Original Article

Medication-associated diethylene glycol mass poisoning: A review and discussion on the origin of contamination

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Abstract Diethylene glycol (DEG), an extremely toxic chemical, has been implicated as the etiologic agent in at least 12 medication-associated mass poisonings over the last 70 years. Why DEG mass poisonings occur remains unclear. Most reports do not contain detailed reports of trace-back investigations into the etiology. The authors, therefore, conducted a systematic literature review on potential etiologies of these mass poisonings. The current available evidence suggests that substitution of DEG or DEG-containing compounds for pharmaceutical ingredients results from: (1) deception as to the true nature of certain ingredients by persons at some point in the pharmaceutical manufacturing process, and (2) failure to adhere to standardized quality control procedures in manufacturing pharmaceutical products intended for consumers. We discuss existing guidelines and new recommendations for prevention of these incidents.
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Introduction

Medication-associated diethylene glycol mass poisoning, a term we abbreviate *MDMP*, has occurred at least 12 times over the last 70 years.[1–18] The first documented mass poisoning occurred in 1937,

when the Massengill Company introduced in the United States without any pre-marketing toxicity testing an elixir of sulfanilamide with DEG as the intended primary diluent.[1–3,18] At least 105 people died as a result of that incident, which was an important factor responsible for passage of the 1938 Food, Drug, and Cosmetic Act. The Act gave the federal Food and Drug Administration (FDA) new authority to require pharmaceutical manufacturers to document the safety of new drugs through pre-marketing testing.[3]

Since that first documented event of MDMP, at least 11 other similar poisoning events have occurred throughout the world.[4–17]

The authors participated directly in the field investigation of a recent mass poisoning, in the Republic of Panama in 2006, where diethylene glycol (DEG) was discovered in a sugarless expectorant preparation. DEG was used in the product in place of pharmaceutical grade glycerin (a safe and commonly used diluent in pharmaceutical formulations) because it had been mislabeled.

This discovery raised numerous questions about how and why this mass poisoning and others like it continue to occur. A review of similar mass poisonings revealed no common explanation of contamination. We hypothesized that commonly used diluents in pharmaceutical formulations can be tainted with DEG in their manufacture. By performing a systematic and comprehensive review of DEG-associated documents, we have attempted to identify how and why these poisonings occur.

Methods

We conducted a search on PubMed, using the MEDLINE and OLDMEDLINE databases from January 1950 to November 2006 and the keywords *diethylene glycol, propylene glycol, glycerin, glycerol* and *glycol*. The keywords were used alone as well as with the modifiers *toxicity, contamination, outbreak* and *epidemic*.

References cited in the retrieved articles were reviewed for the purpose of identifying non-indexed reports. Bibliographies of referenced articles were also searched, and key references were identified and reviewed. We also used a popular Internet search engine with the same keywords.

We reviewed information on Current Good Manufacturing Practices (CGMP) from the World Health Organization (WHO) and the FDA, along with pharmaceutical compendia such as the US Pharmacopoeia (USP). Because we found little information on the glycerin manufacturing process in peer-reviewed medical literature databases, we queried alternative sources. We reviewed book chapters from toxicology texts, unpublished technical documents, and reports. Finally, we asked professionals with specialized expertise in the chemical and pharmaceutical fields at two chemical-associated professional specialty organizations and three private chemical manufacturing companies for additional information.

The results of the first search identified manufacturing processes for glycerin, including methods that use microorganisms. We searched the same databases a second time using additional keywords: *yeast, Saccharomyces cerevisiae, osmotolerant yeast, Candida, Debaryomyces, Hansenula, Pichia, Saccharomyces, Schizosaccharomyces, Torulaspora* and *Zygosaccharomyces*, each alone and again with the previously listed modifiers. Finally, we used additional modifiers: *ethanol + fermentation, diethylene glycol, glycerin, propylene glycol, microbial fermentation, industrial* and *manufacturing*.

One author, a board-certified medical toxicologist (JS), reviewed for relevance, abstracts of peer-reviewed scientific publications found on PubMed. *Relevance* was loosely defined as any identifiable article that discussed diluent manufacturing in regard to the aforementioned items or a DEG-associated poisoning event. The index or first page of non-scientific documents appearing on websites and in technical documents was also reviewed when initially judged to be potentially relevant to the topic. If relevance was found, the document was reviewed in its entirety.

