ACTA SCIENTIFIC NUTRITIONAL HEALTH (ISSN:2582-1423)

Volume 5 Issue 2 February 2021

Editorial

General Anesthetics

Dalamagka Maria*

Anaesthesiology Department, General Hospital of Larissa, Greece

***Corresponding Author:** Dalamagka Maria, Anaesthesiology Department, General Hospital of Larissa, Greece.

Received: December 01, 2020

Published: December 30, 2020

General anesthetics are administered to approximately 50 million patients each year in the United States. Anesthetic vapors and gases are also widely used in dentists' offices, veterinary clinics, and laboratories for animal research. All the volatile anesthetics that are currently used are halogenated compounds destructive to the ozone layer. These halogenated anesthetics could have potential significant impact on global warming. The widely used anesthetic gas nitrous oxide is a known greenhouse gas as well as an important ozone-depleting gas. These anesthetic gases and vapors are primarily eliminated through exhalation without being metabolized in the body, and most anesthesia systems transfer these gases as waste directly and unchanged into the atmosphere. Little consideration has been given to the ecotoxicological properties of gaseous general anesthetics. Our estimation using the most recent consumption data indicates that the anesthetic use of nitrous oxide contributes 3.0% of the total emissions in the United States. Studies suggest that the influence of halogenated anesthetics on global warming will be of increasing relative importance given the decreasing level of chlorofluorocarbons globally. Despite these nonnegligible pollutant effects of the anesthetics, no data on the production or emission of these gases and vapors are publicly available. Since Fox., *et al*. [1] first published their warning in 1975, concern has been repeatedly expressed about the potential harm that the release of halogenated general anesthetic gases poses to the global environment. All the volatile anesthetics that are currently used (halothane, isoflurane, enflurane, sevoflurane, and desflurane) are halogenated compounds potentially destructive to the ozone layer. The widely used anesthetic gas nitrous oxide (N_2O) is an established greenhouse gas. A recent report suggests that N_2O is also an important ozone-depleting gas. As the world population continues to grow and as modern anesthesia becomes available to more regions of the world, the global use of volatile anesthetics and N_2O will rapidly grow. General anesthetics were administered to approximately 50 million patients in the United States in 2006, according to data released by the National Center for Health Statistics Anesthetic vapors and gases are also widely used in dentists' offices, veterinary clinics, and laboratories for animal research. A key attribute that differentiates all of these anesthetic gases from other medical drugs is that they are substantially eliminated through exhalation, without being metabolized in the body. At present, most anesthesia systems transfer these waste gases directly and unchanged into the atmosphere. Although the introduction of scavenging systems has significantly reduced spillage of general anesthetics into the operating room, they are still exhausted into the environment. Little consideration has been given to the ecotoxicological properties of gaseous general anesthetics. Chemically, halogenated volatile anesthetics are closely related to the chlorofluorocarbons (CFCs), which play major roles in ozone depletion. The effect of a volatile anesthetic on ozone depletion will depend on its molecular weight, the number and type of halogen atoms, and its atmospheric lifetime (defined as the time taken to remove or transform 1/e, or 63%, of an emitted gas). The atmospheric lifetime of these trace gases depends on their removal by chemical reaction with radicals, photolysis, and dry or wet deposition, such as "rainout." Those species with a tropospheri lifetime of more than 2 years are then believed to reach the stratosphere in significant quantities. The tropospheric lifetime of halogenated anesthetics is much shorter than that of CFCs, because hydrogen atoms of the anesthetic molecules are susceptible to attack by hydroxyl radicals in the troposphere, making them less likely to reach the stratosphere.

