

# U.S. FDA Regulatory Approval of Ozone as an Antimicrobial Agent – What Is Allowed and What Needs to Be Understood

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## Abstract

In response to a Food Additive Petition submitted during August 2000, the U.S. Food and Drug Administration formally approved the use of ozone as an *Antimicrobial Agent for the Treatment, Storage and Processing of Foods in Gas and Aqueous Phases*. The approval was published on June 26, 2001 (FDA, 2001).

Whenever a governmental approval is published, it is usually replete with references to regulations published earlier, as well as numerous conditions. The purpose of this paper is to discuss the FDA approval for ozone and to describe the specific conditions under which ozone may be used when it comes into contact with foods.

## Background

Prior to mid-1997, there were few or no commercial applications of ozone in food processing or treatment in the United States. The reason was entirely regulatory in nature, and had nothing at all to do with the technology of ozone. The regulatory control over the use of ozone is the Federal Food, Drug and Cosmetic Act, passed in the late 1950s and under which the Food and Drug Administration is required to operate. The Act defines any material that comes in contact with food to be a “food additive”, which must be approved by the FDA prior to use.

Attempts to gain U.S. Food and Drug Administration approval for the use of ozone in contact with foodstuffs have been long and arduous. In the early 1980s, the International Bottled Water Association petitioned the FDA to affirm that the application of ozone to disinfect bottled water under specified conditions is GRAS. The conditions included a *maximum* dosage of ozone of 0.4 mg/L over 4 minutes contact time, and that the water to be treated must meet the potable water requirements of the U.S. Environmental Protecting Agency. The FDA approved IBWA’s petition for ozone in bottled water, and in 1982 published in the *Code of Federal Regulations* a formal FDA

regulation affirming GRAS Status for use of ozone (FDA, 1982). Later, the FDA also approved the use of ozone as a *sanitizing agent* for bottled water treatment lines, under a similar GRAS petition.

Unfortunately, the GRAS approval for ozone disinfection of bottled water in 1982 contained the statement [21 C.F.R. 184.1(b)(2)] “All other food additive applications for ozone must be the subject of appropriate Food Additive Petitions.” This statement effectively mandates the filing of Food Additive Petitions in order to gain FDA approval for other uses of ozone in direct contact with foods.

Over the intervening years, several food additive petitions were submitted to the FDA to approve applications of ozone in contact with specific foods – poultry in particular. However, each of these petitions was withdrawn (without prejudice) for one reason or another.

### **The 1997 EPRI GRAS Declaration**

In June 1997, an Expert Panel of Food Scientists convened by the EPRI (EPRI, 1997) concluded the following:

**“The available information supports the safety of ozone when used as a food disinfectant or sanitizer, and further, that the available information supports a GRAS classification of ozone as a disinfectant or sanitizer for foods when used at levels and by methods of application consistent with good manufacturing practices (authors’ underscoring for emphasis).”**

In April, 1997, FDA published a notice in which the agency proposed that any organization willing to affirm a substance as GRAS when coming into contact with foods is free to utilize that substance, provided the organization is willing to accept responsibility for its actions (FDA, 1997). In other words, since affirming a substance to be GRAS does *not* imply formal regulatory approval by the FDA, it is up to the affirming organization, or any organization intending to apply ozone in contact with foods, to understand what ozone is all about, how it is generated and applied, in what exposure levels, and what the consequences of its use are in terms of providing specific benefits. Included in this caution is knowing what disadvantages might accrue from the over-application of ozone to the particular food(s) being treated.

### **Post-1997 Regulatory Developments with Ozone in the USA**

EPRI’s GRAS affirmation gave a clear green light to food processors to test and use ozone for a variety of food processing applications. Nevertheless the lack of *specific regulatory approval for ozone* published in the *Federal Register* continued to disturb many food processors and continued to slow the broader acceptance of ozone in the food industry.

FDA recognized this, and also recognized that most applications for ozone in food treatment involve Antimicrobial properties of ozone. However, the statement in the 1982 GRAS approval for ozone in bottled water disinfection which says, “All other food applications for ozone must be the subject of appropriate food additive petition(s)”, continued to impede the development of ozone for food processing applications.