Results

We identified by the searches more than 6000 citations. Approximately 150 documents were deemed relevant, then retrieved and reviewed in their entirety. Of these, 125 were peer-reviewed publications, with the remaining items being primarily technical or policy documents, websites and book chapters. Professionals in two federal agencies and one international chemical manufacturing company agreed to be interviewed after formal requests for

Table 1: Past instances of medication-associated diethylene glycol mass poisoning

Country/ year	*Vehicle*	*Implicated diluent*	*DEG (%) final product*	*DEG (%) in raw ingredient/ intended diluent*	*Suspected location of original mislabeling*	*Suspected location of false USP designation*	*Other agents detected in implicated raw ingredient*	*Country of origin (raw ingredient or intended diluent)*	*Reference or source*
Panama (2006)	Sugar-free prescription cough syrup	Glycerin	8% v/v	22% v/v	China	Panamanian Broker	Sorbitol (53%) Sugar (23%) Glycerin (1%)	China	Schier[15] Barr[19]
France (2004)	Herbal remedy to enhance water excretion	DEG was intended diluent	Unknown	Unknown	Not applicable	Not applicable	Unknown	Unknown	Prescrire Inter[17]
India (1998)	Cough syrup Paracetamol syrup	Unknown Propylene glycol	17.5% v/v 15.4% w/w	Unknown	Unknown	Unknown	Unknown	Unknown	Hari[13] Singh[12]
Haiti (1995)	Paracetamol syrup	Glycerin	14% v/v	24% v/v	China	Chinese manufacturer or broker	Sugar (23%) Water (32%) Glycerin (1-4%)	China	O'Brien[11] Junod[14] WHO Document, General Policy Issues[30]
Bangladesh (1995)	Paracetamol syrup	Propylene glycol and /or glycerol	Unknown	Unknown	Unknown	Unknown	Unknown	Unknown	Hanif[7]
Venezuela (1992)	Acetaminophen syrup Vitamin and Anti-anemic syrups	Propylene glycol Propylene glycol	28% w/v 4–25% w/v	Unknown	Unknown	Unknown	Unknown	Unknown	Baffi[33]
Argentina (1992)	Propolis syrup (upper respiratory medicinal agent)	Propylene glycol	65% w/v	Unknown	Unknown	Unknown	Unknown	Unknown	Drut[9] Ferrari[10]

Table 1: *Continued*

Country/ year	*Vehicle*	*Implicated diluent*	*DEG (%) final product*	*DEG (%) in raw ingredient/ intended diluent*	*Suspected location of original mislabeling*	*Suspected location of false USP designation*	*Other agents detected in implicated raw ingredient*	*Country of origin (raw ingredient or intended diluent)*	*Reference or source*
Nigeria (1990)	Paracetamol syrup	Propylene glycol	Unknown	Unknown	Unknown	Unknown	Unknown	Unknown	Okuonghae[6]
India (1986)	Glycerine	Glycerine	18.5% v/v	18.5% v/v	Unknown	Unknown	Polyglycol 51% v/v Water 21% v/v Glycerol 9% v/v	India	Pandya[4]
Spain (1985)	Burn cream	Sodium lauryl sulfate	7 grams/ kilogram product	Unknown/ Not applicable	Unknown	Unknown	Sodium lauryl sulfate	Unknown	Cantarell[8]
South Africa (1969)	Sedative formulations (Pronap and Plaxim)	Propylene glycol	Unknown	Unknown	Unknown	Unknown	Unknown	Unknown	Bowie[5]
United States (1937)	Elixir of Sulfanilamide	Diethylene glycol	72% v/v	Unknown	Not applicable	Not applicable	Unknown	United States	Geiling[1]and Leech[2]

v/v=volume per volume
w/v=weight per volume
w/w=weight per weight

Table 2: Identified production methodologies for glycerin and propylene glycol with potential contaminants and toxic effects

