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Comment on the Paper Entitled “Arginine and Caries Prevention: A Systematic Review”

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Dear Editor,

The Colgate-Palmolive Company is extremely proud of the clinical program conducted on the addition of 1.5% arginine to fluoride toothpaste. This program to date consists of 9 clinical efficacy studies, published in four peer-reviewed journals including *Caries Research*. It was conducted in collaboration with leading dental universities around the world and involved more than 16,000 participants. These studies demonstrated that the arginine plus fluoride formula, compared to regular fluoride toothpaste, consistently reduced new cavities by up to 20% at 2 years [Kraivaphan, 2013; Li et al., 2015] and reversed early caries lesions by approximately half in 6 months [Yin et al., 2013a, b; Srisilapanan, 2013]. Furthermore, a community-based study conducted in Thailand demonstrated that when arginine plus fluoride toothpaste was incorporated into a well-conducted school-based oral health program, up to 40% reductions in dental decay could be demonstrated [Petersen et al., 2015].

We were therefore extremely disappointed to see a recent review [Ástvaldsdóttir et al., 2016] (the “review”) in the journal, which we believe to be both out of date and in some instances factually incorrect.

The review was based on a literature search of the Cochrane database conducted in April 2014 (dated February 2014) and submitted to the journal on the January 28, 2016. The company has made the authors aware of highly relevant additional studies that were missing from the review. These studies were included in another systematic review of arginine-containing toothpaste [Li et al., 2015] published in November 2015 in the journal 2 months prior to submission of the current manuscript. It is the duty of authors of systematic reviews to ensure that data included are as up to date as possible, and the authors’ disappointing reliance on a search of the literature nearly 2 years prior to the submission of the review throws their conclusions into serious doubt.

We disagree with the statement “techniques measuring the outcomes in the adult studies were not validated and were at higher risk of bias.” Root caries is an increasing problem in elders, and the method used to measure the hardness of lesions was a method of assessment widely used in clinical studies, including some of those reported in this journal. We provided research evidence on the validity of the methods used, which again the authors chose to disregard without rationale. In addition, one of the studies omitted by

the authors used an electrical caries monitor to objectively measure remineralization, an approach that the authors included as one of their *a priori* outcome measures.

Where the reviewers have required additional data and clarification, for example with regard to randomization, the company has provided detailed information, but the reviewers have chosen to disregard it. Similarly, where other factual inaccuracies in the review have been pointed out, these too have not been addressed. For example, the statement that “there is no evidence as to whether arginine added to fluoride-containing dentifrices causes any complication and/or side effects” is incorrect. Rather, 3 of the 4 studies reviewed contained statements that no adverse events attributable to products were reported in the trials, and we have confirmed to the authors that there has never been a single adverse event attributable to the arginine product reported in any of the studies we have conducted.

With regard to the use of the a nonfluoride toothpaste in 2 of the 3 quantified light-induced fluorescence 6-month studies, all students had supervised brushing in the schools, which would account for the fact that even the nonfluoride toothpaste participants showed a reduction in lesion size at the end of the study, as was acknowledged by the authors. Ethics were reviewed by the Institutional Review Board (Ethics Committee) of Sichuan University, home to one of China’s leading dental schools. It is this review board that is best qualified to judge the ethics of a research program in China. This review recognized the compelling reason to include a nonfluoride control group in the study in order to gather direct evidence of the efficacy of fluoride toothpaste in the Chinese setting and thereby increase acceptance of fluoride as the standard of care in China. It is somewhat inconsistent for the authors to infer that clinical trial results derived from an Asian population are not transferable to the Swedish population whilst the Chinese and other Asian communities should accept the evidence provided by studies on fluoride toothpastes predominantly conducted in the West.

Colgate-Palmolive believes in robust criticism that is based on facts and conducted with the goal of improving research outcomes, but we do not believe that this review serves that goal. With a program that included 2 large clinical studies assessing caries at the cavitation level and 3 studies assessing the ability to remineralize enamel lesions, 2 to remineralize root caries lesions and a community-based intervention, our investigation of the arginine product is one of the largest caries clinical trial programs sponsored by industry. We have attempted to address caries prevention and treatment in a wide variety of populations using a wide range of methods and clinical trial designs. These were well-conducted, high-quality studies published in peer-reviewed journals and consistently showed a significant benefit for the addition of arginine to fluoride toothpaste.

