ORIGINAL SUBMISSION

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A professional corporation

GRN 000585

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GRAS Notification Program
Office of Food Additive Safety
Food and Drug Administration
5100 Paint Branch Parkway
College Park, MD 20740

Re: GRAS Notice for use of 1-methylcyclopropene "1-MCP"

To the US FDA:

Claim of Exemption

For the reasons set forth in this document, Cellresin Technologies, LLC, 1789 Buerkle Circle, St. Paul, MN 55110-5254, believes its proposed use of 1-methylcyclopropene ("1-MCP") in food packaging is exempt from regulation as a food additive under Section 409 of the federal Food, Drug and Cosmetic Act, 21 U.S.C. Sec. 348, because the proposed use is Generally Recognized As Safe for use as an ethylene inhibitor in food packaging substrates for packaging specific fruits and vegetables.

The basis of Cellresin's conclusion is scientific procedures, specifically, (1) that the expected dietary exposure to 1-MCP from the proposed use will not exceed 0.5 parts per billion, and (2) that the publicly available information about the safety of 1-MCP establishes that these exposures will be both safe and generally recognized as safe. Moreover, the expected potential levels of exposure to impurities in 1-MCP are so low as to be generally recognized as of no safety concern either.

The data and information that are the basis of Cellresin's conclusion that its proposed use of 1-MCP is GRAS are available for FDA's review and copying at reasonable times at the company's address stated above, or will be sent to FDA upon request.

Identity of notified substance

1-methylcyclopropene ("1-MCP").

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Self-limiting levels of use

The technology involves incorporation of an ethylene inhibitor, 1-MCP, into food packaging substrates including flexible films, lidding film, labels, inserts, and paper and paperboard.[1]

The substance 1-MCP is a well-known inhibitor of ethylene. Ethylene occurs naturally in most fruits, vegetables, flowers and plants, and causes them to grow and mature, but also, eventually, to over-ripen and spoil.

When deployed in the packaging using the Cellresin technology, the 1-MCP binds to the ethylene receptor sites and, essentially, acts as a switch to temporarily turn the sites off, thereby blocking maturation. The plant becomes dormant, and it doesn't ripen.

1-MCP is already used as a maturation-retarding fumigant for fruits and vegetables, and is regulated as such by the US Environmental Protection Agency.

Cellresin has designed the packaging to precisely and consistently deliver 1-MCP at the mid – ppb (v/v) range in the package headspace. Adjustments to modulate 1-MCP release are easily accomplished by changes in the physical package structure and the amount of 1-MCP contained in the package structure. Moisture released from the respiring plant triggers 1-MCP release from the package structure. Released 1-MCP binds to the receptor sites preventing exogenous ethylene from binding to the sites.

Twelve to twenty-four hours of exposure to 1-MCP is sufficient for treatment, although additional exposure time is not detrimental. When 1-MCP is removed from the environment around the plant, the plant starts growing new receptor sites, maturation resumes at first slowly as new sites propagate, and the plant ripens or decays progressively but at a slower than normal rate.

Basis of GRAS determination

Cellresin's conclusion that its proposed use of 1-MCP is GRAS has two independent bases, either one of which would be sufficient by itself to establish GRAS status. There is both a clear record of safety within publicly available information and very low expected levels of exposure.

The record of publicly available data, and analyses of that data by other government bodies in the US and elsewhere, establishes both that 1-MCP is safe when used as Cellresin intends, and that such safety is widely and publicly known and accepted. Moreover, even if that record did not exist, the very low levels of exposure to 1-MCP and its impurities that are expected as a result of the intended use are below levels widely recognized as safe, specifically the FDA's Threshold of Regulation of 0.5 parts per

[1] Cellresin assumes all workers handling 1-MCP for this application will utilize appropriate safety equipment.

billion in the human diet and for carcinogenic impurities below 50 parts per trillion in the human diet.

The thorough examinations of the safety of 1-MCP and its impurities that have already been undertaken by the US Environmental Protection Agency and the European Food Safety Authority confirm not only the safety of the expected exposures involved here, but are themselves evidence of general recognition.