However, a concern has been raised about very short-lived compounds (with a lifetime of a few months or less) and their potentially significant contribution to ozone destruction. Once anesthetics reach the stratosphere, chlorine-containing anesthetics such as halothane, isoflurane, and enflurane may be more destructive to the ozone layer than are newer drugs, such as sevoflurane and desflurane, which are halogenated entirely with fluorine. By measuring the rate of reaction with hydroxyl radicals, Brown., *et al*. [2] have calculated that the tropospheric lifetimes of halothane, enflurane, and isoflurane are 2, 6, and 5 years, respectively. A more recent evaluation of the lifetimes of halogenated volatile anesthetics and their potential contribution to ozone depletion has been reported by Langbein., *et al*. [3]. Using measurements of hydroxyl radical reaction kinetics and ultraviolet absorption spectra of anesthetics, we estimated the total atmospheric lifetimes of these anesthetics at 4.0 to 21.4 years. Contributions to total stratospheric ozone depletion were reported as approximately 1% for halothane and 0.02% for enflurane and isoflurane, suggesting that these anesthetics can play important roles in ozone depletion. The global warming potential (GWP) of halogenated anesthetics is reported to range from 1230 (isoflurane) to 3714 (desflurane) times the GWP of carbon dioxide (CO_2). Recently, Ryan and Nielsen reported on the impact of halogenated volatile anesthetics on global warming within the framework of common clinical practice, an approach that has not been taken before. Their study suggests that all the anesthetics (isoflurane, sevoflurane, and desflurane) can have a significant influence on global warming with the greatest impact produced by atmospheric desflurane. With an atmospheric lifetime of approximately 120 years, N_2O is a remarkably stable gas. N_2O traps thermal radiation escaping from the Earth's surface, contributing to what is known as the "greenhouse effect". The GWP of N_2O is approximately 300 times more than that of CO_2. N_2O, along with CO_2 and methane, are the most influential long-lived greenhouse gases among all gases encompassed by the Kyoto Protocol. N_2O is produced by human sources including agriculture (nitrogen-based fertilizers) and the use of fossil fuels, as well as natural sources in soil and water, such as microbial action in moist tropical forests. The N_2O concentration is reported to be steadily increasing at a rate of 0.7 to 0.8 parts per billion (ppb) per year in past decades, and N_2O currently contributes about 6% of the total radiative forcing (difference between incoming and outgoing radiation energy within the Earth's atmosphere). In addition, N_2O is a primary source of stratospheric nitrogen oxides, referring specifically to NO and NO_2. Both destroy ozone. Although the ozone depleting potential (ODP) of N_2O (0.017) is lower than that of CFCs (only 10% of N_2O is converted to nitrogen oxides), N_2O emission is reported to be the single largest ODP-weighted emission and is expected to remain the largest for the rest of this century. Sherman and Cullen first reported in 1988 that N_2O, the most popular anesthetic gas, could contribute to global warming, and estimated that approximately 1% of total N_2O production was used for clinical anesthesia on the basis of the number of surgical procedures in the United States, approximately 21 million cases at that time. They estimated the worldwide annual use of N_2O for anesthesia to be 0.5 to 1.0 × 109 moles (2.2 to 4.4 × 104 tons). Although the precise quantities manufactured for medical use are unavailable to the public, we can estimate the most recent consumption of N_2O for anesthetic purposes. Our institution consumed 20.2 tons of N_2O for anesthetic use in 2006 for approximately 40,000 procedures that were performed with an anesthesiologist present. In the United States, approximately 70 million procedures were performed in 2006 with an anesthesia provider (all types of anesthesia included), according to data from the National Center for Health Statistics. Extrapolating from these figures, we estimate that approximately 3.5 × 104 tons of N_2O were used for anesthetic purposes for 70 million patients in 2006 in the United States. The latest inventory of green ho. General anesthetics are administered to approximately 50 million patients each year in the United States. Anesthetic vapors and gases are also widely used in dentists' offices, veterinary clinics, and laboratories for animal research. All the volatile anesthetics that are currently used are halogenated compounds destructive to the ozone layer. These halogenated anesthetics could have potential significant impact on global warming. The widely used anesthetic gas nitrous oxide is a known greenhouse gas as well as an important ozone-depleting gas. These anesthetic gases and vapors are primarily eliminated through exhalation without being metabolized in the body, and most anesthesia systems transfer these gases as waste directly and unchanged into the atmosphere. Little consideration has been given to the ecotoxicological properties of gaseous general anesthetics. Our estimation using the most recent consumption data indicates that the anesthetic use of nitrous oxide contributes 3.0% of the total emissions in the United States. Studies suggest that the influence of halogenated anesthetics on global warming will be of increasing relative importance given the decreasing level of chlorofluorocarbons globally. Despite these non-negligible pollutant effects of the anesthetics, no data on the production or emission of these gases and vapors are publicly available. Since Fox., *et al*. [1] first published their warning in 1975, concern has been repeatedly expressed about the potential harm that the release of halogenated general anesthetic gases poses to the global environment. All the volatile anesthetics that are currently used (halothane, isoflurane, enflurane, sevoflurane, and desflurane) are halogenated compounds potentially destructive to the ozone layer. The widely used anesthetic gas nitrous oxide (N_2O) is an established greenhouse gas. A recent report suggests that N_2O is also an important ozone-depleting gas. As the world population continues to grow and as modern anesthesia becomes available to more regions of the world, the global use of volatile anesthetics and N_2O will rapidly grow. General anesthetics were administered to approximately 50 million patients in the United States in 2006, according to data released by the National Center for Health Statistics Anesthetic vapors and gases are also widely used in dentists' offices, veterinary clinics, and laboratories for animal research. A key attribute that differentiates all of these anesthetic gases from other medical drugs is that they are substantially eliminated through exhalation, without being metabolized in the body. At present, most anesthesia systems transfer these waste gases directly and unchanged into the atmosphere. Although the introduction of scavenging systems has significantly reduced spillage of general anesthetics into the operating room, they are still exhausted into the environment. Little consideration has been given to the ecotoxicological properties of gaseous general anesthetics. Chemically, halogenated volatile anesthetics are closely related to the chlorofluorocarbons (CFCs), which play major roles in ozone depletion. The effect of a volatile anesthetic on ozone depletion will depend on its molecular weight, the number and type of halogen atoms, and its atmospheric lifetime (defined as the time taken to remove or transform 1/e, or 63%, of an emitted gas). The atmospheric lifetime of these trace gases depends on their removal by chemical reaction with radicals, photolysis, and dry or wet deposition, such as "rainout." Those species with a tropospheri lifetime of more than 2 years are then believed to reach the stratosphere in significant quantities. The tropospheric lifetime of halogenated anesthetics is much shorter than that of CFCs, because hydrogen atoms of the anesthetic molecules are susceptible to attack by hydroxyl radicals in the troposphere, making them less likely to reach the stratosphere. However, a concern has been raised about very short-lived compounds (with a lifetime of a few months or less) and their potentially significant contribution to ozone destruction. Once anesthetics reach the stratosphere, chlorine-containing anesthetics such as halothane, isoflurane, and enflurane may be more destructive to the ozone layer than are newer drugs, such as sevoflurane and desflurane, which are halogenated entirely with fluorine. By measuring the rate of reaction with hydroxyl radicals, Brown., *et al*. [2] have calculated that the tropospheric lifetimes of halothane, enflurane, and isoflurane are 2, 6, and 5 years, respectively. A more recent evaluation of the lifetimes of halogenated volatile anesthetics and their potential contribution to ozone depletion has been reported by Langbein., *et al*. [3]. Using measurements of hydroxyl radical reaction kinetics and ultraviolet absorption spectra of anesthetics, we estimated the total atmospheric lifetimes of these anesthetics at 4.0 to 21.4 years. Contributions to total stratospheric ozone depletion were reported as approximately 1% for halothane and 0.02% for enflurane and isoflurane, suggesting that these anesthetics can play important roles in ozone depletion. The global warming potential (GWP) of halogenated anesthetics is reported to range from 1230 (isoflurane) to 3714 (desflurane) times the GWP of carbon dioxide (CO_2). Recently, Ryan and Nielsen reported on the impact of halogenated volatile anesthetics on global warming within the framework of common clinical practice, an approach that has not been taken before. Their study suggests that all the anesthetics (isoflurane, sevoflurane, and desflurane) can have a significant influence on global warming with the greatest impact produced by atmospheric desflurane. With an atmospheric lifetime of approximately 120 years, N_2O is a remarkably stable gas.N_2O traps thermal radiation escaping from the Earth's surface, contributing to what is known as the "greenhouse effect". The GWP of N_2O is approximately 300 times more than that of CO_2. N_2O, along with CO_2 and methane, are the most influential long-lived greenhouse gases among all gases encompassed by the Kyoto Protocol. N_2O is produced by human sources including agriculture (nitrogen-based fertilizers) and the use of fossil fuels, as well as natural sources in soil and water, such as microbial action in moist tropical forests. The N_2O concentration is reported to be steadily increasing at a rate of 0.7 to 0.8 parts per billion (ppb) per year in past decades, and N_2O currently contributes about 6% of the total radiative forcing (difference between incoming and outgoing radiation energy within the Earth's atmosphere). In addition, N_2O is a primary source of stratospheric nitrogen oxides, referring specifically to NO and NO2. Both destroy ozone. Although the ozone depleting potential (ODP) of N_2O (0.017) is lower than that of CFCs (only 10% of N_2O is converted to nitrogen oxides), N_2O emission is reported to be the single largest ODP-weighted emission and is expected to remain the largest for the rest of this century. Sherman and Cullen first reported in 1988 that N_2O, the most popular anesthetic gas, could contribute to global warming, and estimated that approximately 1% of total N_2O production was used for clinical anesthesia on the basis of the number of surgical procedures in the United States, approximately 21 million cases at that time. They estimated the worldwide annual use of N_2O for anesthesia to be 0.5 to 1.0 × 109 moles (2.2 to 4.4 × 104 tons). Although the precise quantities manufactured for medical use are unavailable to the public, we can estimate the most recent consumption of N_2O for anesthetic purposes.

