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(54) **STABLE, HIGHLY PURE L-CYSTEINE COMPOSITIONS FOR INJECTION AND METHODS OF USE**

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See application file for complete search history.

(56) **References Cited**

U.S. PATENT DOCUMENTS

4,385,086 A * 5/1983 Nakayama C09D 4/00 427/387
5,072,002 A 12/1991 Clive et al.
(Continued)

OTHER PUBLICATIONS

"Guidelines for the Use of Parenteral and Enteral Nutrition in Adult and Pediatric Patients," ASPEN Board of Directors and the Clinical Guidelines Task Force, Journal of Parenteral and Enteral Nutrition, 26(1 Suppl.):1SA-138SA, (2002).
(Continued)

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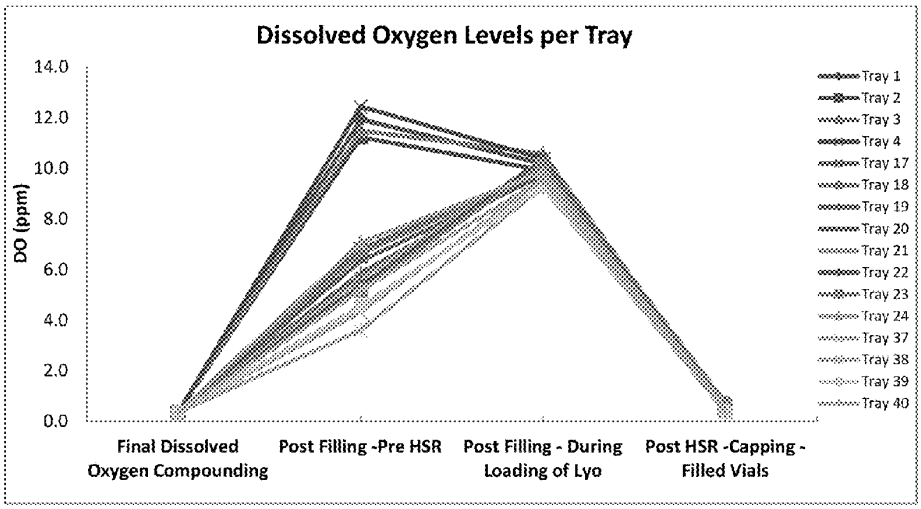
(57) **ABSTRACT**

The subject matter described herein is directed to stable L-cysteine compositions for injection, comprising: L-cysteine or a pharmaceutically acceptable salt thereof and/or hydrate thereof in an amount from about 10 mg/mL to about 100 mg/mL; Aluminum in an amount from about 1.0 parts per billion (ppb) to about 250 ppb; cystine in an amount from about 0.01 wt % to about 2 wt % relative to L-cysteine; pyruvic acid in an amount from about 0.01 wt % to about 2 wt % relative to L-cysteine; a pharmaceutically acceptable carrier, comprising water; headspace O_2 that is less than 1.0%; dissolved oxygen present in the carrier in an amount from about 0.01 parts per million (ppm) to about 1 ppm, wherein the composition is enclosed in a single-use container having a volume of from 10 mL to 100 mL. Also described are compositions for a total parenteral nutrition regimen and methods for their use.

27 Claims, 5 Drawing Sheets



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(56) **References Cited**

U.S. PATENT DOCUMENTS

6,051,567	A	4/2000	Abrahamson et al.
6,382,442	B1	5/2002	Thibault et al.
6,992,218	B2	1/2006	Dietlin et al.
7,323,206	B1	1/2008	Driscoll et al.
9,220,700	B2	12/2015	Savarese et al.
10,493,051	B1	12/2019	Sutterer et al.
10,543,186	B1	1/2020	Sutterer et al.
2019/0233153	A1	8/2019	Hofstetter
2019/0247307	A1	8/2019	Hofstetter

OTHER PUBLICATIONS

"Acetadote (acetylcysteine) injection, for intravenous use: Prescribing Information [package insert]," Cumberland Pharmaceuticals Inc., 12 pages, (2017).

"Aluminum in Large and Small Volume Parenterals Used in Total Parenteral Nutrition," Federal Register, 65(17):4103-4111, (2000).

"Aluminum in Large and Small Volume Parenterals Used in Total Parenteral Nutrition; Delay of Effective Date," Federal Register, 66(18):7864-7865, (2001).

"Aminosyn [prescribing information and label]," Hospira, Inc., 19 pages, (2012).

"Aminosyn [prescribing information and label]," Hospira, Inc., 28 pages, (2019).

"ASHP Guidelines on the Safe Use of Automated Compounding Devices for the Preparation of Parenteral Nutrition Admixtures," Automation and Information Technology—Guidelines, 63-67, (2000).

