



Memorandum

Date	March 28, 2016
From	[REDACTED] Toxicologist, Division of Biotechnology & GRAS Notice Review (DBGNR), Office of Food Additive Safety (OFAS), HFS-255  Through: [REDACTED] Toxicology Supervisor, DBGNR, OFAS, HFS-255 [REDACTED]
Subject	Update on the review of the safety of betel nut use as an ingredient in conventional foods.
To	[REDACTED] Director, DBGNR, OFAS, HFS-255

The purpose of this memorandum is to provide an update on the previous review of safety information pertaining to betel nut use as an ingredient in food <sup>a</sup> ([REDACTED] August 17, 2004). In the previous memorandum, OFAS laid out concerns related to betel nut’s use and its association with genotoxicity, carcinogenicity, as well as reproductive and developmental toxicity.



For the purpose of updating the Agency’s knowledge base on toxicological effects of betel nut consumption, I searched PubMed from August 2004 to February 22, 2016 for new scientific articles, utilizing the search term “betel nut”. The updated literature search retrieved approximately 1100 publications. The search was narrowed by refining and limiting the search terms to “betel nut,” “adverse effects” and “toxicity,” which resulted in approximately 90 articles (English language only). These articles, in general, relate to possible toxic endpoints, mechanistic studies, biomarker determination, and scientific reviews of betel nut. No new toxicological studies or other information were identified that contradict the Agency’s position regarding betel nut, which is that there is no basis for concluding that food safety experts, generally, would recognize the use of betel nut in food as safe.

The literature search found several betel nut review articles; the most recent discusses the traditional uses, botany, phytochemistry, pharmacology and toxicology<sup>1</sup>. Other published articles focus on adverse endpoints including: effects on reproduction <sup>2-8</sup>, effects on development <sup>9</sup>, cytotoxicity <sup>10-13</sup>, mutagenic potential <sup>14-15</sup>, immunological effects <sup>16-20</sup>, neurotoxicity <sup>21</sup>, effects in metabolic syndrome <sup>22</sup>, oral fibrosis <sup>23-24</sup>, and periodontal disease <sup>40-41</sup>. In addition, other publications show research aimed at determining betel nut induced mechanistic changes including: effects on mitosis

<sup>a</sup> In this document, the term “food” refers to conventional food products and not dietary supplement products. We note that under section 201(ff)(2)(B) of the FD&C Act (21 U.S.C. 321(ff)(2)(B)), the term “dietary supplement” means a product that, among other requirements, “is not represented for use as a conventional food or as a sole item of a meal or the diet.”

<sup>25</sup>, effects on gene regulation <sup>26-33</sup>, gene mutation <sup>34-38</sup>, effects on DNA repair <sup>39</sup>, and effects on cell cycle <sup>42-43</sup>. Finally, some authors are trying to elucidate biomarkers for betel nut toxicity <sup>44-46</sup>.

To expand further on some of the publications which link betel nut exposure to adverse effects since the last OFAS literature review (August 17, 2004) we will highlight some of the negative effects reported in publications from our current literature search. Recent publications show that betel nut consumption has reproductive effects including; decreased sperm motility <sup>2,5,7</sup>, decreased sperm count and production <sup>3,5</sup>, decreased embryo implantation rate <sup>4</sup>, and decreased birth weight and length <sup>6</sup>. In addition, betel nut ingestion is linked to developmental effects such as decreased growth rates and motor impairment <sup>9</sup>, as well as neurotoxic effects such as neuronal cell death <sup>21</sup>. Furthermore, published articles show immunological effects such as decreased total thymocytes <sup>16</sup>, apoptosis of T-cells <sup>16</sup>, modulation of antigen-specific immune responses <sup>17,20</sup>, and suppression of T-cell activation <sup>18</sup>. Also, articles cite cytotoxicity via necrosis <sup>10</sup> which leads to oral fibrosis <sup>11,23</sup>. Finally, periodontal disease including tooth loss <sup>41</sup> is also a concern linked with betel nut use.

## Conclusions

In reviewing the recent literature, there is no evidence to contradict the conclusions made in the previous betel nut memorandum (August 17, 2004); and in fact the updated scientific information reinforces the Agency's concerns and position that betel nut use in food is unsafe.



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