Diluent	*General method of production*	*Potential contaminants or toxic agents/intermediates used in the manufacturing/purification process*[a]	*Toxic effect*
Glycerin	From natural fats and oils Includes hydrolysis, saponification, alcoholysis of animal fats and vegetable oils. Use of non-food grade fats and oils can lead to contaminants (Jungermann[22])	Trimethylene glycol (Jungermann[22]) Formic acid (Jungermann[22]) Various aldehydes, ketones, sulfur compounds, and other products (Jungermann[22])	Coma, metabolic acidosis Blindness Variable and agent-dependent
	From petrochemicals (synthetic)	Acrolein (Jungermann[22]) Methanol (Jungermann[22]) Dichlorohydrins/Epichloro-hydrin (Jungermann[22])	Irritation Blindness Allergic contact dermatitis
	Hydrogenolysis of carbohydrates	Ethylene glycol (Jungermann[22])	Acute renal failure
	Microbial fermentation[a] Use of simple sugars and carbohydrates for fermentation by micro-organisms. Potential contaminants, intermediates, recovery solvents in purification processes are micro-organism and method dependent	Dioxane, ether, butanol, aniline (Rehm[23]); used in purification and recovery process for glycerin Various other polyols and polyhydroxy alcohols (Rehm,[23]Wang,[24]Spencer[25])	Variable and agent-dependent Variable and agent-dependent
Propylene Glycol	Hydration of propylene oxide	Di and tri-propylene glycol along with other glycols (Harbison,[26]Innovation Group,[27]Shell[28]) Chlorhydrin(Harbison[26]) Hypochlorous acid (Harbison[26]) Propylene oxide (Harbison[26])	Variable and agent-dependent

[a]Various different carbohydrates can be used for fermentation. Diethylene glycol was suspected and investigated as a possible source of fermentation in the Haiti mass poisoning.

information. The detailed information on the 12 documented MDMPs can be found in Table 1.

In Table 2, we list the principal methods identified for production of propylene glycol and glycerin, as well as potential contaminants, toxic chemicals and intermediate compounds used or produced in manufacture, or any subsequent processes – purification, for example. No single, obvious source of contamination was identified that would conclusively explain either all instances or any agent-specific instances of MDMP. Several of the published reports of MDMP discuss or hypothesize (but do not provide definitive evidence) that DEG may have been substituted for either glycerin or propylene glycol – a safe and more expensive diluent – with the basic intent of financial gain.

Discussion

Our review of the 11 published reports of MDMP, along with firsthand knowledge of the 12th, the 2006 event in Panama, provided little insight into the underlying origins of these poisonings.[1,2,4–18] The review did confirm a potential association with two common diluents used in medications: glycerin and propylene glycol. These agents have a large number of commercial, industrial and medicinal applications, the last as medication diluents.[22,29] Diluents are inert ingredients used in pharmaceutical formulations for many reasons, including to dilute active ingredients; to provide bulk, form or consistency to a pharmaceutical formulation; or as a vehicle to deliver the pharmaceutical product orally, topically or parenterally. It is possible, therefore, that contamination was due to an intentional or unintentional error in manufacturing of a diluent. In 9 of 12 of MDMPs we studied, glycerin or propylene glycol was either confirmed or suspected to be the likely agent for which a DEG-containing product was substituted (Table 1), although detailed information was lacking. No specific mention of a confirmed or suspected diluent was made in two of the remaining three events.[8,12,13,17] If contamination occurred from a specific error in manufacturing of a diluent, it seems unlikely that it would be shared among two different diluents with different manufacturing methods.[22,29]

In an attempt to understand the origins of these events, we reviewed evidence from past MDMPs and considered known manufacturing methods for the two most commonly implicated

diluents. We believe that existing safeguards, if used properly, can prevent these kinds of events.

Review of evidence from past mass poisoning events

Detailed information on how and when DEG ended up in a pharmaceutical product is available for only two events.[11,14,30,31] In the first case, a nationally circulated and recognized periodical concluded, after its own investigation, that in the 2006 Panama event, DEG was intentionally substituted for glycerin and labeled as 99.5 per cent pure glycerin in order to sell it for a higher price.[31] Integrity verification processes to be performed during transit and at the final destination were either not performed or insufficient. In addition, during shipment, a new label appeared, describing the contents as pharmaceutical-grade (Figure 1).[31]