"Chapter 18: Preparation of Parenteral Nutrition," Aseptic Processing Manual, NHS Technical Specialist Education and Training Group, 24 pages, (2018).

"Cysteine Hydrochloride [FDA package insert]," Hospira, Inc., 7 pages, (2007).

"Cysteine Hydrochloride Injection [Material Safety Data Sheet]," Hospira Inc., 6 pages, (2011).

"Cysteine Hydrochloride Injection [prescribing information]," Hospira, Inc., 4 pages, (2004). [Retrieved from the Internet Dec. 28, 2016: <URL: https://dailymed.nlm.nih.gov/dailymed/archives/fdaDrugInfo.cfm?archiveid=113819>].

"Cysteine," TOXNET: Toxicology Data Network, National Library of Medicine HSDB Database, 20 pages, (2016). [Retrieved from the Internet Jun. 27, 2017: <URL:https://toxnet.nlm.nih.gov/cgi-bin/sis/search/a?dbs+hsdb:@term+@DOCNO+2109>].

"Cysteine: Pediatric drug information," Lexicomp, Inc., 4 pages, (1978).

"Determination That Cysteine Hydrochloride Injection, USP, 7.25%, Was Not Withdrawn From Sale for Reasons of Safety or Effectiveness," Federal Register, 75(107):31790-31791, (2010).

"Effect of L-Cysteine (Acetium® Capsules) in Restoration of the Structure and Function of Gastric Mucosa After H. pylori Eradication in Patients with Atrophic Gastritis. A randomized, controlled trial.," Study Protocol, BIOHIT HealthCare, 45 pages, (2016).

"Guideline on the Use of Parenteral Nutrition in Neonatal and Paediatric Units," Clinical Practice Guideline, Royal College of Physicians in Ireland, 46 pages, (2016).

"L-Cysteine [product information]," Sigma-Aldrich, Inc., 2 pages, (2003).

"L-Cysteine Hydrochloride [prescribing information and label]", Sandoz Inc., 6 pages, (2010).

"L-Cysteine Hydrochloride Injection, USP [prescribing information]," American Regent, Inc., 2 pages, (2009).

"L-Cysteine Hydrochloride Injection,solution [drug label information]", Sandoz Inc.,(2018).

"L-Cysteine Hydrochloride Monohydrate [product information]," Sigma-Aldrich, Inc., 1 page, (2006).

"PROSOL [prescribing information and label]," Baxter Healthcare Corporation, 14 pages, (2014).

"Safe Practices for Parenteral Nutrition Formulations," National Advisory Group on Standards and Practice Guidelines for Parenteral Nutrition, Journal of Parenteral and Enteral Nutrition, 22(2):49-66, (1998). [Retrieved from the Internet Mar. 12, 2015: <URL: https://onlinelibrary.wiley.com/doi/10.1177/014860719802200249>].

"Scientific Opinion on the safety and efficacy of L-cysteine hydrochloride monohydrate as a flavouring additive for pets," European Food Safety Authority Journal, 11(10):3437, 13 pages, (2013).

"The Provision of Parenteral Nutrition within Neonatal Services—A Framework for Practice," British Association of Perinatal Medicine, 27 pages, (2016).

"Travasol [prescribing information and label]," Baxter Healthcare Corporation, 19 pages, (2017).

"Trophamine [prescribing information and label]," B. Braun Medical Inc., 21 pages, (2014).

"Trophamine® (Amino Acid Injections) [package insert]," B. Braun Medical Inc., pp. 5-16, (2003).

Abdulrazik et al., "Formulation for Slow Release of Oral Radiation-Protection Drugs," Int. J. Nucl. Med. Biol., 11(1):53-54, (1984).

Advenier et al., "Aluminum Contamination of Parenteral Nutrition and Aluminum Loading in Children on Long-Term Parenteral Nutrition," Journal of Pediatric Gastroenterology and Nutrition, 36(4):448-453, (2003). [Retrieved from the Internet Jun. 6, 2018: <URL: https://journals.lww.com/jpgn/Fulltext/2003/04000/Aluminum_Contamination_of_Parenteral_Nutrition_and.5.aspx#pdf-link>].

Allen, Jr., Loyd V., "L-Cysteine Hydrochloride 50 mg/mL Injection," U.S. Pharmacist, 36(9):41-42, (2011). [Retrieved from the Internet May 26, 2016: <URL: https://www.uspharmacist.com/article/lcysteinehydrochloride50mgmlinjection>].

Allen, Loyd V., "Chapter 1: Guidelines for Compounding Practices," The Art, Science, and Technology of Pharmaceutical Compounding, 4th Ed.:1-18, (2012).

Allwood et al., "Compatibility and Stability of Additives in Parenteral Nutrition Admixtures," Nutrition 14(9):697-706, (1998).