Consequently, in mid-1999, the FDA suggested to the EPRI that a single FAP which provides FDA with specific data showing the Antimicrobial properties of ozone in a number of food processing applications could be reviewed quickly, and if approved, would overcome the requirement of the 1982 GRAS regulation regarding “other food uses for ozone”. EPRI agreed with this FAP approach and, with considerable support from several interested food processing organizations, developed such a FAP and formally filed it with the FDA in August 2000 (EPRI, 2000). FDA approval of this FAP was published June 26, 2001 (FDA, 2001).

Details of the Food Additive Petition have been discussed by Rice and Graham (2000a, 2000b), and Rice et al. (2001). The entire FAP is available in the CD-Rom disk containing the Proceedings of the IOA/PAG 2001 Annual Conference held in Newport Beach, California, May 5-9, 2001, and is available by contacting the International Ozone Association, Pan American Group, 31 Strawberry Hill Avenue, Stamford, CT 06902-2608, USA (tel: 203-348-3542; fax: 203-967-4845; mistok@int-ozone-assoc.org).

Formal regulatory approval by the FDA for the use of ozone as an Antimicrobial Agent in direct contact with foods clears away the regulatory hurdle that has impeded application of ozone to foods in the United States, and will reassure food processing firms wishing to improve the qualities of their products by approaches involving ozone.

### **The Regulatory Approval of Ozone**

The specific language contained in FDA (2001) is as follows, with certain phrases highlighted by the current authors in bold-italic, for discussion and explanation in the balance of this paper:

#### **“21 CFR PART 173 -- SECONDARY DIRECT FOOD ADDITIVES PERMITTED IN FOOD FOR HUMAN CONSUMPTION**

1. The authority citation for 21 CFR part 173 continues to read as follows,

**Authority:** 21 U.S.C. 321, 342, 348.

2. Section 173.368 is added to subpart D to read as follows:

#### **§173.368 Ozone.**

Ozone (CAS Reg. No. 10028-15-6) may be safely used in the treatment, storage, and processing of foods, including meat and poultry (***unless such use is precluded by standards of identity in 9 CFR part 319***), in accordance with the following prescribed conditions:

(a) The additive is an unstable, colorless gas with a pungent, characteristic odor, which occurs freely in nature. It is produced commercially by passing electrical discharges or ionizing radiation through air or oxygen.

(b) The additive is ***used as an Antimicrobial agent as defined in 170.3(o)(2) of this chapter.***

(c) The additive *meets the specifications for ozone in the Food Chemicals Codex, 4th ed. (1996), p. 277*, which is incorporated by reference. The Director of the Office of the Federal Register approves this incorporation by reference in accordance with 5 U.S.C. 552(a) and 1 CFR part 51. Copies are available from the National Academy Press, 2101 Constitution Ave. NW., Washington, DC 20055, or may be examined at the Office of Premarket Approval (HFS-200), Center for Food Safety and Applied Nutrition, Food and Drug Administration, 200 C St. SW., Washington, DC, and the Office of the Federal Register, 800 North Capitol St. NW., suite 700, Washington, DC.

(d) The additive *is used in contact with food*, including meat and poultry (unless such use is precluded by standards of identity in 9 CFR part 319) in the gaseous or aqueous phase *in accordance with current industry standards of good manufacturing practice*.

(e) When used on raw agricultural commodities, *the use is consistent with section 201(q)(1)(B)(i) of the Federal Food, Drug, and Cosmetic Act* (the act) and *not applied for use under section 201(q)(1)(B)(i)(I), (q)(1)(13)(i)(II), or (q)(1)(B)(i)(III) of the act*.

Dated: June 15, 2001.

L. Robert Lake, Director of Regulations and Policy, Center for Food Safety and Applied Nutrition. [FR Doc. 01-15963 Filed 6-25-01; 8:45 am].”