However, the worldwide anesthetic use of N_2O, including all developed and developing countries, are not available. Until those data are obtained, a warning that the medical use of N_2O can be a significant contributor to overall greenhouse gas emissions should be maintained. The use of volatile anesthetics could be reduced by up to 80% to 90% if closed circuit anesthesia were widely used for all patients, and to a lesser degree if "low-flow" anesthesia were routinely used. Although closed-circuit anesthesia is not a difficult technique with modern anesthesia systems for well-trained anesthesiologists, continuous accurate gas monitoring is required to prevent inadequate oxygenation or volatile anesthetic concentration. Shifting to total IV anesthesia would eliminate the use of anesthetic gases. Nevertheless, many anesthesiologists may still prefer volatile anesthetics and N_2O, and their use is almost always required for anesthesia in infants and children. Modifying our practice towards more conservation of anesthetic gases can usually be done without compromising patient care if appropriate monitoring is used, and these techniques should be available to most anesthesiologists in developed countries. Doyle., *et al*. [4] have shown that silica zeolite (Deltazite™) was effective at completely removing isoflurane (1% in exhaled gases) in the scavenging line for a period of 8 hours. The trapped halogenated agents could then be reprocessed by steam extraction or fractional distillation for reuse. Reprocessing techniques are essential to reducing the amount of the anesthetics released into the atmosphere because disposal does not change the eventual fate of the anesthetics. A technique for conserving halogenated anesthetic vapors using a zeolite filter at the Y-piece connector has been proposed by Thomasson., *et al*. and the principles of this technique have been used to develop an anesthetic conserving device (ACD). The system is closed to volatile anesthetics, but it is open to oxygen; volatile anesthetics are supplied to the ACD through a syringe pump. This system has been shown to successfully reduce the total amount of volatile anesthetics released by 40%–75%, suggesting that the ACD may provide an alternative to low-flow systems. First reported >50 years ago, the anesthetic property of xenon has been revisited. Xenon is a naturally occurring atmospheric trace gas, existing at 0.08 parts per million (ppm), with no known detrimental ecotoxicological effect. The pharmacokinetic benefits of xenon include profound analgesia, neuroprotection, and hemodynamic stability. Xenon also has an extremely low blood–gas partition coefficient, which lends itself to rapid induction and emergence. However, clinical use of xenon has been limited mostly by its high cost of manufacture, which involves fractional distillation of liquid air. Furthermore, the production of xenon consumes enormous amounts of energy (220 W/h per 1 L of xenon gas), significantly more energy than that required for N_2O production. Routine use of xenon for clinical anesthesia would only be economically possible with a closed-circuit system that recycles the rare gas. An ideal inhaled anesthetic should be safe, effective, and environmentally benign. This third characteristic has received insufficient consideration in part because of uncertainties on the environmental effects of gaseous anesthetics. Key criteria that will determine the global environmental impact of alternatives to halogenated anesthetics and N_2O are their atmospheric lifetime, GWP, and ODP. These characteristics should be determined for existing anesthetics, and for any new anesthetic gases before widespread clinical use. Novel anesthetic gases should be adopted only if the clinical benefits outweigh any adverse environmental consequences. Although anesthetic gases are considered medically essential, an appreciable change is occurring in medical society. CFC propellants were previously considered medically essential for metered dose inhalers, but these have now been replaced with hydrofluoroalkane propellants. Current evidence may be insufficient for determining whether the contribution of waste anesthetics to the global climate change is significant. However, it is likely that anesthetic gas contributions, calculated in full carbon equivalents, will become an important part of efforts to limit the production of greenhouse and ozone-depleting gases. In summary, the use of N_2O in medicine contributes to both global warming and ozone depletion. The use of halogenated anesthetics is a concern for producing global warming. In addition, the influence of halogenated anesthetics on ozone depletion will be of increasing relative importance, given the decreasing level of CFC usage globally. Furthermore, it should be recognized that other uses of anesthetic gases, including the use of N_2O in dental offices and anesthetic gases in veterinary clinics and animal laboratories, may make significant additional contributions to adverse environmental change. It is essential to collect primary information on the quantities of N_2O and halogenated volatile anesthetics manufactured or used, especially in consideration of serious international efforts to successfully reduce the emissions of ozone-depleting substances and greenhouse gases. We should develop tools for monitoring the use of ecotoxic gases, and initiate an international dialogue on these medically useful pollutants [5-9].