Anderson et al., "Physical Compatibility of Calcium Chloride and Sodium Glycerophosphate in Pediatric Parenteral Nutrition Solutions," Journal of Parenteral and Enteral Nutrition, 40(8):1166-1169, (2016, Epub. 2015). [Retrieved from the Internet Oct. 24, 2015: <URL: https://onlinelibrary.wiley.com/doi/epdf/10.1177/0148607115592673>].

(56) **References Cited**

OTHER PUBLICATIONS

Ayers et al., "A.S.P.E.N. Parenteral Nutrition Safety Consensus Recommendations," Scholarship and Professional Work—COPHS, Butler University, 66 pages, (2014).
Baines et al., "The Association Between Cysteine, Bone Turnover, and Low Bone Mass," Calcif Tissue Int, 81(6):450-454, (2007).
Balogh, Judit Kovácsné, "Preparation and examination of TPN systems for the individual clinical therapy," (Ph.D. Thesis), Semmelweis University, Hungary, 116 pages, (2007).
Bengoa et al., "Amino acid-induced hypercalciuria in patients on total parenteral nutrition," The American Journal of Clinical Nutrition, 38(2):264-269, (1983). [Retrieved from the Internet Dec. 14, 2017: <URL: https://academic.oup.com/ajcn/article-abstract/38/2/264/4690894>].
Bettner et al., "Effects of pH, Temperature, Concentration, and Time on Particle Counts in Lipid-Containing Total Parenteral Nutrition Admixtures," Journal of Parenteral and Enteral Nutrition, 10(4):375-380, (1986). [Retrieved from the Internet Mar. 10, 2015: <URL: https://onlinelibrary.wiley.com/doi/epdf/10.1177/014860718601000437 5>].
Bishop et al., "Aluminum Neurotoxicity in Preterm Infants Receiving Intravenous-Feeding Solutions," The New England Journal of Medicine, 336(22):1557-1561, (1997). [Retrieved from the Internet Jun. 5, 2018: <URL: https://www.nejm.org/doi/full/10.1056/NEJM199705293362203>].
Bistrian, Bruce R., "Brief History of Parenteral and Enteral Nutrition in the Hospital in the USA," Nestlé Nutr Inst Workshop Ser Clin Perform Program, 12:127-136, (2009).
Bjelton et al., "Availability of Cysteine and of L-2-Oxo-Thiazolidine-4-Carboxylic Acid as a Source of Cysteine in Intravenous Nutrition," Journal of Parenteral and Enternal Nutrition, 14(2):177-182, (1990).
Bohrer et al., Aluminum Loading in Preterm Neonates Revisited, JPGN, 51(2):237-241, (2010).
Bohrer et al., "Influence of the glass packing on the contamination of pharmaceutical products by aluminum. Part II: Amino acids for parenteral nutrition," J. Trace Elem. Med. Biol., 15(2-3):103-108, (2001).
Bohrer et al., "Influence of the glass packing on the contamination of pharmaceutical products by aluminum. Part III: Interaction container-chemicals during heating for sterilisation," J. Trace Elem. Med. Biol., 17(2):107-115, (2003).
Borges-Santos et al., "Plasma glutathione of HIV+ patients responded positively and differently to dietary supplementation with cysteine or glutamine," Nutrition, 28(7-8):753-756, (2012).
Boullata et al., "A.S.P.E.N. Clinical Guidelines: Parenteral Nutrition Ordering, Order Review, Compounding, Labeling, and Dispensing," Journal of Parenteral and Enteral Nutrition, 38(3):334-377, (2014).
Brigham et al., "The Concentrations of Cysteine and Cystine in Human Blood Plasma," J Clin Invest., 39(11):1633-1638, (1960).
Brown et al., "Potential Aluminum Exposure from Parenteral Nutrition in Patients with Acute Kidney Injury," The Annals of Pharmacotherapy, 42(10):1410-1415, (2008).
Bulbul et al., "Letter to the Editor: Nutritional support in preterm infants," Pediatrics and Neonatology, 58(6):562, (2017).
Bullock et al., "Emulsion Stability in Total Nutrient Admixtures Containing a Pediatric Amino Acid Formulation," Journal of Parenteral and Enteral Nutrition, 16(1):64-68, (1992). [Retrieved from the Internet Feb. 10, 2015: <URL: https://onlinelibrary.wiley.com/doi/pdf/10.1177/014860719201600164>].
Calkins et al., "Effect of High-Dose Cysteine Supplementation on Erythrocyte Glutathione: a Double-Blinded, Randomized Placebo Controlled Pilot Study in Critically Ill Neonates," JPEN J Parenter Enteral Nutr., 40(2):226-234, (2016).
Carlson et al., "Neonatal Parenteral and Enteral Nutrition: A Resource Guide for the Student and Novice Neonatal Nurse Practitioner," National Association of Neonatal Nurse Practitioners, 23 pages, (2010).