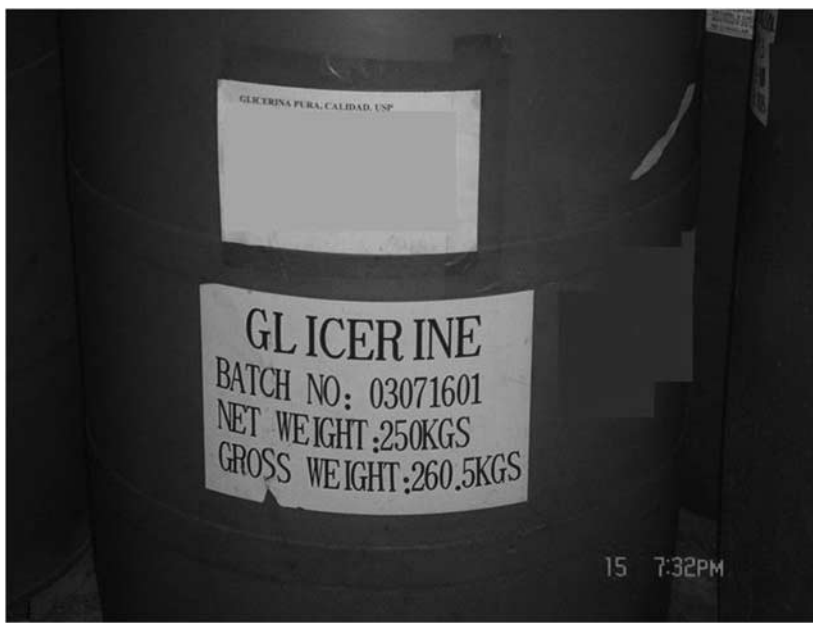

Figure 1: An original 55 gallon drum of the implicated material is shown. The first label demonstrates that the material is clearly marked as 'Glycerine' but gives no indication as to its purity. The second is from a different company (the photo has been partly obscured or edited) and is marked as 'glycerina pura' or pure glycerin. The third label has been completely obscured due to the presence of identifying information but did not contain any information on purity. The different labels demonstrate the ready visibility of conflicting information and the potential for confusion.

The origin of contamination in the second event in Haiti is unclear. But in both the Haiti and Panama events, the implicated raw materials were found to contain added chemicals that could have altered the results when basic physical properties, such as the pH, were tested.[14,30] The implicated raw material, 'glycerin' from Panama contained DEG (23 per cent), glycerol (<1 per cent) and sorbitol (53 per cent). Follow-up testing (specific gravity, residue on ignition, and fatty acids and esters) of additional samples of the implicated Panamanian 'glycerin' revealed results consistent with what would be expected for glycerin, along with the presence of a starch-like carbohydrate residue material. Analysis of several samples of the implicated raw material from the Haiti mass poisoning contained by weight DEG (20–26 per cent), sucrose (21–23 per cent) and sorbitol (20–23 per cent).[30,32] In both the Haiti and Panama events, the concentration of DEG in the raw material labeled as glycerin was similar. And in both instances, impurities of starch-like materials and sorbitol were found. These impurities can also alter the mixture's chemical and physical properties.

Although there is no definitive evidence, a plausible explanation may include an intentional attempt to make the product look on superficial appearance and testing like what it is being falsely claimed to be, or not so different as to alert officials on visual inspection. If we are correct, reliance on general testing methods, such as the use of pH, specific gravity and other basic, non-specific testing techniques, can be falsely reassuring. Of the 12 documented MDMP events that discuss propylene glycol as the suspected agent for which DEG may have been substituted, six of the reports hypothesize that it may have been done for financial gain.[5–7,10,13,33] Supporting this notion is the fact that pharmaceutical-grade diluents, especially propylene glycol, are inherently more costly because of processes needed for purification and contaminant removal to make a diluent suitable for human consumption.

Review of manufacturing methodologies for glycerin and propylene glycol

We conducted an exhaustive review of manufacturing methodologies for these two diluents. We were unable to identify any glycerin or propylene glycol production method that specifically suggested a

source of DEG. We did find many potential opportunities for other contaminants to be introduced during manufacturing steps, especially during glycerin production (Table 2). Such contaminants are product- and method-dependent. Contamination results from use of inferior, non-food-grade fats and oils in hydrolysis, saponification or alcoholysis to produce glycerin.[22] Hydrogenolysis of carbohydrates to produce glycerin can also create by-products such as ethylene glycol; by-products that would normally be removed to create a pharmaceutical-grade product.