Bibliography

1. Fox JW., *et al*. "Letter: Stratospheric ozone destruction and halogenated anaesthetics". *Lancet* 1 (1975): 864.
2. Brown AC., *et al*. "Tropospheric lifetimes of halogenated anaesthetics". *Nature* 341 (1989): 635-637.
3. Langbein T., *et al*. "Volatile anaesthetics and the atmosphere: atmospheric lifetimes and atmospheric effects of halothane, enflurane, isoflurane, desflurane and sevoflurane". *British Journal of Anaesthesia* 82 (1999): 66-73.
4. Byrick R and Doyle DJ. "Volatile anaesthetics and the atmosphere: an end to 'scavenging'?". *British Journal of Anaesthesia* 86 (2001): 595-596.
5. Logan M and Farmer JG. "Anaesthesia and the ozone layer". *British Journal of Anaesthesia* 63 (1989): 645-647.
6. McCulloch A. "Volatile anaesthetics and the atmosphere: atmospheric lifetimes and atmospheric effects of halothane, enflurane, isoflurane, desflurane and sevoflurane". *British Journal of Anaesthesia* 84 (2000): 534-536.
7. Pierce JMT and Linter SPK. "Anesthetic agents and the ozone layer". *Lancet* 333 (1989): 1011-1012.
8. Rogers RC and Ross JAS. "Anaesthetic agents and the ozone layer". *Lancet* 333 (1989): 1209-1210.
9. Sherman SJ and Cullen BF. "Nitrous oxide and the greenhouse effect". *Anesthesiology* 68 (1988): 816-817.

	2003-2004 Vitamin D (D2 + D3) (µg) of Adults 19+ Years of Age						
Significant food groups	**OJ consumers**		**OJ non-consumers**		**OJ consumers vs OJ non-consumers**		
	Mean	SE	Mean	SE	Beta	SE	P value
All Foods	4.82	0.33	4.42	0.17	0.40	0.33	0.2467
Orange Juice	0.00	0.00	0.00	0.00	.	.	.
Mixed Dishes - Mexican	0.01	0.00	0.03	0.01	-0.02	0.01	0.0085
Coffee and Tea	0.02	0.01	0.07	0.02	-0.05	0.02	0.0136
White Potatoes	0.02	0.00	0.04	0.00	-0.01	0.00	0.0157
Cooked Grains	0.00	0.00	0.00	0.00	0.00	0.00	0.0182
Sweetened Beverages	0.03	0.01	0.05	0.01	-0.02	0.01	0.0266
Poultry	0.04	0.01	0.05	0.00	-0.01	0.01	0.0413
2015-2016 Vitamin D (D2 + D3) (µg) of Adults 19+ Years of Age							
All Foods	5.49	0.23	4.54	0.16	0.95	0.30	0.0060
Orange Juice	0.70	0.07	0.00	0.00	0.70	0.07	<0.0001
100% Juice	0.70	0.07	0.00	0.00	0.70	0.07	<0.0001
Alcoholic Beverages	0.00	0.00	0.01	0.00	-0.01	0.00	0.0054
Mixed Dishes - Sandwiches (single code)	0.12	0.02	0.17	0.01	-0.05	0.02	0.0134
Protein and Nutritional Powders	0.02	0.01	0.11	0.03	-0.09	0.04	0.0191
Milk	1.54	0.16	1.07	0.08	0.47	0.21	0.0371

Supplemental Table 10: Significant Food Sources of Vitamin D (D2 + D3) (µg) of Adults 19+ Years of Age by Orange Juice (OJ) Consumption and by Survey Year.

	2003-2004 Zinc (mg) of Adults 19+ Years of Age						
Significant food groups	**OJ consumers**		**OJ non-consumers**		**OJ consumers vs OJ non-consumers**		
	Mean	SE	Mean	SE	Beta	SE	P value
All Foods	12.63	0.48	11.94	0.19	0.69	0.43	0.1278
Orange Juice	0.20	0.01	0.00	0.00	0.20	0.01	<0.0001
100% Juice	0.23	0.01	0.02	0.00	0.21	0.01	<0.0001
Fruits	0.12	0.01	0.07	0.00	0.06	0.01	0.0004
Coffee and Tea	0.09	0.01	0.13	0.01	-0.05	0.01	0.0008
Diet Beverages	0.01	0.00	0.01	0.00	-0.01	0.00	0.0035
Snack/Meal Bars	0.03	0.01	0.07	0.01	-0.04	0.01	0.0045
Breads, Rolls, Tortillas	0.59	0.04	0.49	0.02	0.10	0.04	0.0150
Ready-to-Eat Cereals	1.29	0.22	0.82	0.06	0.46	0.21	0.0425
2015-2016 Zinc (mg) of Adults 19+ Years of Age							
All Foods	11.54	0.42	11.17	0.20	0.38	0.47	0.4363