As usually is the case with government regulations, the citations to other regulations can cause some confusion and uncertainty. In the balance of this paper, the authors will address those issues in an attempt to remove those uncertainties.

### **Explanation of Regulatory Language**

1. “Ozone (CAS Reg. No. 10028-15-6) may be safely used in the treatment, storage, and processing of foods, including meat and poultry (*unless such use is precluded by standards of identity in 9 CFR part 319*), in accordance with the following prescribed conditions:”

This requirement goes to the purity of food additives in general. Specific language is as follows:

“A food does not conform to the definition and standard of identity –

- a. If it contains an ingredient for which no provision is made in such definition and standard, unless such ingredient is an incidental additive and introduced at a non-functional and insignificant level as a result of its deliberate and purposeful addition to another ingredient permitted by the terms of the applicable standard and the presence of such incidental additive in unstandardized foods has been exempted from label declaration as provided in Sec. 101.100 of this chapter.
- b. If it fails to contain any one or more of ingredients required by such definition and standard.

- c. If the quantity of any ingredient or component fails to conform to the limitation, if any, prescribed therefor by such definition and standard.”

**Authors’ comment:** Since the only potential constituents of ozone added to foods are nitrogen plus other trace gases present in air/oxygen from which ozone is generated (carbon dioxide, water vapor, argon, etc.), the use of ozone should ***not*** be precluded by standards of identity in 9 CFR part 319.

2. ***“The additive is used as an Antimicrobial agent as defined in 170.3(o)(2) of this chapter”***

Specific definition of the term “Antimicrobial agent” in this section is as follows:

***“Antimicrobial agents”:*** Substances used to preserve food by preventing growth of microorganisms and subsequent spoilage, including fungistats, mold and rope inhibitors, and the effects listed by the National Academy of Sciences/National Research Council under ‘preservatives’.”

**Authors’ comment:** Although the authors have not pursued the “effects listed by the National Academy of Sciences/National Research Council under ‘preservatives’ ”, the FDA definition of “Antimicrobial agents” should be clear and no further discussion is necessary.

3. ***“The additive meets the specifications for ozone in the Food Chemicals Codex, 4th ed. (1996), p. 277, which is incorporated by reference.”***

Pertinent sections under “Ozone” in the Food chemicals Codex are as follows:

**“DESCRIPTION** – Ozone is an unstable gas with a pungent, characteristic odor. It is produced *in situ* from oxygen either by ultraviolet irradiation of air or by passing a high-voltage discharge through air. It is a potent oxidizing agent that decomposes at ambient temperature to molecular oxygen.”

**“Functional Use in Foods** – Antimicrobial and disinfectant for water to be used for direct consumption, such as for ice, or for indirect consumption, such as for water used in the treatment or display of fish, produce, and other perishable foods. It is also used in the treatment of wastewater.”

Also included in the “Ozone” section of the Food Chemicals Codex are directions for identifying ozone by comparison of the spectrophotometric absorbance of Alizarin violet 3 R solutions, one a blank and the other treated with ozone. Additionally, instructions are provided for assaying solutions for ozone using the decolorization of potassium indigo trisulfonate.

4. The additive ***is used in contact with food***, including meat and poultry (unless such use is precluded by standards of identity in 9 CFR part 319) in the gaseous or aqueous phase ***in accordance with current industry standards of good manufacturing practice.***

**Authors' comments:** By “good manufacturing practice” in relation to ozone treatment, the FDA means the exposure of foods to sufficient ozone (concentrations and time of exposure) sufficient to accomplish its intended purpose. In general, but certainly when using ozone, this is *not* a case of “if a little bit of ozone provides X amount of beneficial effect, then a lot more ozone will provide a lot more benefit.” There are two major issues to consider: (a) what minimum exposure to ozone is necessary to provide Antimicrobial benefits on specific foodstuffs? and (b) above what higher level does ozone damage the food to which it is applied or result in off-gassing of ozone sufficient to violate OSHA PEL<sup>1</sup> or STEL<sup>2</sup> and/or EPA environmental limits?