The last glycerin production method, microbial fermentation, appears to be unusually susceptible to contamination. The use of microorganisms to produce glycerin[24,25,34–37] is increasingly popular, especially in developing countries such as China.[24] If inferior raw materials are used, this method is particularly prone to contamination during the manufacturing process[20,22,24,34] (Table 2). Both the Haiti and the Panama events involved mislabeled glycerin shipped from China. This led us to hypothesize that DEG contamination of glycerin might have occurred during the manufacturing process.

Microbial fermentation methods for glycerin production rely heavily on cheap carbon sources, such as simple sugars – beet sugar molasses, for example – and specific microorganisms to metabolize them[24,34,35] (Table 2). Contamination could hypothetically occur when inexpensive carbon-containing compounds other than simple sugars are used for microbial fermentation. No evidence exists to confirm or reject this hypothesis.[20,22,24,34] After the Haiti event, FDA officials visited the Chinese manufacturer of the implicated 'glycerin'; the manufacturer had reportedly used a microbial fermentation method.[30] The FDA specifically checked for DEG as the original carbon source for fermentation, but ultimately excluded this possibility.[30] It remains unclear if DEG would be a suitable carbon source for glycerin production by microbial fermentation.

Propylene glycol is primarily manufactured on a commercial basis by hydration of propylene oxide, using high temperature and high pressure.[23,27,29,38] Propylene is treated with hypochlorous acid, a chlorhydrin intermediate and other catalytic agents, such as calcium or sodium hydroxide, to produce propylene oxide, a chemical moderately toxic to the skin and mucous membranes.[28] Manufacturing by-products of this process may appear, but DEG has not been identified as one of them (Table 2).

Verification of documentation and pharmaceutical integrity

Counterfeit drugs make up approximately 10 per cent of the global pharmaceutical market, and they exceed 50 per cent in parts of Africa and Asia. Recent estimates describe a US$35 billion industry, and it is growing. Counterfeit drugs were reported to kill an estimated 192 000 patients in 2001 in China alone.[21] The primary problem in China appears to be related to chemical companies that manufacture and export pharmaceutical ingredients that have not been certified or inspected by appropriate Chinese regulatory authorities.[21,31,39]

Nations have available to them several established methods to prevent problems caused by counterfeit drugs and materials in their pharmaceutical industries. The USP, an independent organization serves as the 'official public standards-setting authority for all prescription and over-the-counter medicines, dietary supplements, and other healthcare products manufactured and sold in the US'.[40] The USP is recognized by the US Food, Drug and Cosmetic Act of 1938, and maintains monographs for many agents used in pharmaceutical preparations. These monographs outline proper procedures for verification of material integrity[40,41]; procedures that apply to pharmaceutical products in the United States regardless of where the ingredients originate. The FDA has authority to enforce compliance with USP National Formulary standards by companies within the United States and for products shipped from outside nations for distribution inside the United States.[42] More than 130 countries use the USP,[40] whereas other nations use analogous compendia.[43]

The USP monograph for glycerin includes a specific test for DEG, to be applied to glycerin-containing products manufactured, held or distributed for drug use.[44,45] The FDA has also developed general CGMP for finished pharmaceuticals.[41,45] The requirements are designed to promote and specify proper practices and procedures for drug manufacturers. They include detailed information on testing for raw ingredients intended for pharmaceuticals. Title 21 of the Code of Federal Regulations, Section 211.84(d)(2), for example, states that, 'At least one test shall be conducted to verify the identity of each component of a drug product. Specific identity tests, if they exist, shall be used'.[41] The Section goes on to clarify that each

component in a pharmaceutical formulation should be tested to confirm the stated purity, strength and quality. A report of analysis may be used in lieu of this testing if a specific identity test is done and if the supplier's reliability is confirmed through episodic validation of supplier testing results. This report is referred to as a Certificate of Analysis (COA), a document that accompanies the product being shipped, attesting to the integrity of the ingredients.