Orange Juice	0.21	0.01	0.00	0.00	0.21	0.01	<0.0001
100% Juice	0.24	0.02	0.02	0.00	0.22	0.02	<0.0001
Diet Beverages	0.00	0.00	0.01	0.00	0.00	0.00	0.0013
Mixed Dishes - Mexican	0.44	0.10	0.65	0.09	-0.21	0.06	0.0032
Breads, Rolls, Tortillas	0.55	0.05	0.42	0.01	0.13	0.05	0.0183
Plain Water	0.07	0.01	0.08	0.00	-0.02	0.01	0.0299
Milk	0.54	0.05	0.37	0.03	0.16	0.07	0.0304
Coffee and Tea	0.10	0.02	0.15	0.01	-0.04	0.02	0.0422

Supplemental Table 11: Significant Food Sources of Zinc (mg) of Adults 19+ Years of Age by Orange Juice (OJ) Consumption and by Survey Year.

	2003-2004 Dietary Fiber (g) of Adults 19+ Years of Age						
Significant food groups	**OJ consumers**		**OJ non-consumers**		**OJ consumers vs OJ non-consumers**		
	Mean	SE	Mean	SE	Beta	SE	P value
All Foods	17.66	0.63	15.07	0.34	2.59	0.48	0.0001
Orange Juice	0.64	0.02	0.00	0.00	0.64	0.02	<0.0001
100% Juice	0.71	0.03	0.05	0.01	0.66	0.03	<0.0001
Fruits	2.20	0.18	1.30	0.07	0.91	0.16	0.0001
Coffee and Tea	0.01	0.00	0.03	0.01	-0.02	0.01	0.0090
Breads, Rolls, Tortillas	2.18	0.14	1.78	0.09	0.40	0.14	0.0095
Mixed Dishes - Mexican	0.24	0.03	0.62	0.16	-0.38	0.14	0.0152
Ready-to-Eat Cereals	1.10	0.17	0.71	0.06	0.39	0.16	0.0255
2015-2016 Dietary Fiber (g) of Adults 19+ Years of Age							
All Foods	19.48	0.80	16.92	0.40	2.56	0.82	0.0068
Orange Juice	0.89	0.04	0.00	0.00	0.89	0.04	<0.0001
100% Juice	0.94	0.04	0.06	0.01	0.88	0.04	<0.0001
Eggs	0.01	0.00	0.02	0.00	-0.02	0.00	0.0002
Cheese	0.00	0.00	0.02	0.00	-0.01	0.00	0.0039
Alcoholic Beverages	0.00	0.00	0.01	0.00	-0.01	0.00	0.0042
Yogurt	0.02	0.01	0.05	0.01	-0.03	0.01	0.0099
Breads, Rolls, Tortillas	1.99	0.18	1.56	0.05	0.43	0.18	0.0303

Supplemental Table 12: Significant Food Sources of Dietary Fiber (g) of Adults 19+ Years of Age by Orange Juice Consumption and by Survey Year.

	2003-2004 Sodium (mg) of Adults 19+ Years of Age						
Significant food groups	**OJ consumers**		**OJ non-consumers**		**OJ consumers vs OJ non-consumers**		
	Mean	SE	Mean	SE	Beta	SE	P value
All Foods	3725.38	84.92	3604.40	38.70	120.98	95.69	0.2254
Orange Juice	6.09	0.23	0.00	0.00	6.09	0.23	<0.0001
Coffee and Tea	11.02	0.86	16.43	1.25	-5.41	1.53	0.0030
Alcoholic Beverages	7.20	0.90	17.06	2.73	-9.86	2.82	0.0033
Breads, Rolls, Tortillas	343.58	20.01	280.61	8.91	62.97	19.59	0.0058
100% Juice	15.49	3.48	6.08	1.67	9.41	3.72	0.0231
Fruits	2.52	0.35	1.65	0.15	0.87	0.37	0.0314
Ready-to-Eat Cereals	79.29	11.00	56.24	3.50	23.05	10.28	0.0405
2015-2016 Sodium (mg) of Adults 19+ Years of Age							
All Foods	3662.01	88.87	3523.51	47.83	138.50	112.96	0.2390
Orange Juice	6.35	0.35	0.00	0.00	6.35	0.35	<0.0001
Diet Beverages	2.72	0.68	11.98	1.36	-9.26	1.35	<0.0001
Breads, Rolls, Tortillas	234.03	14.46	187.04	7.30	46.99	17.06	0.0148
Plain Water	36.07	2.52	43.41	1.89	-7.33	2.70	0.0160
Ready-to-Eat Cereals	63.96	9.30	39.47	2.47	24.49	9.98	0.0268
Coffee and Tea	14.65	1.86	19.79	1.02	-5.14	2.12	0.0286
Milk	56.67	5.52	39.50	3.07	17.17	7.14	0.0295
Sweetened Beverages	30.87	4.30	40.87	2.62	-10.01	4.51	0.0426
Candy	5.72	1.34	9.52	0.98	-3.79	1.71	0.0428
Protein and Nutritional Powders	3.23	1.77	11.48	2.77	-8.25	3.74	0.0435
Plant-based Protein Foods	46.15	9.15	70.10	6.08	-23.95	11.10	0.0476

Supplemental Table 13: Significant Food Sources of Sodium (mg) of Adults 19+ Years of Age by Orange Juice (OJ) Consumption and by Survey Year.