In defining “Antimicrobial agents”, the FDA is showing concern that the agent be added in sufficient amounts/dosages/exposure to accomplish the intended purpose of controlling microorganisms. Clearly, the user of ozone clearly should not want to cavalierly add excessive ozone to the food product. In addition to costing more money for excess ozone, if there is clear damage to the food product (e.g., bleaching of carrots and broccoli, breaking down of coatings on cranberries, etc.), the ultimate consumer surely will shy away from purchase of such over-ozonated products.

Consequently, it is incumbent upon the potential user of ozone to conduct sufficient testing and evaluation of ozone for controlling microorganisms on specific foods under consideration, so as to clearly define the minimum and maximum ozone exposures required by those foods.

5. When used on raw agricultural commodities, *the use is consistent with section 201(q)(1)(B)(i) of the Federal Food, Drug, and Cosmetic Act* (the act) and *not applied for use under section 201(q)(1)(B)(i)(I), (q)(1)(13)(i)(II), or (q)(1)(B)(i)(III) of the act.*

This point goes to the issue of pesticide chemicals coming into contact with foods. In general, many chemicals that control microorganisms on foods are classified as pesticides. The question now becomes “is ozone to be considered a pesticide when used to control microorganisms on foods?”

In 1998, the U.S. Congress enacted the Antimicrobial Regulation Technical Corrections Act. This Act amended the Federal Food, Drug, and Cosmetic Act with respect to defining “pesticide chemicals” as follows:

“Section 201(q) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 321(q)) is amended by striking ‘(q)(1)’ and all that follows through the end of subparagraph (1) and inserting the following:

‘(q)(1)(A) Except as provided in clause (B), the term ‘pesticide chemical’ means any substance that is a pesticide within the meaning of the Federal Insecticide, Fungicide, and Rodenticide Act, including all active and inert ingredients of such pesticide.

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<sup>1</sup> PEL = Permissible Exposure Limit = 0.1 ppm time-weighted average over 8 hrs

<sup>2</sup> STEL = Short Term Exposure Limit = 0.3 ppm, not to exceed 15 min exposure time no more than three times per day

**Authors' comment:** Ozone is not a pesticide within the meaning of the Federal Insecticide, Fungicide, and Rodenticide Act (however ozone generators are regulated by that Act -- see below). Therefore, the provisions of Section 201(q)(1)(A) are not applicable to ozone.

‘(B) In the case of the use, with respect to food, of a substance described in clause (A) to prevent, destroy, repel, or mitigate microorganisms (including bacteria, viruses, fungi, protozoa, algae, and slime), the following applies for purposes of clause (A):

‘(i) The definition in such clause for the term ‘pesticide chemical’ does not include the substance if the substance is applied for such use on food, or the substance is included for such use in water that comes into contact with the food, in the preparing, packing, or holding of the food for commercial purposes.

**Authors' comment:** Since ozone is to be applied for use on food, or is to be included for such use in water that comes into contact with food, in the preparing, packing, or holding of the food for commercial purposes, – then ozone does not fall under the definition of ‘pesticide chemical’. Therefore, the use of ozone applied in the gaseous form or in aqueous solution on raw agricultural commodities is consistent with section 201(q)(1)(B)(i) of the Federal Food, Drug, and Cosmetic Act.

Amendment of Section 201(q)(1)(B)(i) of the Act (by the Antimicrobial Regulation Technical Corrections Act of 1998) continues:

‘(I) The substance is applied in the field (in which raw agricultural commodities are grown).

‘(II) The substance is applied at a treatment facility where the raw agricultural commodities are the only food treated, and the treatment is in a manner that does not change the status of the food as a raw agricultural commodity (including treatment through washing, waxing, fumigating, and packing such commodities in such manner).

‘(III) The substance is applied during the transportation of such commodity between the field and such a treatment facility.

**Authors' comment:** These three sub-paragraphs read on a “pesticide **chemical**”, as defined in the Federal Insecticide, Fungicide, and Rodenticide Act (the FIFRA, which is administered by the U.S. Environmental Protection Agency, not the U.S. FDA). Since ozone is not classified as a “pesticide chemical” under the FIFRA, the above exclusions do not apply to ozone.

