Statement of the International Food Additives Council and the European Chemical Industry Council on Jin et al., "High Dietary Inorganic Phosphate Increases Lung Tumorigenesis and Alters Akt Signaling," published in *American Journal of Respiratory Critical Care Medicine,* January 2009

The International Food Additives Council (IFAC) and the European Chemical Industry Council (CEFIC)[1] offer the following comments regarding a study, "High Dietary Inorganic Phosphate Increases Lung Tumorigenesis and Alters Akt Signaling," by Jin et al, published in the *American Journal of Respiratory and Critical Care Medicine*, January, 2009.[2] The study reports that high consumption of dietary inorganic phosphate increased lung tumorigenesis in lung cancer susceptible mice. Researchers stated that they fed a "normal" amount of inorganic phosphate to one group and a "high" amount of inorganic phosphate to a second group of K-*ras* ^{LA1} mice, a genetically modified strain of mice highly susceptible to lung cancer. Researchers found that both groups of mice developed lung cancer, but those fed high amounts of phosphate (Pi) developed more tumors. Through further investigation, researchers noted that the Akt signaling pathway, a common signaling pathway in cancer leading to altered protein translation and increased cell proliferation, was altered due to the increased phosphate intake, leading to more tumors in the mice. The authors conclude, "our results clearly demonstrated that increased uptake of dietary Pi stimulated pulmonary tumorigenesis parallel with Akt-mediated signals and suggest that careful regulation of dietary consumption of Pi may be critical for lung cancer prevention as well as treatment."

Inorganic phosphates have a long history of safe use in food. For decades numerous toxicology studies have examined the safety of phosphate based food additives. These toxicological studies have been reviewed by several panels of internationally recognized experts and form the science upon which worldwide regulatory approval has been granted to phosphate based food additives.

The study by Jin et al is very limited and its results are contrary to numerous toxicological studies, using acute and chronic exposures, which clearly demonstrate the safety of phosphate based food additives. Further, it is not scientifically credible to think that a minor alteration of the diet alone, such as reducing phosphate consumption, would be effective in preventing such a profound disease as lung cancer, which is known to be multifactoral. In fact, the American Lung Association's 2008 review on lung cancer reports that smoking is the number one cause of human lung cancer (80-90%) with radon ranking second (9-14%).[3]

The animals used in this study were genetically modified animals that are not representative of the normal mouse population, or the human population. A key gene involved in the formulation of lung tumors has been manipulated so that the mice examined in this study are more susceptible to developing lung tumors. Both groups of mice, even the low dose group, developed tumors. However, the group fed more

phosphate developed more tumors. The conclusion, however, that increased uptake of dietary phosphate stimulated tumorigenesis is misleading and ambiguous; the only conclusion that the data supports is that increased phosphate consumption can lead to increased tumors in mice with pre-existing propensity to develop tumors. The findings cannot be directly extrapolated to humans, nor can they be used for human risk assessment.. Although the authors show that the Akt signaling pathway is altered via phosphate consumption, possibly responsible for increased tumor formation, it is currently unclear if this pathway is regulated in the same manner in humans as in mice.

Additionally, the authors assume that feeding the same percentage of phosphate in the diet to mice and humans would result in the intake of the same percent of body weight in phosphate for mice and humans. However, mice consume at least six to eight times the amount of food expressed as a percent body weight as humans.[4] Thus, although the percentage of phosphates consumed may be representative of the percentage of phosphate humans ingest from food, the total amount of phosphates per unit of body weight ingested is in fact much higher in mice than it would be in humans. This differential is equivalent to 30-times more phosphate ingested by the low dose level in this study than is estimated to be the maximum human phosphate consumption level from all sources. The high dose used in this experimental study with mice would provide at commensurate level of 60-times higher than the maximum human dietary exposure estimate. Further, as the experimental animals used in this study were 5- and 6-week old animals and not fully grown, their feed consumption would be expected to be even higher than the adult mouse values used above, and hence would result in an even greater differential from estimated human consumption. Thus, the significant increase of the phosphate concentration in the serum, which reportedly resulted in a carcinogenic effect in the study in mice, would not likely be obtained (even with supplementation) in humans.[5]

Further, the researchers do not specify which type of phosphate the mice were fed nor was evidence provided as to its source and level of impurities which might result in a confounding effect in the results obtained. In addition, the cation associated with the phosphate salt (e.g., calcium, sodium, potassium, etc.) could have some effects on the mice; the cation used was not stated specifically in this report. During the study, calcium (Ca^{2+}) serum levels (measured presumably to determine effects due to calcium loading which would have occurred from use of a calcium phosphate salt as the test agent) remained unchanged. At the same time, parathyroid hormone (PTH) levels were elevated. The authors concluded that the increased endogenous PTH levels were necessary for calcium regulation and maintenance of a homeostatic state in the body. The authors went on to state that "evidence suggests that PTH might be a cancer promoter." Of significance to the findings and conclusions in this study, the authors stated that "increased PTH levels may be responsible for increased lung tumorigenesis found in our study." Thus, recognizing this potentially significant confounding factor, drawing conclusions from this study about phosphates in general or in particular (as opposed to the cation apparently used as part of the test agent) is not possible.

The study authors state that surveys conducted in various countries indicate that intake of phosphates has increased steadily as Pi-containing foods increased by 17% in the decade

prior to 1993 and also that the use of phosphate as a food additive is continuing to increase. This information is not supported by the reference provided and is incorrect. The reference,[6] cited to support this data, only mentions the consumption of phosphates in the American diet; no data is given for other countries. In the United States, since 1980, the International Food Additives Council (IFAC) has conducted surveys regarding phosphorus added to food which have consistently confirmed that less than 10% of the Maximum Tolerable Daily Intake (MTDI) for phosphorus, set by the Joint FAO/WHO Expert Committee on Food Additives, comes from food additive sources. Additionally, IFAC data shows no significant change in phosphate intake during this time.[7] Further, it should be noted that phosphorous is an essential nutrient, critically important for every cell of the body, as it is involved in cell signaling, bone formation, and acid-base regulation. There are certain populations in the US who do not consume enough phosphorous on a daily basis. Estimates of usual intakes of phosphorus derived by the Institute of Medicine show a significant proportion of the US population may not be meeting the Daily Recommended Intake levels for phosphorus.[8] Further, an examination of the National Health and Nutrition Examination Surveys (NHANES) 1999-2000 and 2000-2001 combined revealed that at least 10% of men 19-70 years of age fell below the RDI for phosphorus and at least 25% of women aged 31-70 did not achieve the RDI for phosphorus.[9-10]

In conclusion, one must be extremely careful about extrapolating the conclusions of this study to inorganic phosphates in general or any one phosphate in particular. One can only conclude that the feeding of genetically modified mice susceptible to lung tumors a diet of 1 percent of an inorganic salt of unknown identity increased lung tumorigenesis. No direct comparisons of humans can be made, as mice consume a much greater percentage of food per body weight than humans and the mice were genetically susceptible to lung cancer.

International Food Additives Council and European Chemical Industry Council, January 2009

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