EPA REGISTRATION DIVISION COMPANY NOTICE OF FILING FOR PESTICIDE PETITIONS PUBLISHED IN THE FEDERAL REGISTER

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INSTRUCTIONS: **Please utilize this outline in preparing the pesticide petition. In cases where the outline element does not apply, please insert "NA-Remove" and maintain the outline. Please do not change the margins, font, or format in your pesticide petition. Simply replace the instructions that appear in green, i.e., "[insert company name]," with the information specific to your action.**

TEMPLATE:

[Stratacor, Inc.]

[Insert petition number]

EPA has received a pesticide petition ([insert petition number]) from [RegGuide on behalf of Stratacor, Inc.], [6 Christopher Court, Novato, CA 94947] requesting, pursuant to section 408(d) of the Federal Food, Drug, and Cosmetic Act (FFDCA), 21 U.S.C. 346a(d), to amend 40 CFR part 180

To establish an exemption from the requirement of a tolerance for Choline Chloride, CAS No. 67-48-1 under 40 CFR 180.930 when used as an inert ingredient for use as an adjuvant in pesticide formulations applied to livestock. EPA has determined that the petition contains data or information regarding the elements set forth in section 408 (d)(2) of FDDCA; however, EPA has not fully evaluated the sufficiency of the submitted data at this time or whether the data supports granting of the petition. Additional data may be needed before EPA rules on the petition.

A. Residue Chemistry

1. *Plant metabolism.* [NA - Remove.]

2. *Analytical method.* [Because this petition is a request for an exemption from the requirement of a tolerance without numerical limitations, no analytical method is required.]

3. *Magnitude of residues.* [No data are available on the magnitude of residue when applied dermally to animals. However, residues of choline chloride are expected to be negligible due to its high solubility and its rapid biodegradability. Moreover, any exposure to choline chloride residues are not expected to pose a risk. No toxic endpoints have been identified and there has been a long history of significant human dietary and endogenous exposure without documented incident. The constituents of choline chloride

are known to be readily metabolized.]

B. Toxicological Profile

1. *Acute toxicity.* [Choline chloride is not considered to be acutely toxic based on the available data. It is classified into toxicity category III for acute oral toxicity and into toxicity category IV for dermal and inhalation toxicity and dermal and eye irritation. It is not considered to be a dermal sensitizer.]

2. *Genotoxicty.* [Choline chloride does not show a mutagenic, clastogenic or DNA damaging potential when tested *in vitro*; furthermore, it has no structural alerts. There is therefore no indication of a genotoxic potential *in vivo*.]

3. *Reproductive and developmental toxicity.* [No developmental toxic effects were observed in mice after oral doses of 1250 mg/kg/day on gestation days 1 to 18. Doses above the levels recommended currently (4160 mg/kg/day and higher) and associated with maternal toxicity did produce developmental toxic effects, but these were secondary to the maternal toxicity at the excessive doses used. Choline chloride does not produce any significant developmental toxicity in the mouse. It should be noted that the lowest dose used in this study was above the currently recommended top dose for non-toxic compounds, i.e. 1 g/kg/day. The absence of any significant developmental toxicity effects at this level supports the view that the compound does not have any significant developmental toxicity. The top dose used in this study was 20 times that recommended in the current OECD test guideline.]

4. *Subchronic toxicity.* [In a 21-day oral toxicity study in the rat, the no-observed-adverse-effect-level (NOAEL) was determined to be 1,000 mg/kg/day, the highest does tested. In a 28-day oral toxicity study in the mouse, the NOAEL was determined to be 200 mg/kg/day, the highest dose tested.]

5. *Chronic toxicity.* [In a limited 72-week feeding study, Fischer 344 rats were given approximately 500 mg/kg/day of choline chloride via feed, no significant differences between control groups and treated animals were observed with respect to survival rates, body weights, and relative liver weights. The NOAEL was determined to be 500 mg/kg/day.]