Complete reliance on a supplier's COA, without additional, appropriate testing by brokers and the final drug manufacturer, can be disastrous, for the COA does not always accurately reflect what the agent actually is.[11,14,15,31] Shortly after the Panama MDMP events, FDA officials petitioned the USP to modify the glycerin monograph to establish a test for the presence of DEG, as it had been tested for infrequently and as an impurity. The USP will then deem the identity of glycerin to include the absence of DEG, and CGMP regulations will require a test for DEG every time a shipment of glycerin is received at a pharmaceutical manufacturing facility if its products are intended for the US market. FDA also issued guidance to industry, requesting increased vigilance and controls over the use of glycerin and propylene glycol in pharmaceutical product manufacturing.[46]

The WHO has published guidelines similar to the FDA's.[47,48] The International Pharmaceutical Excipients Council (IPEC), a global association of manufacturers and users of pharmaceutical excipients, has developed the *Good Manufacturing Guide for Bulk Pharmaceutical Excipients*. Written in conjunction with WHO, the document closely adheres to WHO's CGMP.[30] WHO and IPEC both state that the final drug product manufacturer is ultimately responsible for the integrity and safety of the product.[30,48]

Appropriate quality control procedures and protocols do not appear to have been followed in the MDMPs we have studied. In the Haiti event, for example, the only reported record of local quality assurance testing included a pH test of the material.[30] A COA indicating a pharmaceutical-grade product did reportedly accompany the material from its point of origin, although no report of testing could be located.[14] Similarly, in the 2006 Panama event, local quality assurance testing used basic testing methodologies such as specific gravity and the results showed the product to be *consistent* with glycerin. The containers of glycerin had at least three separate

labels with conflicting information as to the purity of the compound (Figure 1), demonstrating a failure to ensure appropriate quality control during transit from point of manufacture to final destination.

A global problem

Developing countries are at higher risk for MDMP events. Most of these events have occurred in developing countries. Developing countries lack analytic equipment and/or measurement expertise for purity testing, as prescribed by the USP, WHO or CGMP guidelines.[19] In the Haiti incident, the pharmaceutical company did have the recommended HPLC equipment, but it was not in operation, and no personnel had the knowledge to operate it.

In an increasingly global economy, where raw materials can be produced in one country, brokered in others and finally used in production in still others, opportunities for miscommunication are increased.[30] Materials may change hands many times, between vendors using different languages, thereby imposing professional, linguistic and cultural barriers.

We urge public health authorities to pay attention to purity testing guidance and put in place mechanisms for targeted DEG testing of high-risk raw ingredients like propylene glycol and glycerin at the point of manufacture and downstream use. We suggest that authorities not rely solely on accompanying documentation attesting to material integrity. Definitive and selective testing in accordance with established guidelines should always be done as part of final pharmaceutical manufacture to ensure that the products contain only chemicals safe for human consumption.

Despite adherence to strict policies and procedures such as CGMP, medication-associated poisonings may still occur, even in developed countries. In 2008, a global outbreak of anaphylactoid type reactions to heparin imported from China affected many people in many states in the United States. The heparin contained over-sulfated chondroitin sulfate as a contaminant, the likely cause of the observed illnesses.[49] Although over-sulfated chondroitin sulfate was known to exist before this incident, no one knew that it could contaminate heparin and remain undetected by standard quality control testing methods for heparin.

Imported medications and raw materials used to make medications are subject to the same laws as those agents made domestically, but these unexpected events may still occur. Close adherence to established quality control guidelines for pharmaceuticals can prevent the majority of instances like these. Further protection might be achieved by establishment of better partnerships and mechanisms of communication among public health and regulatory authorities of countries that import and export medications and raw materials to one another.

Conclusion

The most effective intervention to prevent the occurrence of MDMPs is to require and enforce effective quality control procedures by all persons and businesses that handle substances intended for incorporation into pharmaceutical products. Evidence suggests that the most likely primary reasons for the continued occurrence of MDMP appear to be (1) intent to deceive persons and organizations within the pharmaceutical manufacturing process, including brokers and traders, as to an ingredient's true identity, probably for financial gain, and (2) a lack of adherence to universal GMP and adequate quality control standards, thereby leaving vulnerabilities. Effective national-level regulatory oversight programs for pharmaceutical manufacturers are needed to prevent established public health threats such as MDMPs as well as respond rapidly to new and emerging ones.

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Disclaimers

The findings and conclusions in this article are those of the authors and do not necessarily represent the views of the Centers for Disease

Control and Prevention, the Agency for Toxic Substances and Disease Registry or the Food and Drug Administration. The intent of the paper is not to place blame on any particular manufacturer or distributor, but merely to discuss findings in the literature that tend to show possible causes of etiology.

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