Cellresin does not believe that its proposed use of 1-MCP will result in dietary exposures in excess of 0.5 ppb of 1-MCP. This calculation is performed as follows.

We begin with the following commonly accepted assumptions:

- The per capita consumption of tomatoes is 37 kg (based on USDA estimates) per year [http://www.ers.usda.gov/data-products/ag-and-food-statistics-charting-the-essentials/food-availability-and-consumption.aspx[2]]

- The per capita consumption of fruit is 100 kg (based on USDA estimates) per year [http://www.ers.usda.gov/topics/crops/vegetables-pulses.aspx]

- The average American consumes 3000 g of food per day (FDA assumption) [http://www.fda.gov/Food/GuidanceRegulation/GuidanceDocumentsRegulatoryInformation/IngredientsAdditivesGRASPackaging/ucm081818.htm#iie]

- The 1-MCP residual in treated foods is 4 ppb.[3]

Therefore the dietary concentration (DC) would be 0.5 ppb, calculated as follows:

$$DC = \frac{137{,}000\,g\ fruits\&veg}{person \cdot year} \cdot \frac{1\ person}{3000 grams} \cdot \frac{1\ year}{365\ days} \cdot 4\ ppb$$
$$= 0.5\ ppb$$

However, as noted this represents an over-estimate, for at least each of the following reasons:

- Cellresin's technology, embedded in packaging materials, will substitute for those uses of 1-MCP as a fumigant, as packaging containing the

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[2] Crop consumption data represents product availability. Actual consumption rates are lower and reflect processing, paring and distribution losses.

[3] For purposes of this initial, intentionally exaggerated calculation, we begin with the figure that EPA derived, 0.004 ppm, or 4 ppb, which was based on residue found in apples when an exaggerated treatment rate of 1,200 ppb was employed, rather than the intended 1,000 ppb for that particular proposed use. (67 Fed Reg 48796, July 26, 2002).

substance will be applied to fruits or vegetables after harvesting and instead of storage in fumigated facilities. Thus to some extent Cellresin's technology will substitute for other exposures to 1-MCP, and will not add at all to cumulative exposure to 1-MCP of fruits and vegetables, but will simply deliver it via other means.

- Cellresin is unlikely to achieve 100% market share for any of the intended fruits and vegetables, which do not include all fruits and vegetables consumed in the US, yet our calculation above assumes 100% of fruits and vegetables will be treated.

- Many tomato and other fruit and vegetable products are cooked before consumption. Residual 1-MCP would reasonably be expected to be driven out in these products.

When a dietary exposure calculation that incorporates several significant over-estimations nevertheless yields a result indicating dietary exposure from the intended use could at most be at the level of 0.5 ppb, clearly the use will be widely considered safe and generally recognized as safe on that basis alone. This is because the exposure level of 0.5 ppb to non-carcinogens was derived by the FDA based on a thorough examination of the levels at which substances were known to be toxic, and further built in a safety factor. 58 FR 52722, October 12, 1993; 60 FR 36583, July 17, 1995. The level is widely understood, and accepted, as an indicator of safe exposure to non-carcinogens.

Moreover, although two impurities from the manufacture of 1-MCP, 1-chloro-2-methylpropene (1-CMP) and 3-chloro-2-methylpropene (3-CMP), are known carcinogens[4], the levels of exposure to them, if any residues remain, can be expected to be well below any levels presenting safety issues. These impurities were part of the safety evaluation performed by the EPA during the pesticide registration process. Specifically, impurities were reported to be 0.017% of the 1-MCP. Therefore, the total impurities would not exceed:

$$DC = 0.5\ ppb\ x\ 0.00017 = 8.5\ x\ 10^{-5}\ ppb$$ or 85 ppq.

This quantity is approximately 6,000 times lower than the 0.5 ppb level, and well below the 50 parts per trillion level that FDA commonly applies as a risk assessment target for carcinogenic impurities in food contact materials. Clearly, such an exposure is generally recognized as safe on that basis alone.