- **Vitamins:** There was a significant decrease in intakes of folate (β = -2.64 µg/cycle, p = 0.0015, riboflavin (β = -0.02 mg/cycle, p = 0.0156), thiamin (β = -0.01 mg/cycle, p < 0.0014), and vitamin C (β = -1.44 mg/cycle, p < 0.01). In contrast, intakes of niacin (β = 0.26 mg/cycle, p < 0.0012) and vitamin B6 (β = 0.05 mg/cycle, p = <0.0001) increased.
- **Minerals:** Intakes of iron (β = -0.29 mg/cycle, p = <0.0001), sodium (β = -20.33 mg/cycle, p = 0.0082) and zinc (β = -0.23 mg/cycle, p = <0.0001) decreased from 2003-2016. In contrast, intakes of calcium (β = 10.0 mg/cycle, p = 0.0024), magnesium (β = 3.41 mg/cycle, p = 0.0003) and phosphorus (β = 11.37 mg/cycle, p = 0.0017) increased.

Linear trends in nutrient adequacy among adults from NHANES 2003-2016 (Table 3)

The percentage of adults above the AI for dietary fiber increased (β = 0.91g/cycle, p = 0.0061) and the percentage below the EAR for zinc increased (β = 1.07 mg/cycle, p = 0.0203). No significant trend in nutrient adequacy were found among the other nutrients studied.

Percent below EAR or above AI by decile of OJ consumption

Deciles of OJ consumption were determined based on dietary intake data with non-consumers in the first decile and consumers of OJ separated into nine relatively equal groups; mean OJ consumptions of decile 1, decile 5 and decile 10 were 0.216, and 788 g/d. All regression coefficients for assessing change in percentage below the EAR/above the AI across deciles of OJ consumption are presented in supplemental table 1.

- **Folate:** For every gram of OJ consumed the percent of the population with inadequate intake of folate decreased 0.02 percentage units (Figure 1). In other words, for every 120 g (4 fl oz) of OJ consumed the percent of the population with inadequate intake decreased 2.4 percentage points.
- **Riboflavin:** For every gram of OJ consumed the percent of the population with inadequate intake of riboflavin decreased 0.004 percentage units (Figure 1). In other words, for every 120 g (4 fl oz) of OJ consumed the percent of the population with inadequate intake decreased 0.48 percentage points.
- **Thiamin, vitamins B6 and D**: For all three vitamins, for every gram of OJ consumed the percent of the population with inadequate intake of all three vitamins: decreased 0.01 percentage units (Figure 1). In other words, for every 120g (4 fl oz) of OJ consumed the percent of the population with inadequate intake of each of the three vitamins decreased 1.2 percentage points.
- **Calcium:** For every gram of OJ consumed, the percent of the population with inadequate intake of calcium decreased 0.06 percentage units (Figure 2). In other words, for every 120 g (4 fl oz) of OJ consumed the percent of the population with inadequate intake decreased 7.2 percentage points.
- **Phosphorus**: For every gram of OJ consumed the percent of the population with inadequate intake of phosphorus decreased 0.002 percentage units (Figure 2). In other words, for every 120 g (4 fl oz) of OJ consumed the percent of the population with inadequate intake decreased 0.24 percentage points.
- **Zinc:** For every gram of OJ consumed the percent of the population with inadequate intake of zinc decreased 0.01 percentage units (Figure 2). In other words, for every 120 g (4 fl oz) of OJ consumed the percent of the population with inadequate intake decreased 1.2 percentage points.
- **Dietary Fiber:** For every gram of OJ consumed the percent of the population above the AI for dietary fiber increased 0.004 percentage units (Figure 3). Thus, for every 120 g (4 fl oz) of OJ consumed the percent of the population with adequate intake increased 0.48 percentage units.
- **Sodium:** For every gram of OJ consumed the percent of the population above the AI for sodium increased 0.001 percent units (Figure 3). Thus, for every 120 g (4 fl oz) of OJ consumed the percent of the population with adequate intake increased 0.12 percentage units. For other nutrients evaluated (Supplemental Table 1) there were no significant associations of changes in the percentage of the population below the EAR/above the AI across deciles of OJ intake.

Major food sources of energy and nutrient intake by orange juice consumption and survey year

- **Energy:** The food sources of energy intake by OJ consumption that were significantly different for NHANES survey years 2003-2004 and 2015-2016 are presented in table 4. Only the food sources of energy intake that were significantly different among OJ consumers and non-consumers are presented. Of the increased energy in 2003-2004 among OJ consumers (593 KJ) as compared to non-consumers, mostly was due to consumption of OJ (556 KJ) and other 100% juices (554 KJ), whole fruits (123 KJ) and breads/rolls/tortillas (109 KJ) with a concomitant decrease in consumption of sweetened beverages (-184 KJ) and mixed dishes-Mexican (-130 KJ). In 2015-2016, the increased energy intake among OJ consumers (959 KJ) as compared to non-consumers was mostly due to consumption of OJ (598 KJ), other 100% juice (602 KJ) and breads/rolls/tortillas (103 KJ) with a concomitant decrease in consumption of candy (-48 KJ) and coffee/tea (61 KJ).

Significant food sources for all nutrients that showed a significant association of changes in percentage of the population below the EAR/above the AI across deciles of OJ consumption are presented by survey year in supplemental tables 2-13: The significant differences in food sources of iron, magnesium, riboflavin, thiamin, vitamins B6 and D, zinc and dietary fiber among OJ consumers and non-consumers were very small. The most notable differences were found in the food sources of calcium, folate, phosphorus, and sodium. In both survey years, OJ and other 100% juices were the major food sources of calcium, folate, and phosphorus among OJ consumers compared to non-consumers. In 2015-2016, ready-to-eat cereals were a major food source of folate among OJ consumers compared to non-consumers in both survey years, breads/rolls/tortillas were the primary food source of sodium among OJ consumers compared to non-consumers.