Complaint with Request for Temporary Restraining Order, Preliminary and Permanent Injunctions, *Exela Pharma Sciences, LLC* v.*Sandoz, Inc.*, No. 1:19-cv-318, (W.D.N.C., Nov. 6, 2019).
Connelly et al., "Congenital Hypothyroidism Caused by Excess Prenatal Maternal Iodine Ingestion," The Journal of Pediatrics, 161(4):760-762, (2012).
Courtney-Martin et al., "Plasma Aluminum Concentrations in Pediatric Patients Receiving Long-Term Parenteral Nutrition," Journal of Parenteral and Enteral Nutrition, 39(5):578-585, (2014).
Courtney-Martin et al., "The Addition of Cysteine to the Total Sulphur Amino Acid Requirement as Methionine Does Not Increase Erythrocytes Glutathione Synthesis in the Parenterally Fed Human Neonate," Pediatric Research, 67(3):320-324, (2010).
Darkwa et al., "Antioxidant Chemistry: Oxidation of L-Cysteine and Its Metabolites by Chlorite and Chlorine Dioxide," J. Phys. Chem. A., 108(26):5576-5587, (2004).
De Cloet et al., "Physicochemical stable standard all-in-one parenteral nutrition admixtures for infants and children in accordance with the ESPGHAN/ESPEN guidelines," Nutrition, 49:41-47, (2018).
Delange, F., "Optimal Iodine Nutrition during Pregnancy, Lactation and the Neonatal Period," Int J Encrinol Metab, 2(1):1-12, (2004).
Delange, Francois, "Iodine deficiency in Europe and its consequences: an update," Eur J Nucl Med, 29(Suppl. 2):S404-S416, (2002).
Delange, Francois, "Iodine requirements during pregnancy, lactation and the neonatal period and indicators of optimal iodine nutrition," Public Health Nutrition: 10(12A):1571-1580, (2007).
Dietary Reference Intakes for Energy, Carbohydrate, Fiber, Fat, Fatty Acids, Cholesterol, Protein, and Amino Acids, The National Academies Press, 1358 pages, (2002). [Retrieved from the Internet Dec. 12, 2017: <URL: http://www.nap.edu/10490>].
Dietary Reference Intakes for Vitamin A, Vitamin K, Arsenic, Boron, Chromium, Copper, Iodine, Iron, Manganese, Molybdenum, Nickel, Silicon, Vanadium, and Zinc, National Academy Press, 800 pages, (2000). [Retrieved from the Internet Dec. 16, 2018: <URL: http://www.nap.edu/catalog/10026.html>].
Dilger et al., "Excess Dietary L-Cysteine, but Not L-Cystine, Is Lethal for Chicks but Not for Rats or Pigs," The Journal of Nutrition, 137(2):331-338, (2007). [Retrieved from the Internet Jun. 28, 2017: <URL:https://academic.oup.com/jn/article/137/2/331/4664534>].
Domingo et al., "Risks of aluminium exposure during pregnancy," Contributions to Science, 1(4):479-487, (2000).
Dumortier et al., "Development of a Thermogelling Ophthalmic Formulation of Cysteine," Drug Development and Industrial Pharmacy, 32(1):63-72, (2006). [Retrieved from the Internet May 12, 2015: <URL: https://www.tandfonline.com/doi/full/10.1080/03639040500390934>].
El-Shenawy et al., "Nephrotoxicity of sodium valproate and protective role of L-cysteine in rats at biochemical and histological levels," J Basic Clin Physiol Pharmacol, 27(5):497-504, (2016). [Retrieved from the Internet May 4, 2016: <URL: https://www.degruyter.com/view/j/jbcpp.2016.27.issue-5/jbcpp-2015-0106/jbcpp-2015-0106.xml>].
Fewtrell et al., "Aluminium exposure from parenteral nutrition in preterm infants and later health outcomes during childhood and adolescence," Symposium 2: Micronutrients under the Microscope, Proceedings of the Nutrition Society, 70(3):299-304, (2011). [Retrieved from the Internet Jun. 4, 2018: <URL: https://www.cambridge.org/core/journals/proceedings-of-the-nutrition-society/article/aluminium-exposure-from-parenteral-nutrition-in-preterm-infants-and-later-health-outcomes-during-childhood-and-adolescence/F5D0A6109616E8C9D7F8C2C707213860/core-reader>].
Flora et al., "Chelation in Metal Intoxication," Int. J. Environ. Res. Public Health, 7(7):2745-2788, (2010).
Fortenberry et al., "Evaluating Differences in Aluminum Exposure through Parenteral Nutrition in Neonatal Morbidities," Nutrients, 9(11):E1249, 6 pages, (2017).
Frey et al., "Confirming the Causative Role of Acetaminophen in Indeterminate Acute Liver Failure Using Acetaminophen-Cysteine Adducts," J. Med. Toxicol., 11(2):218-222, (2015).
Fürst et al., "Parenteral nutrition by a solution of crystalline amino acids," Acta Med Scand Suppl., 472:283-293, (1967).