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[4] These impurities have been the subject of the National Toxicology Program (NTP) carcinogenicity studies and are the focus for the safety assessment. They have been the subject of International Agency for Research on Cancer reviews (IARC, 1995) which concluded that both compounds are mutagenic and 1-chloro-2-methylpropene was classified as possibly carcinogenic to humans (Group 2B) and 3-chloro-2-methylpropene was not classifiable as to its carcinogenicity to humans (Group 3).[Application of the margin of exposure (MoE) approach to substances in food that are genotoxic and carcinogenic – Example: 1-Methylcyclopropene and its impurities (1-chloro-2-methylpropene and 3-chloro-2-methylpropene), Food and Chemical Toxicology 48 (2010) S81–S88].

In addition to the GRAS status of this use being established based on generalized principles of what constitutes safe levels of exposure, it is possible to conclude that this use is GRAS based on scientific procedures. Specifically, the concentrations of 1-MCP exist at trivial levels substantially below levels at which 1-MCP is known to elicit a toxicological response.

There is a great deal of safety information about 1-MCP that would be relevant to an evaluation of the safety of the proposed use by relevant experts or by FDA.

The record of safety for 1-MCP is well-established, and encompasses human and animal exposure as well as the fate in the natural environment. Because it has already been examined and cleared for use by the EPA and in other nations, a great deal is already known about its safety.

In the course of explaining its Final Rule establishing the exemption from the requirement of a tolerance for 1-MCP, the EPA considered the safety of possible dietary exposures from the proposed pesticide use with fresh fruits and vegetables. 67 FR 48796. The EPA determined that an appropriate potential residue level in apples of 0.004 ppm, coupled with the unrealistic assumption that 100% of the diet contained that level of residue, resulted in an estimated daily intake of 0.0001 mg of 1-MCP per kilogram of body weight. The EPA noted that this level represents "90,000 to 150,000-fold less than the 9-15 mg/kg NOAEL indicated in the 90-day inhalation study."[5]

Key features of the body of safety information on 1-MCP, organized by its source, include:

- US Environmental Protection Agency
  - No human toxicological endpoints identified by EPA.
  - Albino rat oral LD50 was >5000 mg/kg; tox category IV.
  - Albino rabbit dermal LD50 was >2000 mg/kg; tox category III.

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[5] EPA's full discussion of this issue is as follows: "The primary source for human exposure to 1-MCP will be from ingestion of the following raw food commodities and the processed food commodities derived from: apples, melons, tomatoes, pears, avocadoes, mangoes, papayas, kiwifruit, plums, apricots and persimmons. Studies submitted (MRID 456090–02) showed residues in treated apples to be extremely low (average residue was 0.004 ppm using an exaggerated treatment rate of 1,200 parts per billion (ppb) versus the 1,000 ppb proposed label rate). A worst-case scenario (using the 0.004 ppm average residue concentration found in treated apples and assuming that concentration is present in 100% of the diet regardless of crops treated) indicates that a daily diet of 1.5 kg/day could contain 0.006 mg 1-MCP. For the general population (assuming an average body weight of 60 kg), this would represent a daily intake of 0.0001 mg 1-MCP/kg body weight which is 90,000 to 150,000-fold less than the 9-15 mg/kg NOAEL indicated in the 90–day inhalation study. Residues in other treated commodities are expected to be similar or even lower since the highest treatment rate is recommended for apples. Processing would be expected to further lower the residue levels in processed food commodities." 67 FR 48797

- Albino rat (gas exposure) LC50 was >165 ppm; tox category IV.
- 4,100-person hours of 1-MCP exposure have been experienced by humans without any known 1-MCP-induced health related problems being reported.
- 1-MCP is not considered a mutagen by EPA.