As all readers of the journal are aware, dental caries remains a significant health problem, and we believe this groundbreaking toothpaste could have a significant impact on the global burden of

disease. We would of course welcome any appropriately conducted studies from any and all interested investigators. However, if the dental community chooses to dismiss all commercially sponsored research as biased and instead only considers noncommercially funded clinical studies in taking vital decisions on the relative benefits of oral care products, we will be potentially missing out on decades of benefit. Such a course would be a disservice to the communities we serve.

We would suggest that key stakeholders, including industry, need to work together in two vital areas: firstly, to determine what is the appropriate level of evidence required to support a new caries intervention and how generalizable are results between populations; and secondly, to define what is the realistic and appropriate role of commercial research versus privately funded research in developing new interventions.

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Reply

The Mouth Is Part of the Body

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In our review “Arginine and Caries Prevention: A Systematic Review” we show that the effect of an arginine supplement in fluoride toothpaste is uncertain. There are several reasons for this conclusion, i.e., the peer-reviewed published studies retrieved from the major medical databases are not of sufficiently high quality, and the selection of study subjects makes it difficult to generalize/extrapolate the results to other conditions (populations). As with all other medical and healthcare research, dental research should be conducted at a high professional level. This means that clinical studies should be assessed in accordance with internationally accepted, standardized norms for scientific stringency in clinical research.

The current review is a Health Technology Assessment (HTA) report and thus comprises a systematic review, an analysis of health economics, and consideration of ethical aspects. The methodology to be applied to HTA reports is also well described and has been internationally agreed to and accepted. However, differences still arise with respect to the results of various HTA reports and systematic reviews addressing the same scientific questions. This is usually attributable to variations in the level of requirements for scientific stringency in the included studies; for example, there

may be differences in requirements for validation of measurement methods. Another reason may be differing requirements with respect to the formulation of the hypothesis of the primary study; for example, it should be comprehensive and presented a priori, and include both positive and negative effects.

An HTA report is based on a systematic search of the literature. The author must determine a cutoff date: more recent studies are neither searched for nor included. This is necessary in order to finalize the work of analysis of the included studies. It is not compatible with good assessment methodology to subsequently include spontaneously identified studies. This may cause selection bias of the included studies; there is a high risk that other relevant studies might be overlooked, for example some which show results contradicting those of randomly identified studies. In practice, a time lapse between the date of the literature search and publication of the article is unavoidable. However, provided the description of the method is transparent, the reader can come to an informed conclusion about the topicality of the literature search.

The primary ethical standpoint on treatment in controlled clinical trials is that whenever a proven effective treatment exists for a given condition, it is unethical to test a new treatment for that con-

dition against a placebo or any other noneffective treatment [World Medical Association, 2013]. This applies not only to trials in the medical and healthcare fields but also to dentistry. A number of systematic reviews have shown strong scientific evidence that the use of fluoride toothpaste is an effective method for preventing caries in the permanent teeth of children and adolescents. It is therefore unethical to undertake studies in which the control group is denied access to treatment with fluoride.

We fully agree with Dr. DeVizio and Dr. Ellwood that it is important to establish appropriate levels of evidence for the managed introduction of pharmaceuticals, medical technology, psychological treatment methods, and surgical techniques. When introduction is managed the level of urgency of several aspects is affected, i.e., the severity of the condition may be a determinant (e.g., if it is a life-threatening condition).

Furthermore, when a study is sponsored commercially, there are established routines for regulating the degree of involvement of the company and its representatives in order to avoid conflicts of interest. It is important that the sponsoring company does not participate in any part of the study procedure. A contract should

be drawn up between the sponsor and the study investigators, stipulating that under no circumstances is the company, and/or its representatives, to be involved in the conduct of the study or in analyzing or presenting the data. This is an established approach within medical and healthcare research, for example within the pharmaceutical sector. As mentioned earlier, we would like to see the same high professional standards pertaining to medical and healthcare research also applied to dental research.

Reference

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