(56) **References Cited**

OTHER PUBLICATIONS

Fusch et al., "Neonatology/Paediatrics—Guidelines on Parenteral Nutrition, Chapter 13," GMS German Medical Science, 7(Doc15):23 pages, (2009).
Ghirri et al., "Iodine Supplementation in the Newborn," Nutrients, 6(1):382-390, (2014).
Gura et al., "Aluminum contamination in products used in parenteral nutrition: Has anything changed?," Nutrition, 26(6):585-594, (2010).
Gura et al., "Recent developments in aluminium contamination of products used in parenteral nutrition," Curr Opin Clin Nutr Metab Care, 9(3):239-246, (2006).
Gura, Kathleen M., "Aluminum contamination in parenteral products," Current Opinions in Clinical Nutrition and Metabolic Care, 17(6):551-557, (2014).
Hardy et al., "Formulation, Stability, and Administration of Parenteral Nutrition With New Lipid Emulsions," Nutrition in Clinical Practice, 24(5):616-625, (2009).
Hardy et al., "P.83: Stability of aqueous cysteine solutions for TPN [Abstract]," Clinical Nutrition, 12(Suppl 2):61, (1993).
Harman et al., "Free Radical Metabolites of L-Cysteine Oxidation," The Journal of Biological Chemistry, 259(9):5606-5611, (1984). [Retrieved from the Internet Feb. 6, 2017: <URL: http://www.jbc.org/content/259/9/5606.full.pdf>].
Heird et al., "Pediatric Parenteral Amino Acid Mixture in Low Birth Weight Infants," Pediatrics, 81(1):41-50, (1988). [Retrieved from the Internet Dec. 8, 2017: <URL: http://pediatrics.aappublications.org/content/81/1/41>].
Hellström et al., "Sa1863. L-Cysteine Slow-Release Capsule Fromulation in Prevention of Gastric Carcinogenesis Associated With Atrophic Gastritis," AGA Abstracts, 146(5, Suppl 1):S-315 (2014).
Helms et al., "Cysteine supplementation results in normalization of plasma taurine concentrations in children receiving home parenteral nutrition," J Pediatr, 134(3):358-361, (1999).
Hernández-Sánchez et al., "Aluminium in parenteral nutrition: a systematic review," European Journal of Clinical Nutrition, 67(3):230-238, (2013).
Heyman et al., "Aluminum Does Not Accumulate in Teenagers and Adults on Prolonged Parenteral Nutrition Containing Free Amino Acids," Journal of Parenteral and Enteral Nutrition, 10(1):86-87, (1986).
Hintz et al., "Aluminum Exposure From Pediatric Pareteral Nutrition: Meeting the New FDA Regulation," JPEN J Parenter Enteral Nutr, 32:242-246, (2008).
Ho et al., "Trend of Nutritional Support in Preterm Infants," Pediatrics and Neonatology, 57(5):365-370, (2016).
Hu et al., "Efficacy and safety of acetylcysteine in "non-acetaminophen" acute liver failure: A meta-analysis of prospective clinical trials," Clin Res Hepatol Gastroenterol, 39(5):594-599, (2015).
Hulst, Jessie, "Principles of feeding the preterm infant," 36th ESPEN Congress, Geneva, 44 pages, (2014).
Huston et al., "Calcium Chloride in Neonatal Parenteral Nutrition Solutions with and without Added Cysteine: Compatibility Studies Using Laser and Micro-Flow Imaging Methodology," PLoS One, 10(8):e0136894, (2015).
Huston et al., "Calcium chloride in neonatal parenteral nutrition: A 15 year experience," Journal of Neonatal-Perinatal Medicine, 10(1):33-38, (2017).
Huston et al., "Calcium Chloride in Neonatal Parenteral Nutrition: Compatibility Studies Using Laser Methodology," PLoS One, 9(9):e106825, (2014).
Ishii et al., "A case of drug-induced ductopenia resulting in fatal biliarv cirrhosis," Liver, 13(4):227-231, (1993).
Ishii et al., "Cystathionine γ-Lyase-deficient Mice Require Dietary Cysteine to Protect against Acute Lethal Myopathy and Oxidative Injury," The Journal of Biological Chemistry, 285(34):26358-26368, (2010).
Jadhav et al., "Parenteral Amino Acid and Metabolic Acidosis in Premature Infants," JPEN J Parenter Enteral Nutr., 31(4):278-283, (2007).
Jalilehvand et al., "Lead(II) Complex Formulation with L-Cysteine in Aqueous Solution," Inorganic Chemistry, 54:2160-2170, (2015).
