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Identification of existing and emerging chemical residue contamination concerns in milk

Martin Danaher[1†] and Kieran Jordan[2]
[1]*Food Safety Department, Teagasc Food Research Centre, Ashtown, Dublin 15, Ireland*
[2]*Food Safety Department, Teagasc Food Research Centre, Moorepark, Fermoy, Co. Cork, Ireland*

In order to maintain the quality of Irish milk and meet increasingly demanding specifications, it is necessary to focus on chemical residues in milk, in addition to other quality issues. The objective of the work was to assess the current status of chemical contaminant analysis and to identify technological and knowledge needs. This was achieved through a review of literature with respect to chemical contaminants. Quaternary ammonium compounds (QACs) have been identified as an area of concern for the dairy industry because of the recent reports of QAC residues in dairy products internationally. Analytical support to analyse QAC residues in milk and dairy products on an ongoing basis is required. Furthermore, the source of QAC residues along the milk production chain needs to be identified. Similarly, analytical support and research is needed in the area of phthalates, to support the development of intervention strategies to reduce contamination, if present. Cephalosporin antibiotics have been a concern for the dairy industry because of the lack of suitable chemical tests to measure these substances.

Keywords: banned substances; biocides; economic adulterants; milk and dairy products; persistent organic pollutants; phthalates; quaternary ammonium compounds; veterinary drugs

Introduction

Chemical contamination of milk with residues can potentially occur from a number of sources including application of agrochemicals (Whelan *et al.* 2011; Power *et al.* 2013a), use of illegal growth-promoting agents (Le Breton *et al.* 2010), contamination from the environment (Anon. 2011b), natural toxins present in feed or forage (Hoogenboom *et al.* 2011; Baliukoniene

†Corresponding author: Dr. Martin Danaher, martin.danaher@teagasc.ie; Tel: +353 1 805 9500; Fax: +353 1 805 9550.

et al. 2012), or during milk processing and packaging (Schettler 2006). In addition, milk can be contaminated through deliberate adulteration for economic gain. An example of this is the addition synthetic chemicals to artificially increase the nitrogen content and thus the value of milk. Abernethy and Higgs (2013) recently reported the development of a method to detect 16 economic adulterants in milk. The method contained a number of contaminants that have been associated with milk contamination in recent years including melamine and dicyandiamide (DCD). Dicyandiamide has been used in agriculture as a nitrification inhibitor to reduce nitrogen losses (O'Connor *et al.* 2013). It has been reported that use of DCD on pastures can result in residues in milk and infant formula (Shen *et al.* 2013). Melamine adulteration in milk has been widely reported following the Chinese milk and infant formula scandal, which resulted in the deaths of six infants (Xin and Stone 2008).

Extensive testing of milk is carried out by the dairy industry and regulatory agencies to protect public health and support the export of Irish food abroad. However, there are increasing international reports of residues being detected in milk (Xin and Stone 2008; Anon. 2012b; Fierens *et al.* 2012; Abernethy and Higgs 2013). This can be largely attributed to improvements in analytical instrumentation, which has supported the development of more sensitive detection methods that can analyse a wide range of residues in milk (Whelan *et al.* 2010; Abernethy and Higgs 2013). In addition, more sophisticated techniques are now being regularly applied, including high resolution mass spectrometry, that can discover new emerging contaminants in foods that were previously unidentified (Stolker *et al.* 2008; Cordewener *et al.* 2009; Kim, Yun and Chung 2009). The Irish dairy industry produces more than 5.2 billion litres of milk annually from 1.1 million dairy cows and is export orientated with 80% of production destined for international markets. The industry was worth approximately €2.66 billion in exports in 2012 (Anon. 2013). With the abolition of quotas in 2015, a 50% increase in output has been targeted. To protect the export of Irish dairy products and to reduce the risk of costly product recalls, further focussed research is needed in the area of chemical contaminant research. This requires the identification of priority contaminants, development of more sophisticated methodology for detection and the application of technology to reduce contamination or monitor product quality.

The objective of this paper is to identify existing and emerging chemical contaminant risks in milk and dairy products. A secondary objective is to identify gaps in knowledge and technology that will enhance the safety and reputation of Irish dairy products.

