Tom Neltner

From: Tom Neltner
Sent: Tuesday, May 2, 2023 9:02 PM
To: MuldoonJacobs, Kristi; Hermansky, Steven
Cc: Melanie Benesh; drmvma@gmail.com; Tom Neltner; Rowden, Jessica
Subject: Piperine - FDA Approved GRAS?
Attachments: Sabinsa gets GRAS for black pepper extract 2010.pdf; Sabinsa The Global Tetrahydropiperine market Size is vast and growing at an impressive rate of 12.2_ CAGR from 2023 to 2030 5-2-23.pdf; GRN-474 Piperine black pepper extract - NRDC Comment - 11-22-13.pdf

Steve and Kristi,

Today, Maricel's Google Alert flagged that "***The Food and Drug Administration (FDA) has approved THP [Tetrahydropiperine] as a Generally Recognized As Safe (GRAS) substance for use in food products. However, the use of THP in pharmaceuticals is subject to strict regulations due to its potential side effects and interactions with other drugs***." [Emphasis added]

Sabinsa and Hong Kang Biology are the two companies that the article claims are operating in the THP market. We are attaching a PDF of the article for your reference.

In our experience, market research reports like this are usually press releases from the manufacturers like Sabinsa masquerading as new information in the hopes of finding new clients.

The chemical is a variant of a black pepper extract that Sabinsa self-affirmed as GRAS in 2010. (See attached press release). FDA reviewed piperine as GRN-474 in 2013 under the trade name of Bioperine. Later that year, the company withdrew the notice for reasons unknown. M.G. Soni signed the GRAS notice and convened a panel of three people that included himself.

As you might recall, Maricel and I submitted the attached comments to FDA regarding this GRAS notice while we were at NRDC. We raised serious concerns about the safety of the substance. As with our other comments on GRAS notices, FDA never responded to those comments.

Beyond the misleading claim of FDA approval, we continue to have serious concerns about the safety of piperine that likely apply to the tetrahydro variant. Chief among our concerns with the GRAS Notice No 474 is the company's apparent selective use of available evidence and flawed exposure and hazard assessments. Specifically:

- Failing to mention that the European Food Safety Authority (EFSA) concluded that additional toxicology and use levels are needed to determine if piperine is safe as a flavor.
- Ignoring FDA exposure assessment guidance by using antiquated data, not considering impact on children or all sources of piperine. Specifically, Sabinsa:
    - Used a 1965 Market Research Corporation of America (MRCA) report on frequency of eating and U.S. Department of Agriculture (USDA) mean portion size to estimate the *per capita* consumption to calculate the estimated daily intake (EDI). The notifier did not explain why it did not use the National Health and Nutrition Examination Survey (NHANES) 2-day food consumption survey data from the past ten years as recommended by FDA;
    - Did not provide an EDI for children; and
    - Did not calculate a cumulative EDI considering all sources of piperine, including dietary supplements (and more specifically the one they make) and natural sources.
- Lacking toxicology testing studies for BioPerine. The notifier:

- Estimated an acceptable daily intake (ADI) based on a no observed adverse effect level (NOAEL) that EFSA said is based on inappropriate studies;
- Did not consider studies showing immunotoxicity and reproductive toxicity, or human studies showing piperine interferes with drug metabolism; and
- Relied on studies the majority of which did not perform toxicological testing but rather "were undertaken to evaluate its efficacy for different health conditions" and tested different black pepper-derived compounds.

For these reasons, we ask that FDA quickly investigate this product and its uses to protect consumers, especially those who might be using one of the drugs that are affected by tetrahydropiperine. From what we have seen, FDA should act quickly to get this product off the market until safety is verified.

Tom

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