Janáky et al., "Mechanisms of L-Cysteine Neurotoxicity," Neurochemical Research, 25(9/10):1397-1405 (2000).
Ji et al., "Excessive L-cysteine induces vacuole-like cell death by activating endoplasmic reticulum stress and mitogen-activated protein kinase signaling in intestinal porcine epithelial cells," Amino Acids, 48(1):149-156, (2015).
John et al., "Total parenteral nutrition usage trends in the United States,"Journal of Critical Care, 40:312-313, (2017).
Kartal et al., "Compatibility of chewing gum excipients with the amino acid L-cysteine and stability of the active substance in directly compressed chewing gum formulation," Journal of Pharmacy and Pharmacology, 60(9):1131-1138, (2008).
Kartal et al., "Formulation and in-vivo evaluation of L-cysteine chewing gums for binding carcinogenic acetaldehyde in the saliva during smoking," Journal of Pharmacy and Pharmacology, 59(10):1353-1358, (2007).
Kartal-Hodzic, Alma, "Formulation studies for eliminating saliva carcinogenic acetaldehyde with L-cysteine containing chewing gum," (Academic Dissertation), Division of Biopharmaceutics and Pharmacokinetics, University of Helsinki, Finland, 60 pages, (2012).
Klein et al., "Hypocalcemia Complicating Deferoxamine Therapy in an Infant with Parenteral Nutrition-Associated Aluminum Overload: Evidence for a Role of Aluminum in the Bone Disease of Infants," Journal of Pediatric Gastroenterology and Nutrition, 9(3):400-403, (1989). [Retrieved from the Internet Jun. 5, 2018: <URL: https://journals.lww.com/jpgn/Abstract/1989/10000/Hypocalcemia_Complicating_Deferoxamine_Therapy_in.24.aspx>].
Klein, Catherine J., "Nutrient Requirements for Preterm Infant Formulas," The Journal of Nutrition, 132(6 Suppl 1):1395S-1577S, (2002). [Retrieved from the Internet Dec. 6, 2017: <URL: http://jn.nutrition.org>].
Kolaric et al., "Solutions Preparing for Total Parenteral Nutrition for Children," Proceedings of the 7th WSEAS International Conference on Mathematics & Computers in Biology & Chemistry, Cavtat, Croatia, 6 pages, (2006).
Koletzko et al., "Guidelines on Paediatric Parenteral Nutrition: 3. Amino Acids," J. Pediatr. Gastroenterol. Nutr., 41(Suppl. 2):S12-S18, (2005).
Komura et al., "Increased Incidence of Cholestasis during Total Parenteral Nutrition in Children," The Kurume Medical Journal, 40(1):7-11, (1993).
Koo et al., "Response to aluminum in parenteral nutrition during infancy," The Journal of Pediatrics, 109(5):877-883, (1986).
Laine et al., "Cysteine usage increases the need for acetate in neonates who receive total parenteral nutrition," The American Journal of Clinical Nutrition, 54(3):565-567, (1991). [Retrieved from the Internet Apr. 14, 2015: <URL: https://academic.oup.com/ajcn/article-abstract/54/3/565/4694399>].
Lapillonne et al., "Quality of newborn care: adherence to guidelines for parenteral nutrition in preterm infants in four European countries," BMJ Open, 3(9):E003478, 8 pages, (2013). [Retrieved from the Internet Jun. 6, 2018: <URL: https://bmjopen.bmj.com/content/3/9/e003478>].
Larchet et al., "Aluminium Loading in Children Receiving Long-term Parenteral Nutrition," Clinical Nutrition, 9(2):79-83, (1990).
Lee et al., "AASLD Position Paper: The Management of Acute Liver Failure: Update 2011," Hepatology, 1-22 and Corrections, (2011).
Lee et al., "Introduction to the Revised American Association for the Study of Liver Diseases Position Paper on Acute Liver Failure 2011," Hepatology, 55(3):965-967, (2012).
Leung et al., "Consequences of excess iodine," Nat Rev Endocrinol., 10(3):136-142, (2014).
Leyden et al., "Stabilization of Solutions of Cysteine and its Derivatives," Can. J. Biochem., 45(4):611-614, (1967). [Retrieved from the Internet Nov. 12, 2014: <URL: https://www.nrcresearchpress.com/doi/pdf/10.1139/o67-071>].
Li et al., "Acute and sub-chronic toxicity of glucose-cysteine Maillard reaction products in Sprague-Dawley rats," Food and Chemical Toxicology, 80:271-276, (2015).