Licensed Agrochemicals

A broad range of compounds including veterinary drugs, feed additives, pesticides and fertilisers are used in agricultural production and can potentially cause contamination at farm level and result in residues in milk. Veterinary drugs represent nearly 300 residues that can occur in milk. This group includes a broad range of substances including antibiotics, anthelmintics, anticoccidial agents, non-steroidal anti-inflammatory drugs (NSAIDs), corticosteroids, insecticides (carbamates, pyrethroids, others,), sedatives, etc. Antibiotics represent one of the most important groups of veterinary drug residues. There are more than 100 licensed antibiotic drugs referenced in EU legislation, belonging to the following groups –

aminoglycosides, cephalosporins, penicillins, lincosamides, macrolides, nitrofurans, phenicols, pleuromutilins, peptides, quinolones, quinoxalines, sulphonamides and tetracyclines (Anon. 2010a). Many of these substances are routinely monitored using inhibitory substance tests and immunoassays if the required detection limits cannot be met by the former. In addition, LC-MS/MS (liquid chromatography coupled to tandem mass spectrometry) based methods are employed for the detection of banned antibiotics such as chloramphenicol, nitrofurans and dapsone. In Ireland, methodology is currently in place that can detect the majority of these substances. However, there are some exceptions, namely, chemical tests for aminoglycoside, cephalosporin and some polypeptide drug residues.

Anthelmintic drug residues have been extensively researched in recent years by Irish researchers through National and European funded research projects (Lavis *et al.* 2003; Keegan *et al.* 2009, 2011; Kinsella *et al.* 2009, 2011; Cooper *et al.* 2011, 2012a,b). LC-MS/MS tests have been developed that cover a wide range of anthelmintic residues down to low ppb (parts per billion) levels in milk (Whelan *et al.* 2010, 2011; Power *et al.* 2013a,b). Furthermore, research has been conducted on the persistence of anthelmintic residues in milk and transfer of residues into dairy products (Whelan *et al.* 2010, 2011; Power *et al.* 2013a,b). Similarly, extensive tests have been developed to detect anticoccidials (Moloney *et al.* 2012; Clarke *et al.* 2013), NSAIDs and corticosteroids in milk (Dowling *et al.* 2010; Malone *et al.* 2010). Results from national residue surveillance testing indicate that residue contamination of milk from these substances is infrequent. Anticoccidials are not included in the Irish residue surveillance program, but the likelihood of these residues in milk is low because animals in Ireland are largely fed on grass or silage, whereas these residues would originate from feed concentrates.

Insecticides are used for the control of external parasites on cattle. Examples of these substances include pyrethroids, carbamates, dicyclanil, amitraz, cyromazine, which are licensed products that have withdrawal periods defined for dairy animals. Data is available on the persistence of many insecticide residues in milk but there is a lack of information on the fate of residues in dairy product manufacture. In addition, there is scant information available on the occurrence of the residues of some of these insecticides in milk because they cannot be easily included in multi-residue detection methods. Examples include dicyclanil, amitraz and cyromazine residues which are not retained on traditional reversed phase chromatographic columns due to their high polarity. New analytical tests are currently under development to detect insecticide residues in dairy products and should be available in 2014.

Banned Drugs and Growth-Promoting Agents

This group includes illegal growth-promoting agents such as stilbenes, thyrostats, β-agonists, steroids and resorcyclic acid lactones. The thyrostat, thiouracil, occurs naturally in brassica crops (Pinel *et al.* 2006; Bussche *et al.* 2011a,b) and has resulted in a number of positive residue findings in animal biofluids collected as part of the Irish national residue control plan (NRCP) over the last couple of years (Anon. 2011a, 2012c). Similarly, semicarbazide (a marker of the nitrofuran drug nitrofurazone) has been frequently detected in plasma samples taken for nitrofuran analysis, which have been collected as part of the NRCP (Anon. 2011a, 2012c;

Radovnikovic *et al.* 2011). It has been demonstrated that the presence of semicarbazide in processed foods was caused in the past by thermal decomposition of a blowing agent, azodicarbonamide, in glass jar gaskets before its use was banned (de Souza, Junqueira and Ginn 2005). In other cases, it has been reported that semicarbazide (SEM) can occur naturally in the food binding agent carageenan. This inadvertantly enters the food chain and may increase by several orders of magnitude following hypochlorite treatment (Hoenicke *et al.* 2004). The remainder of banned substances are closely monitored in Irish food and pose a low risk of residue contamination. Recombinant bovine somatotropin (rBST) is an emerging designer growth promoter, which is not permitted in the European Union (EU), but is widely used outside the EU to increase milk production (Le Breton *et al.* 2010). Analytical tests have only recently been developed to detect this substance and as a result there is no current knowledge of the incidence of rBST residues in milk (Gallo *et al.* 2009; Rochereau *et al.* 2011).

A number of veterinary drugs have been prohibited for use in food producing animals due to concerns over their toxicological properties or their potential for development of antimicrobial resistance including, chloramphenicol, nitrofurans, dapsone and nitroimidazoles. Recent surveillance has shown that chloramphenicol can naturally occur on grass (Berendsen *et al.* 2010, 2011, 2013) and that dapsone (a banned sulphonamide antibiotic) can occur as an impurity in licensed drugs (Anon. 2012a). Both of these studies indicate that low levels of each drug can potentially transfer into milk. This is supported by recent findings, which showed that chloramphenicol residues can occur in pork from contaminated straw bedding.

