	
	7-24-08	30.8	Acetone 823
	7-22-08	49.5	Acetone 1020
	8-20-09	49.1	Acetone 864
	9-24-09	969.0	Ethyl Acetate 1200
	2-25-10	30.1	Ethyl Acetate 1170
	2-25-10	1330.0*	
	2-25-10	54.6	Acetone 731
	2-25-10	59.6	Acetone 391
2-25-10	2880.0		
2-25-10	41.7	Acetone 1050	
2-25-10	57.5	Acetone 1010	
Curcumin extract 90% from various professional brands: finished product	7-24-08	1390.0	Acetone 138 Toluene 7.42 (A USP Class 2 solvent)
	7-24-08	47.2	Acetone 336
	7-24-08	38.0	Acetone 887
	7-24-08	29.6	Acetone 1050 Toluene 8.34
	7-24-08	35.6	Acetone 168 Toluene 2.7
	7-24-08	24.2	Acetone 412 Toluene 6.67 Chloroform 2.88 (A USP Class 2 solvent)
	5-22-09	5.96	

Key: ppm=parts per million; USP=US Pharmacopeia

1,2-Dichloroethane Level in Curcumin Extract	Daily Dose	μg Per Day Ingested	% >Limit of 10 $\mu\text{g}/\text{d}$
2 ppm = 2 $\mu\text{g}/\text{g}$	6 g	12 $\mu\text{g}/\text{d}$	20% over limit
5 ppm = 5 $\mu\text{g}/\text{g}$	6 g	30 $\mu\text{g}/\text{d}$	200% over limit
10 ppm = 10 $\mu\text{g}/\text{g}$	6 g	60 $\mu\text{g}/\text{d}$	500% over limit
50 ppm = 50 $\mu\text{g}/\text{g}$	6 g	300 $\mu\text{g}/\text{d}$	2900% over limit
2880 ppm = 2880 $\mu\text{g}/\text{g}$	6 g	17280 $\mu\text{g}/\text{d}$	172 800% over limit

^a The math is fairly straightforward to determine levels: 1 ppm = 1 mg per 1000 g or 1 $\mu\text{g}/\text{g}$. Thus, 2 ppm = 2 $\mu\text{g}/\text{g}$. Multiply this by 6 g/d and you get 12 $\mu\text{g}/\text{d}$, the first μg Per Day Ingested."

effective at reducing symptoms and you made the determination to keep the patient on curcumin extract long term, we can only imagine how the toxic burden of EDC would affect health and well-being. Some scenarios are illustrated in Table 2.

Conclusion

I am not saying that any particular curcumin extract material or finished product in the marketplace is contaminated with unacceptable levels of EDC. I have only tested a handful of product. I am telling you, the reader, what I have found and the concern that I and all clinicians should have regarding this data. Where you take it from here is up to you. At the very least, I suggest you consider asking your manufacturer to show you a very recent gas chromatography-mass spectrometry solvent residue analysis of their curcumin extract that delineates the level of EDC in the extract. Ideally it would be 0 or <2 ppm (at the most, 3 ppm). The idea is to get the least amount possible—as you can see by the math.

For more information on the toxicological and public health implications of EDC, go to the Agency for Toxic Substance and Disease Registry at <http://www.atsdr.cdc.gov/substances/toxsubstance.asp?toxid=110>.


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