- European Food Safety Authority (EFSA)
  - Conclusion regarding the peer review of the pesticide risk assessment of the active substance
  - ADI of 0.0009 mg/kg bw/day
  - Inhalation AOEL is 0.09 mg/kg bw/day
  - Systemic AOEL is 0.009 mg/kg bw/day
  - EFSA Scientific Opinion on Evaluation of the Toxicological Relevance of Pesticide Metabolites for Dietary Risk Assessment
    - Acute Reference Dose (ARfD): 0.07
    - NOAEL (mg/kg bw/d)*: 70
    - Cramer Class: 2

- Canadian Pest Management Regulatory Agency Developmental Toxicity (rodent):
  - Maternal NOAEL 45 mg/kg bw/day, LOAEL 142 mg/kg bw/day;
  - Fetal NOAEL 440 mg/kg bw/day

- Netherlands, 1-MCP Risk Assessment Rat (inhalation): LC50 >2.5 mg/L2

- Food and Agriculture Organization (FAO) of the United Nations:

  - 1-MCP has been reviewed for classification by European Chemicals Bureau (ECB) in November 2006 and January, 2007. ECB has concluded that no health classification is needed for 1-MCP up to a maximum concentration of 5.0% in alpha-cyclodextrin.

Conclusion

Cellresin believes its proposed use of 1-MCP as a component of packaging materials to be used at wholesale and during distribution is as a "processing aid" as that term is defined by the FDA's regulation. The regulation defining "processing aid", 21 CFR 70.3(o)(24), provides that it is a "[S]ubstance[s] used as manufacturing aid[s] to enhance the appeal or utility of a food or food component, including clarifying agents, clouding agents, catalysts, flocculents, filter aids, and crystallization inhibitors, etc." As used here, 1-MCP is intended to enhance the utility of foods by extending their shelf life.

Importantly, when 1-MCP is used in this manner, when consumers consume the food, 1-MCP is no longer present in significant amounts (if any), and will no longer have any functional effect on the food. Once the packaging is no longer present, the 1-MCP is

removed as well, and the food's receptors for ethylene are no longer blocked and can resume having their natural effect on the food. As a processing aid meeting those conditions – not present at significant amounts and no longer having a functional effect on the food -- 1-MCP would not need to be listed as an ingredient in the ingredient list element of packaged food labels.

When 1-MCP is used as proposed by Cellresin as a component of packaging materials that remain with the food all the way through consumer use, an important distinction will need to be made for regulatory purposes between scenarios in which the 1-MCP no longer continues to have effect, and scenarios in which it does continue to have such effect.

If it no longer has any effect the use is clearly as a "processing aid," and more specifically, one that no longer is present in significant amounts and no longer has any technical effect in the food.

If the 1-MCP remains in the packaging to the point of consumer use, and continues to have effect through and including the moment the package is opened by the consumer, only then might 1-MCP potentially be considered for regulatory purposes to be a chemical preservative whose presence would need to be disclosed in the food's ingredients list, if there is one (some fresh foods are exempt from having to list ingredients when displayed at retail). 21 CFR 101.100(c).

For the above stated reasons, Cellresin believes its proposed use of 1-MCP is GRAS. Please let us know if the FDA has any questions about Cellresin's conclusions.

[redacted]

Eric F. Greenberg

List of References

1. Final Rule: 1-Methylcyclopropene; Exemption from the Requirement of a Tolerance, 67 FR 48796, July 26, 2002.

2. USDA ERS - Food Availability and Consumption

3. USDA ERS - Vegetables & Pulses

4. Ingredients, Additives, GRAS & Packaging _ Guidance for Industry_ Preparation of Premarket Submissions for Food Contact Substances_ Chemistry Recommendations

5. US Environmental Protection Agency, Office of Pesticide Programs, Biopesticide Registration Action Document, 1- Methylcyclopropene (PC Code 224459).

6. Scientific Opinion on Evaluation of the Toxicological Relevance of Pesticide Metabolites for Dietary Risk Assessment, EFSA Panel on Plant Protection Products and their Residues (PPR), EFSA Journal 2012;10(07):2799.

7. EFSA Scientific Report (2005) 30, 1-46, Conclusion on the peer review of 1-methylcyclopropene: Conclusion regarding the peer review of the pesticide risk assessment of the active substance 1-methylcyclopropene finalized: 2 May 2005.

8. Canadian Pest Management Regulatory Agency, Regulatory Note REG2004-07, 1-methylcyclopropene

9. Netherlands, 1-MCP Risk Assessment.

10. FAO Specifications and Evaluations for Agricultural Pesticides, 1-Methylcyclopropene.

SUBMISSION END