6. *Animal metabolism.* [All species are capable of synthesizing choline in the liver by the methylation of ethanolamine, which uses methyl groups from S-adenosyl methionine. The process occurs in two steps, each involving a different methyl transferase.]

7. *Metabolite toxicology*. [There are no metabolites of toxicological concern.]

8. *Endocrine disruption*. [Choline chloride is not a known endocrine disruptor nor are its metabolites related to any class of known endocrine disruptors.]

C. Aggregate Exposure

1. *Dietary exposure.* [Choline is a dietary component and found in foods as free choline and as esterified forms such as phosphocholine, glycerophosphocholine, sphingomyeline and phosphatidylcholine. It functions as a precursor for acetylcholine, phospholipids and the methyl donor betaine and is important for the structural integrity of cell membranes, methyl metabolism, cholinergic neurotransmission, transmembrane signaling and lipid and cholesterol transport and metabolism.]

i. *Food.* [Dietary exposure to choline chloride when used in products applied to livestock as an inert ingredient is expected to be negligible. It is typically used at low concentrations, it biodegrades rapidly once applied and dissociates readily when in contact with water, making its persistence as a residue even more unlikely. This use of choline chloride is not likely to contribute significantly to human dietary exposure. Humans are already exposed to choline chloride in the diet. It is produced endogenously and it is found naturally in foods in the human diet.]

ii. *Drinking water.* [No significant residues of choline chloride are expected in drinking water when products are used according to label instructions. It is applied terrestrially as a plant growth regulator and as an inert in pesticide formulations to growing crops. Applications to livestock would not be expected to add significantly to drinking water residues. Choline chloride is very soluble in water and it biodegrades rapidly once applied. Both choline and chloride, the constituents of choline chloride, are ubiquitous in the environment and there is a long history of incidental exposure through drinking water.]

2. *Non-dietary exposure.* [Based on the physical and chemical properties of choline chloride, risk from inhalation exposure would be minimal. Exposure via the dermal route may occur for those individuals applying the product, but it is not expected to be readily absorbed through skin (<1% dermal absorption). Due to the rapid degradation of the compound and the natural presence of choline and chloride in the environment, exposure from use of choline chloride as an inert ingredient in products applied to livestock is not expected to increase the aggregate exposure.]

D. Cumulative Effects

[Choline chloride has not been found to share a common mechanism of toxicity with any other substances and does not appear to produce a toxic metabolite produced by other substances.]

E. Safety Determination

1. *U.S. population.* [Evidence from animal studies and from human exposure indicates that choline chloride has low toxicity, is not mutagenic and has no developmental toxicity. This is not unexpected in view of its presence in the diet and its production in metabolic processes in the body. It fulfills key roles in nerve transmission, cell membrane integrity and lipid metabolism. Only limited animal data are available on

effects on fertility, but the normal exposure of humans to appreciable amounts of choline chloride both from the diet and formed from normal metabolic processes would argue against it having any significant adverse effects on fertility. This is supported by the fact that it has been widely used as an animal feed additive for decades with no apparent adverse effects being noted.]

2. *Infants and children*. [Choline is a natural component of a variety of commonly consumed foods and has been added to infant formula as a dietary supplement for decades. It is also made endogenously in the human body. Choline chloride has been used as a widespread nutrient in animal feed since the 1930's without adverse effects reported on fertility or teratogenicity. Although one study in mice did show developmental effects, they were only seen at very high doses (≥4,160 mg/kg/day) and only in the presence of maternal toxicity. There were no observed adverse effects for both mothers and pups exposed to 1,250 mg/kg/day. Evidence has shown that choline has beneficial properties in regards to proper growth and development and neurological function. Exposure to choline chloride is not expected to significantly increase from pre-existing levels found in commonly eaten foods. Residues from use on livestock is expected to be insignificant. It is typically used at low concentrations as an inert ingredient, biodegrades rapidly once applied and dissociates readily when in contact with water making its persistence as a residue unlikely.]

F. International Tolerances

[The Codex Alimentarius has not established a maximum residue limit (MRL) for choline chloride.]