### **EPA Requirements for Ozone Under the FIFRA**

When the FIFRA was enacted years ago, EPA was required to regulate any chemical for which a pesticidal claim is made. An example of a claim made by purveyors of ozone equipment that can be considered to be a pesticidal claim is “ozone kills/inactivates microorganisms, fungi, molds, algae, etc.). Pesticides historically are chemicals of commerce that are supplied in bulk in cylinders or containers that are shipped throughout a geographic region. Ozone does not fall into that category

of “chemicals”, in that it is generated and used on-site, is not transported or stored, and quickly dissipates or is self-destroyed during use.

Consequently, in interpreting the requirement of the FIFRA, EPA concluded that ozone is not a “pesticide chemical”, and therefore the gas itself is not to be regulated under the FIFRA. However, ozone generators, while not chemicals, are regulated under the FIFRA as “pesticide devices”, as is equipment that produces ultraviolet radiation.

Under the FIFRA, EPA requires that all pesticide devices (which includes ozone generators) that are made or distributed in the USA, for which a pesticidal claim is made must carry an Establishment Number. This is a number granted by the EPA upon receipt of a properly completed EPA Form 3540-8 (rev. 5/99), “APPLICATION: ESTABLISHMENT REGISTRATION FOR PESTICIDE AND DEVICE PRODUCERS”. The application form can be obtained currently by contacting Ms. Carol L. Buckingham (Room 6118), U.S. Environmental Protection Agency, Agriculture and Ecosystem Division (2225A), 401 M Street, SW, Washington, DC 20460 USA, tel: 202-564-5008.

Once an Establishment Number has been assigned to a manufacturing facility, that number is required to be placed on devices (ozone generators) produced at that facility.

An establishment number does not constitute EPA regulatory approval for the use of ozone on foods (such as that granted by the FDA on June 26, 2001). It merely confirms that the facility that manufactures ozone generating devices has complied with the registration requirements of the FIFRA.

The complete regulations applicable to Pesticide Producing Establishments (including those producing pesticide devices == ozone generators) are available on the Internet at <http://www.access.gpo.gov/nara/cfr/cfr-table-search.html>. Establishment regulations are in title 40, Part 167 of the Code of Federal Regulations.

### **Now that Ozone is Legal For Use on Foods, What Next?**

The primary question asked by those in the agricultural and food industries when confronted with ozone and its approval by the FDA is, “How much ozone do I need to apply to do what I want it to do?” Unhappily, the best and most truthful answer is, “Aside from some guidance from the published literature, the wise approach is for the want-to-be-ozone-user to determine, by actual testing, the appropriate ozone dosage and exposure times for the specific agricultural and/or food product(s) to be treated.”

In the Food Additive Petition submitted to the FDA, there is a table (reproduced below) which reports ozone dosage/exposure data obtained during specific studies. These data are most useful as guidance to the prospective ozone user, with the caution that the user *must* determine the minimum ozone dosage/exposure level necessary to accomplish the intended effect (Good Manufacturing Practice). At the same time, the prospective user *should* determine the maximum ozone dosage/exposure level that will cause damage to the agricultural or food product being treated. If ozone is evaluated in this manner for each potential application, the user will have a comfortable operating range of ozone dosage/exposure. This will allow the user to specify ozone treatment



conditions that will always ensure attaining ozone's intended effect(s) while also ensuring that excess ozone sufficient to damage the food product will be avoided.

