

# Safety Evaluation of NEM® Ends in GRAS



Chicken eggs have been a staple of many cultures' diets for centuries and are well-accepted as being safe to eat. Some cultures are also known to consume the egg shells and eggshell membranes in various ways. Egg shells are a natural source for calcium and have been evaluated for safety in a number of animal and human

studies carried out primarily in Europe and Asia (1; 2; 3). Eggshell meal (both shell and membrane) has been officially recognized by the Association of American Feed Control Officials (AAFCO) as being safe as a feed additive for both companion and livestock animals since 1982 (4). Eggshell membranes are an abundant raw material that are a novel source for naturally occurring bioactive compounds such as glucosamine, chondroitin sulfate, hyaluronic acid, collagen, and sulfur-rich proteins. Eggshell membrane has not previously been evaluated for safety through standard laboratory and animal model



toxicological studies. NEM®, an eggshell membrane derived product for oral administration, has been shown to naturally contain a number of components such as glucosamine, chondroitin sulfate, dermatan sulfate, hyaluronic acid, collagen, etc. that are found in joints and connective tissues and are thought to be beneficial via supplementation. As the mechanism of action remains to be determined for NEM®, a broad and thorough safety evaluation was initiated to support its use. To this end, NEM® was evaluated for any toxic damage to cells (cytotoxicity), toxic damage to genetic material such as DNA (genotoxicity), and toxic damage to organs or other critical systems in an animal model (acute & 90-day repeated-dose oral toxicity).

In laboratory tests (*in vitro*), NEM® was shown to be non-cytotoxic up to 100 µg for 20 hours of exposure and non-genotoxic up to 5,000 µg. There were no signs of acute toxicity in rats at a single oral dose of up to 2,000 mg/kg body weight nor were there any signs of chronic toxicity (via food intake, body weight, urinalysis, hematology, clinical chemistry, or histopathological evaluation) in rats at a repeated oral dose of up to 2,000 mg/kg body weight per day for 90 days. This dose corresponds to nearly fifty times (**50X**) the human equivalent dose of 500 mg per day (5). Even at the highest dose, there was no observable effect (NOEL) from NEM®, much less an observable adverse effect (NOAEL). Following the completion of the studies, this information was submitted to an independent expert panel comprised of toxicologists, pharmacologists, & medical doctors to evaluate the overall safety of NEM® for human consumption. This evaluation includes historical use, safety studies, and adverse event data from human clinical trials with NEM® (6; 7). The expert panel concluded that NEM® qualified as Generally Recognized As Safe (GRAS) with an Allowable Daily Intake of up to 14 grams per day. In light of the substantial scientific evidence, it's clear that NEM® has an excellent safety profile and is safe for human consumption either in food products or as a dietary supplement.



For more information on ESM Technologies, please visit [www.ESMIngredients.com](http://www.ESMIngredients.com) or call 866.804.8034.



## References

1. *Effect of 1 $\alpha$ -hydroxyvitamin D3 and egg-shell calcium on bone metabolism in ovariectomized osteoporotic model rats.* Hirasawa T, Omi N, and Ezawa I. 2001, J Bone Miner Metab, Vol. 19, pp. 84-88.
2. *Eggshell powder, a comparable or better source of calcium than purified calcium carbonate: piglet studies.* Schaafsma A, and Beelen GM. 1999, J Sci Food Agric, Vol. 79, pp. 1596-1600.
3. *Short-term Effects of A Chicken Egg Shell Powder Enriched Dairy-based Product on Bone Mineral Density in Persons With Osteoporosis or Osteopenia.* Schaafsma A, and Pakan I. 12, 1999, Bratisl Lek Listy, Vol. 100, pp. 651-656.
4. **Association of American Feed Control Officials.** Section 9 - Animal Products. *AAFCO Official Publication.* s.l. : Association of American Feed Control Officials, 2009.
5. *Guidance for Industry: Estimating the Maximum Safe Starting Dose in Initial Clinical Trials for Therapeutics in Adult Healthy Volunteers.* Center for Drug Evaluation & Research, U.S. Food & Drug Administration. Rockville, MD : U.S. Dept. of Health & Human Services, 2005.
6. *Eggshell membrane: A possible new natural therapeutic for joint and connective tissue disorders. Results from two open-label human clinical studies.* Ruff KJ, DeVore DP, Leu MD, and Robinson MA. 2009, Clin Interv Aging, Vol. 4, pp. 235-240.
7. *Eggshell membrane in the treatment of pain and stiffness from osteoarthritis of the knee: a randomized, multicenter, double-blind, placebo-controlled clinical study.* Ruff KJ, Winkler A, Jackson RW, DeVore DP, and Ritz BW. 2009, Clin Rheumatol, Vol. 28, pp. 907-914.