Discussion

Approximately 13% of adults reported consuming OJ with a mean intake of 39.5 g/d (1.3 fl oz) which was equivalent to 76 KJ (18.2 kcal) or 0.89% of total energy intake. On average adults consumed 0.92 cup eq of total fruits (2015-2016); 65% were from whole fruit and 27% from FJ (50% was from OJ). The recommended amount of fruits in the Healthy US-Style Eating Pattern at the 2,000-calorie level is 2 cup eq/d. given that FJ can be part of healthy eating patterns, at least half of the recommended amount of fruits should come from whole fruits because it is higher in fiber than FJ [7] Based on the newly release recommendation the mean amount of total fruits consumed is far below the recommended amount and the proportion of whole fruit compared to FJ consumed is well within the recommended distribution.

The intake of fruits have significantly changed in the diets of adults from 2003-2016. Despite no significant change in consumption of fruits, the consumption of whole fruits increased with a concomitant decrease in consumption of FJ, specifically both OJ and other 100% juices. This is consistent with the latest vital signs report by the Centers for Disease Control and Prevention [51,53].

Nutrient intake in adults has also changed from 2003-2016. Total energy intake decreased along with a decrease in intake of carbohydrates, specifically total sugars and added sugars. Total fiber intake increased with no significant trends in intakes of total protein, total fat, and saturated fat. Intakes of niacin and vitamin B6 increased while intakes of riboflavin, thiamin, and vitamin C decreased. Intakes of calcium, magnesium, and phosphorus in-

1. US Department of Agriculture. “United states orange juice domestic consumption by year”. (2020).
2. U S Department of Agriculture. “Fooddata central, orange juice, raw”. Agriculture Research Services 2019. (2020).
3. Khan T A., *et al*. “A lack of consideration of a dose-response relationship can lead to erroneous conclusions regarding 100% fruit juice and the risk of cardiometabolic disease”. *European Journal of Clinical Nutrition* 73.12 (2019): 1556-1560.
4. Walker R W., *et al*. “Fructose content in popular beverages made with and without high-fructose corn syrup”. *Nutrition* 30.7-8 (2014): 928-935.
5. Dietary Guidelines Advisory Committee. “Scientific report of the 2015 dietary guidelines advisory committee: Advisory report to the secretary of health and human services and the secretary of agriculture”. U.S. Department of Agriculture, Agricultural Research Service 2015 (2020).
6. Bray G A., *et al*. “Consumption of high-fructose corn syrup in beverages may play a role in the epidemic of obesity”. *American Journal of Clinical Nutrition* 79.4 (2004): 537-543.
7. Dietary Guidelines Advisory Committee. Scientific report of the 2020 dietary guidelines advisory committee: Advisory report to the secretary of agriculture and the secretary of health and human services. Washington, DC: Agricultural Research Services (2020).
8. Rampersaud G C. “A comparison of nutrient density scores for 100% fruit juices”. *Journal of Food Science* 72.4 (2007): S261-266.
9. Byrd-Bredbenner C., *et al*. “Satisfying america’s fruit gap: Summary of an expert roundtable on the role of 100% fruit juice”. *Journal of Food Science* 82.7 (2017): 1523-1534.
10. Crowe-White, K., *et al*. “Impact of 100% fruit juice consumption on diet and weight status of children: An evidence-based review”. *Critical Reviews in Food Science and Nutrition* 56.5 (2016): 871-884.
11. Auerbach B J., *et al*. “Fruit juice and change in bmi: A meta-analysis”. *Pediatrics* 139.4 (2017).
12. Nicklas T A., *et al*. “Association between 100% juice consumption and nutrient intake and weight of children aged 2 to 11 years”. *Archives of Pediatrics and Adolescent Medicine* 162.6 (2008): 557-565.

13. O'Neil CE., *et al*. "Fruit juice consumption is associated with improved nutrient adequacy in children and adolescents: The nhanes 2003-2006". *Public Health Nutrition* 15.10 (2012): 1871-1878.

14. Murray R D. "100% fruit juice in child and adolescent dietary patterns". *Journal of the American College of Nutrition* 39.2 (2020): 122-127.

15. O'Neil CE., *et al*. "Diet quality is positively associated with 100% fruit juice consumption in children and adults in the united states: Nhanes 2003-2006". *Nutritional Journal* 10.17 (2011): 1-10.

16. Clemens R., *et al*. "Squeezing fact from fiction about 100% fruit juice". *Advances in Nutrition* 6.2 (2015): 236S-243S.

17. Crowe-White K., *et al*. "Metabolic impact of 100% fruit juice consumption on antioxidant/oxidant status and lipid profiles of adults: An evidence-based review". *Critical Reviews in Food Science and Nutrition* 57.1 (2017): 152-162.

18. Auerbach B J., *et al*. "Review of 100% fruit juice and chronic health conditions: Implications for sugar-sweetened beverage policy". *Advances in Nutrition* 9.2 (2018): 78-85.

19. Hebden L., *et al*. "Fruit consumption and adiposity status in adults: A systematic review of current evidence". *Critical Reviews in Food Science and Nutrition* 57.12 (2017): 2526-2540.

20. American academy of pediatrics: Committee on nutrition. "The use and misuse of fruit juice in pediatrics". *Pediatrics* 107.5 (2001): 1210-1213.

21. O'Neil C E., *et al*. "100% orange juice consumption is associated with better diet quality, improved nutrient adequacy, decreased risk for obesity, and improved biomarkers of health in adults: National health and nutrition examination survey, 2003-2006". *Nutritional Journal* 11 (2012): 107.

22. Wang Y., *et al*. "Impact of orange juice consumption on macronutrient and energy intakes and body composition in the us population". *Public Health Nutrition* 15.12 (2012): 2220-2227.