(56) **References Cited**

OTHER PUBLICATIONS

Lima-Rogel et al., "Aluminum Contamination in Parenteral Nutrition Admixtures for Low-Birth-Weight Preterm Infants in Mexico," Journal of Parenteral and Enteral Nutrition, 40(7):1014-1020, (2016).
Look et al., "Is the Increase in Serum Cystathionine Levels in Patients with Liver Cirrhosis a Consequence of Impaired Homocysteine Transsulfuration at the Level of γ-Cystathionase?," Scand J Gastroenterol, 35(8):866-872, (2000). [Retrieved from the Internet Oct. 25, 2014: <URL: https://www.tandfonline.com/doi/abs/10.1080/003655200750023255>].
Mackay et al., "Physical Compatibility of Sodium Glycerophosphate and Calcium Gluconate in Pediatric Parenteral Nutrition Solutions," JPEN J Parenter Enteral Nutr, 39(6):725-728, (2015, Epub. 2014). [Retrieved from the Internet Apr. 6, 2014: <URL: http://pen.sagepub.com/content/early/2014/03/31/0148607114528982>].
Mackay et al., "The Solubility of Calcium and Phosphate in Two Specialty Amino Acid Solutions," Journal of Parenteral and Enteral Nutrition, 20(1):63-66, (1996). [Retrieved from the Internet Apr. 17, 2015: <URL: https://onlinelibrary.wiley.com/doi/epdf/10.1177/014860719602000163>].
Malloy et al., "Cyst(e)ine measurements during total parenteral nutrition," The American Journal of Clinical Nutrition, 37(2):188-191, (1983). [Retrieved from the Internet Apr. 14, 2015: <URL: https://academic.oup.com/ajcn/article-abstract/37/2/188/4690722>].
Malloy et al., "Cysteine Supplementation During Total Parenteral Nutrition (TPN) [Abstract]," Clinical Nutrition, 1(Suppl.):49, (1982).
Malloy et al., "Cysteine Supplementation of Total Parenteral Nutrition: the Effect in Beagle Pups," Pediatric Research, 18(8):747-751, (1984).
Malloy et al., "Total Parenteral Nutrition in Sick Preterm Infants: Effects of Cysteine Supplementation with Nitrogen Intakes of 240 and 400 mg/kg/day," Journal of Pediatric Gastroenterology and Nutrition, 3(2)239-244, (1984).
Manz, Friedrich, "L-Cysteine in metabolic acidosis of low-birth-weight infants," Am J Clin Nutr, 57(3):455-456, (1993). [Retrieved from the Internet Apr. 16, 2015: <URL: https://academic.oup.com/ajcn/article-abstract/57/3/455/4715721>].
Mattox et al., "Chapter 142: Parenteral Nutrition," Pharmacotherapy: A Pathophysiologic Approach, 10e, McGraw Hill, Ed. Joseph T. DiPiro et al., 38 pages, (2016). [Retrieved from the Internet Dec. 5, 2017: <URL: https://accesspharmacy.mhmedical.com/content.aspx?bookid=1861&sectionid=146076679>].
McCarthy et al., "Standardised versus Individualized Parenteral Nutrition," Irish Medical Journal, 109(4):10 pages, (2016). [Retrieved from the Internet Jun. 6, 2018: <URL: http://imj.ie/standardised-versus-individualised-parenteral-nutrition-further-food-for-thought/>].
McClave et al., "Guidelines for the Provision and Assessment of Nutrition Support Therapy in the Adult Critically Ill Patient: Society of Critical Care Medicine (SCCM) and American Society for Parenteral and Enteral Nutrition (A.S.P.E.N.)," Journal of Parenteral and Enteral Nutrition, 40(2):159-211, (2016).
Memorandum in Support of Plaintiff's Motion for Ex Parte Temporary Restraining Order and Preliminary Injunction, *Exela Pharma Sciences, LLC* v.*Sandoz, Inc.*, No. 1:19-cv-318, (W.D.N.C., Nov. 6, 2019).
Metabolic Processes in the Foetus and Newborn Infant, Nutricia Symposium, Ed. J. H. P. Jonxis et al., H. E. Stenfert Kroese N.V., 317 pages, (1971).
Miller et al., "Decreased Cysteine and Proline Synthesis in Parenterally Fed, Premature Infants," Journal of Pediatric Surgery, 30(7):953-958, (1995).
Miller, Sarah J., "Parenteral Nutrition," U.S. Pharmacist, 7(HS10-H520):31 pages, (2006). [Retrieved from the Internet Sep. 26, 2018: <URL: https://www.uspharmacist.com/article/parenteral-nutrition>].
Mirtallo et al., "Safe Practices for Parenteral Nutrition," Journal of Parenteral and Enteral Nutrition, 28(6):S39-S70, (2004). [Retrieved from the Internet Jan. 23, 2014: <URL: https://journals.sagepub.com/doi/abs/10.1177/0148607104028006s39>].