Table 1. Examples of Effective Continuous Ozone Treatment Conditions for Some Selected Individual Foods and Target Applications

Food Type and Application	Continuous Ozone Exposure Conditions			Comments and/or References
	Minimum Residual Level in		Minimum Treatment Time, minutes	
	Air mg/m <sup>3</sup> (ppm)	Water mg/L (ppm)		
Poultry carcasses		6	30	EPRI, 1999b
<i>Salmonella</i> on chicken carcasses		0.35	30	Caracciolo, 1990 – 40 MPN/g Salm → <3. 930 <i>Proteus</i> → 9
Poultry chiller water		3.0-4.5	45	Sheldon & Brown, 1986a; 78, 91, 81% redns of APC, coliforms and <i>Salmonella</i>
Spent broiler neck chiller water		3.0-4.5	15	Sheldon & Chang, 1987a; 99.5, 99.52, 99.5, 99.9% redns of APC, coliforms, <i>E. coli</i> , and <i>Salmonella</i>
Poultry chiller water		3-7	15-30 – BOC Macron™ Loop	Ark. Ag. Exptl. Sta., 1997; > 90% redns of APC, <i>E. coli</i> , and coliforms
Poultry hatchery – air disinfectant	1.51-1.65% by weight		8	Whistler & Sheldon, 1989b; >4-7-logs redn in bacteria & fungi
Chicken Broiler Parts		3.8	20	Yang & Chen, 1979b; 85-90% count reduction
Beef muscle slices	0.6		constant @ 0.3 °C	Kaess & Weidemann, 1968
Fresh mackerel, gutted and washed		0.6	30	Haraguchi et al., 1969; Washing repeated E.O.D.
<i>Vibrio</i> control in shrimp mariculture		0.07-0.08 (seawater)	3-6 hrs	Blogoslawski et al., 1993

Apples in Storage	1-2; 85-90% RH		1 hour/day	Smock & Watson, 1941 lowers/eliminates molds
Molds on Newtown apples stored 3 mos.	1-2		3 months	Smock & van Doren, 1939; no mold growth; no scald
Spores ( <i>P. expansum</i> ; <i>S. fructicola</i> ) on apples	0.6; 85-90% RH		3-4 hrs	Smock & Watson, 1941
Fruit storage – general conditions	1-3; >90% RH		2-3 hrs/day	Kuprianoff, 1953
Thornless blackberries storage	0.1-0.3 @ 2°C		12 days	Barth et al., 1995; O <sub>3</sub> suppressed fungal growth 12 days
Grapes storage	0.1		20-40	Sarig et al., 1996; O <sub>3</sub> reduced fungal berry decay
Strawberries		2.7	0.5	Lyons-Magnus, 1999; Reduced <i>E. coli</i> , SPC
Chinese cabbage washing		2-3	< 60	Kondo et al., 1989; > 90% redn in total bacterial counts
Broccoli washing Carrots washing Broccoflower washing		1.1 0.64 1.08	10 10 10	Hampson et al, 1994; 3-log redn of APC 2-log redn of APC 1-2 log redn of APC
Carrots storage	15 µL/L air		8 h/day @ 2°C	Liew & Prange, 1994; gave some disease protection with minimal change (lighter color)
Broccoli florets washing		1	10-50, then 4 days storage	Zhuang et al., 1996; microbial growth inhibited
Broccoli washing Broccoflower washing Carrots washing		1 1 1	6.0/1-log 7.5/1-log 9.6/1-log	Hampson & Fiori, 1997; for higher log-inacts, increase [O <sub>3</sub> ] or contact time with wash water
Lettuce		1.3	3	Kim et al., 1999b; 3- to 4-log count reduction
Whole Grains	50		120	Naito et al., 1987a

Japanese raw noodles	0.5 ~ 50		6 hr	Naito et al., 1989c; increases storage life 2-5 times
Confectionery plant air	0.03-0.112 O <sub>3</sub> generated by UV bulbs		10 h/day at night (no workers)	Naitoh, 1989d; lowered airborne bacterial & fungal counts ~ 50%
Ground Black Pepper	6.7		60	Zhao & Cranston, 1995
<i>Bacillus cereus</i> spores		2.5	5	Broadwater et al., 1973
<i>Bacillus cereus</i> vegetative		0.12	5	ditto
<i>E. coli</i>		0.26	1.7	Farooq & Akhlaque, 1983
<i>Salmonella</i> <i>typhimurium</i>		0.26	1.7	ditto
Sanitizing wine processing equipment with water washing		1.5	~ 2	Hampson, 2000; reduces plate counts 63.2-99.9%

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