23. Yang M., *et al*. "Orange juice, a marker of diet quality, contributes to essential micronutrient and antioxidant intakes in the united states population". *Journal of Nutrition Education and Behavior* 45.4 (2013): 340-348.

24. Rampersaud GC and M F Valim. "100% citrus juice: Nutritional contribution, dietary benefits, and association with anthropometric measures". *Critical Reviews in Food Science and Nutrition* 57.1 (2017): 129-140.

25. Simpson E J., *et al*. "Orange juice consumption and its effect on blood lipid profile and indices of the metabolic syndrome; a randomised, controlled trial in an at-risk population". *Food Function* 7.4 (2016): 1884-1891.

26. Papandreou D., *et al*. "Consumption of raw orange, 100% fresh orange juice, and nectar- sweetened orange juice-effects on blood glucose and insulin levels on healthy subjects". *Nutrients* 11.9 (2019).

27. Papandreou D and E Magriplis. "Consumption of raw orange, 100% fresh orange juice, and nectar- sweetened orange juice-effects on blood glucose and insulin levels on healthy subjects". *Nutrients* 11.9 (2019).

28. Xi B., *et al*. "Intake of fruit juice and incidence of type 2 diabetes: A systematic review and meta-analysis". *PLoS One* 9.3 (2014): e93471.

29. Scheffers F R., *et al*. "Pure fruit juice and fruit consumption and the risk of cvd: The european prospective investigation into cancer and nutrition-netherlands (epic-nl) study". *British Journal of Nutrition* 121.3 (2019): 351-359.

30. Wang Y., *et al*. "Effects of chronic consumption of specific fruit (berries, citrus and cherries) on cvd risk factors: A systematic review and meta-analysis of randomised controlled trials". *European Journal of Nutrition* (2020).

31. Aptekmann N P and T B. César. "Long-term orange juice consumption is associated with low ldl-cholesterol and apolipoprotein b in normal and moderately hypercholesterolemic subjects". *Lipids and Health Disease* 12 (2013): 119.

32. Busing F., *et al*. “High intake of orange juice and cola differently affects metabolic risk in healthy subjects”. *Clinical Nutrition* 38.2 (2019): 812-819.

33. Morand C., *et al*. “Hesperidin contributes to the vascular protective effects of orange juice: A randomized crossover study in healthy volunteers”. *American Journal of Clinical Nutrition* 93.1 (2011): 73-80.

34. Oude Griep L M., *et al*. “Association of raw fruit and fruit juice consumption with blood pressure: The intermap study”. *American Journal of Clinical Nutrition* 97.5 (2013): 1083-1091.

35. Lee S G., *et al*. “Impact of orange juice consumption on bone health of the u.S. Population in the national health and nutrition examination survey 2003-2006”. *Journal of Medicinal Food* 17.10 (2014): 1142-1150.

36. Kean R J., *et al*. “Chronic consumption of flavanone-rich orange juice is associated with cognitive benefits: An 8-wk, randomized, double-blind, placebo-controlled trial in healthy older adults”. *American Journal of Clinical Nutrition* 101.3 (2015): 506-514.

37. Bedford, E. “Orange juice domestic consumption in the united states from 2008/09 to 2019/20”. Statista (2020).

38. Ahluwalia N., *et al*. “Update on nhanes dietary data: Focus on collection, release, analytical considerations, and uses to inform public policy”. *Advances in Nutrition* 7.1 (2016): 121-134.

39. Centers for Disease Control and Prevention and National Center for Health Statistics. “National health and nutrition examination survey, survey methods and analytic guidelines” (2020).

40. National Health and Nutrition Examination Survey. “Mec in-person dietary interviewers procedures manual pdf” (2002).

41. Centers for Disease Control and Prevention. “Nchs research ethics review board (erb) approval” (2017).

42. Centers for Disease Control and Prevention and National Center for Health Statistics. “National health and nutrition examination survey (nhanes), response rates and population totals” (2020).

43. “National health and nutrition examination survey (nhanes) analytic and reporting guidelines” (2020).

44. National health and nutrition examination survey (nhanes). “Questionnaires, datasets, and related documentation” (2020).

45. Nhanes. “Documentation, codebooks, sas code” (2020).

46. National health and nutrition examination survey. “Anthropometry procedures manual pdf” (2020).

47. National Heart, Lung, and Blood Institute. “Overweight and obesity” (2020).

48. United States Department of Agriculture and Agricultural Research Service. “Usda food and nutrient database for dietary studies” (2019).

49. National Center for Health Statistics. “The nhanes 2002 mec in-person dietary interviewers procedures manual” (2002).

50. U S Department of Agriculture. “What we eat in america/ nhanes overview”. Food Surveys Research Group October (2019).

51. National Cancer Institute. “Usual dietary intakes: The nci method”. Epidemiology and Genomics Research Program (2020).

52. Dietary reference intakes: Applications in dietary assessment. Washington, DC: The National Academies Press (2000).

53. Moore L V and F E Thompson. “Adults meeting fruit and vegetable intake recommendations - united states, 2013”. *MMWR Morbidity and Mortality Weekly Report* 64.26 (2015): 709-713.

54. Vance V A., *et al*. “Self-reported dietary energy intake of normal weight, overweight and obese adolescents”. *Public Health Nutrition* 12.2 (2009): 222-227.

55. Rennie K L., *et al*. "Secular trends in under-reporting in young people". *British Journal of Nutrition* 93.2 (2005): 241-247.

56. Briefel R R., *et al*. "Dietary methods research in the third national health and nutrition examination survey: Underreporting of energy intake". *The American Journal of Clinical Nutrition* 65.4 (1997): 1203S-1209S.

57. Champagne C M., *et al*. "Underreporting of energy intake in biracial children is verified by doubly labeled water". *Journal of the American Dietetic Association* 96.7 (1996): 707-709.