Moreno et al., "Aluminium in the neonate related to parenteral nutrition," Acta Paediatr, 83(1):25-29, (1994).
Moreno Villares et al., "Current use of parenteral nutrition in a pediatric hospital. Comparison to the practise 8 years ago," Nutr. Hosp., 20(1):46-51, (2005).
Mühlebach, Stefan, "Parenteral Nutrition: The Role of the Pharmacist in the Era of 3-chamber Bags," 27th ESPEN Congress, Brussels, 49 pages, (2005).
Mundi et al., "Prevalence of Home Parenteral and Enteral Nutrition in the United States [Abstract]," Nutr Clin Pract., 32(6):799-805, (2017). [Retrieved from the Internet Jun. 6, 2018: <URL: http://journals.sagepub.com/doi/pdf/10.1177/0884533617718472>].
Murphy et al., "Annual Summary of Vital Statistics: 2013-2014," Pediatrics, 139(6):e20163239, (2017). [Retrieved from the Internet Jun. 6, 2018: <URL: http://pediatrics.aapublications.org/content/139/6/e20163239>].
Nguyen et al., "Effect of Increasing Glutathione With Cysteine and Glycine Supplementation on Mitochondrial Fuel Oxidation, Insulin Sensitivity, and Body Composition in Older HIV-Infected Patients," J Clin Endocrinol Metab,, 99(1):169-177, (2014). [Retrieved from the Internet Dec. 12, 2017: <URL: https://academic.oup.com/jcem/article-abstract/99/1/169/2836223>].
Niermeyer et al., "Optimized calcium/phosphorus solubility in a parenteral nutrition solution containing dicarboxylic amino acids and cysteine," Journal of the American College of Nutrition, 5(5):459-466, (1986). [Retrieved from the Internet Apr. 21, 2015: <URL: https://www.tandfonline.com/doi/pdf/10.1080/07315724.1986.10720149>].
Nishiyama et al., "Transient Hypothyroidism or Persistent Hyperthyrotropinemia in Neonates Born to Mothers with Excessive Iodine Intake," Thyroid, 14(2):1077-1083, (2004).
Ogawa et al., "Comparisons of Aluminum and Silica Elution from Various Glass Vials," Chemical and Pharmaceutical Bulletin, 64:150-160, (2016).
Olney et al., "Brain Damage in Infant Mice following Oral Intake of Glutamate, Aspartate or Cysteine," Nature, 227(5258):609-611, (1970).
O'Neal et al., "Compliance with safe practices for preparing parenteral nutrition formulations," Am J Health Syst Pharm, 59(3):264-269, (2002).
Parikh et al., "Physical compatibility of neonatal total parenteral nutrient admixtures containing organic calcium and inorganic phosphate salts," Am J Health Syst Pharm, 62(11):1177-1183, (2005).
Patanwala et al., "Antiemetic Therapy for Nausea and Vomiting in the Emergency Department," The Journal of Emergency Medicine, 39(3):330-336, (2010).
Patel et al., "Total parenteral nutrition for premature infants: practice aspects," Journal of Nature and Science (JNSCI), 3(1):e301, 6 pages, (2017).
Patt et al., "Cysteine Protection against X Irradiation," Science, 110(2852):213-214, (1949).
Paulikova et al., "Iodine toxicity in ruminants," Vet. Med.—Czech, 47(12):343-350, (2002).
Pertkiewicz et al., "Basics in clinical nutrition: Stability of parenteral nutrition admixtures," e-SPEN, the European e-Journal of Clinical Nutrition and Metabolism, 4(3):e117-e119, (2009).
Pilaniya et al., "Recent trends in the impurity profile of pharmaceuticals," J Adv Pharm Technol Res., 1(3):302-310, (2010).
Plogsted et al., "Parenteral Nutrition L-Cysteine Product Shortage Considerations," Nutrition in Clinical Practice, 30(4):579-580, (2015).
Poole et al., "Aluminum Exposure From Pediatric Parenteral Nutrition: Meeting the New FDA Regulation," Journal of Parenteral and Enteral Nutrition, 32(3):242-246, (2008).
Poole et al., "Aluminum Exposure in Neonatal Patients Using the Least Contaminated Parenteral Nutrition Solution Products," Nutrients, 12(4):1566-1574, (2012).
Pyati et al., "Absorption of iodine in the neonate following topical use of povidone iodine," The Journal of Pediatrics, 91(5):825-828, (1977).

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