Persistent Organic Pollutants

This group includes a broad range of substances including organochlorines [polychlorinated biphenyls (PCBs), dioxins, furans, and dioxin like PCBs], perfluorinated substances and brominated flame retardants. Trace background levels of organochlorine residues can occur in milk due to environmental contamination. Organochlorine residues are routinely monitored in national monitoring programmes for feed and food. Methodology is currently in place at regulatory laboratories such as The State Laboratory and the Pesticide Control Laboratory. Scientific opinions have been published by the European Food Safety Authority (EFSA) on brominated flame retardants (BFRs) and perfluorinated substances (Anon. 2008, 2010b, 2011b, 2012d,e). Brominated flame retardants are mixtures of man-made chemicals that are added to a wide variety of products, including for industrial use, to make them less flammable. They are used commonly in plastics, textiles and electrical/electronic equipment. In the EU, the use of certain BFRs is banned or restricted; however, due to their persistence in the environment there are still concerns about the risks these chemicals pose to public health. BFR-treated products, whether in use or waste, ‘leach’ BFRs into the environment and contaminate the air, soil and water. These contaminants may then enter the food chain where they mainly occur in food of animal origin, such as fish, meat, milk and derived products.

The European Food Safety Authority has published opinions on the persistence organic pollutants in food. Polybrominated diphenyl ethers (PBDEs) are used in the manufacture of plastics, textiles, electronic castings, and circuitry. The European Food Safety Authority considers PBDEs as a potential health concern with respect to the current dietary exposure. In addition, because products containing PBDEs are still in use, the surveillance of PBDEs should continue (Anon. 2011b). There is convincing evidence (including more extensive toxicity data) that the emerging BFR tris(2,3-dibromopropyl) phosphate (TDBPP) and the novel BFR 2,2-Bis(bromomethyl)-1,3-propanediol (DBNPG) are genotoxic and carcinogenic, warranting further surveillance of their occurrence in the environment and in food (Anon. 2012e). Based on the limited experimental data on environmental behaviour, 1,2-bis(2,4,6-tribromophenoxy)ethane (BTBPE) and hexabromobenzene (HBB) were identified as compounds that could raise a concern as reports indicate that they can accumulate in the body over time.

Production and Processing Contaminants

Contaminants, such as biocides, phthalates and nitrates or nitrites (NOx) can occur in milk either during dairy production on farms or at processing facilities.

Nitrates and nitrites

High levels of NOx in food and water are undesirable because nitrate can be converted to nitrite which can oxidise blood haemoglobin to methaemoglobin resulting in a reduced oxygen supply to body tissues. This is of particular concern for infants who are biochemically disposed towards both an enhanced conversion of nitrate to nitrite and a reduced reconversion of methaemoglobin to haemoglobin. In addition, nitrite can react with constituents of the food to form N-nitroso compounds which have been identified as potential carcinogens. In studies carried out by Teagasc in the late 1990s, 22 to 33% of samples analysed contained nitrate levels in excess of the limit of 30 mg/kg (O'Keeffe and Kennedy 1998). These elevated levels were associated with the first production runs immediately following equipment cleaning and were not found during later production runs.

Biocides

Biocides have emerged as a residue in milk in recent years. Iodine residues were initially discovered (Gleeson *et al.* 2009), followed by trichloromethane residues from chlorine containing detergents and disinfectants (Ryan *et al.* 2012, 2013) and more recently quaternary ammonium compound (QAC) residues (Anon. 2012b). Some of these agents can be applied as teat disinfectants and/or for cleaning/disinfecting milking parlour equipment on farms (Kesler *et al.* 1948). They can also be used for cleaning at milk processing facilities, dairy powder production facilities and at retail level (Mousavi, Butler and Danaher 2013). Quaternary ammonium compounds are disinfectant compounds in which four organic groups are linked to a nitrogen atom, producing a cation (Figure 1). Quaternary ammonium compounds are used in the manufacture of many detergent and disinfectant products either as the main ingredient or as an added compound to improve the antimicrobial effectiveness of the cleaning agent. The Federal Institute of Risk Analysis in Berlin has reported that the QAC compound, didecyldimethylammonium chloride (DDAC) is frequently detected in dairy products (Anon. 2012b). Levels are frequently detected in excess of the proposed EU Maximum Residue Limits (MRLs) of 0.5 mg/kg for food and feed and 0.01 mg/kg for infant formula. The maximum concentrations reported in milk, cheese, yogurt, cream and ice cream in an international study were 0.15, 0.235, 0, 6.72 and 19.1 mg/kg, respectively. It was proposed that DDAC residues may be due to disinfection of milking equipment or processing equipment (Anon. 2012b). However, there is a lack of data to draw any definite conclusion on this matter.

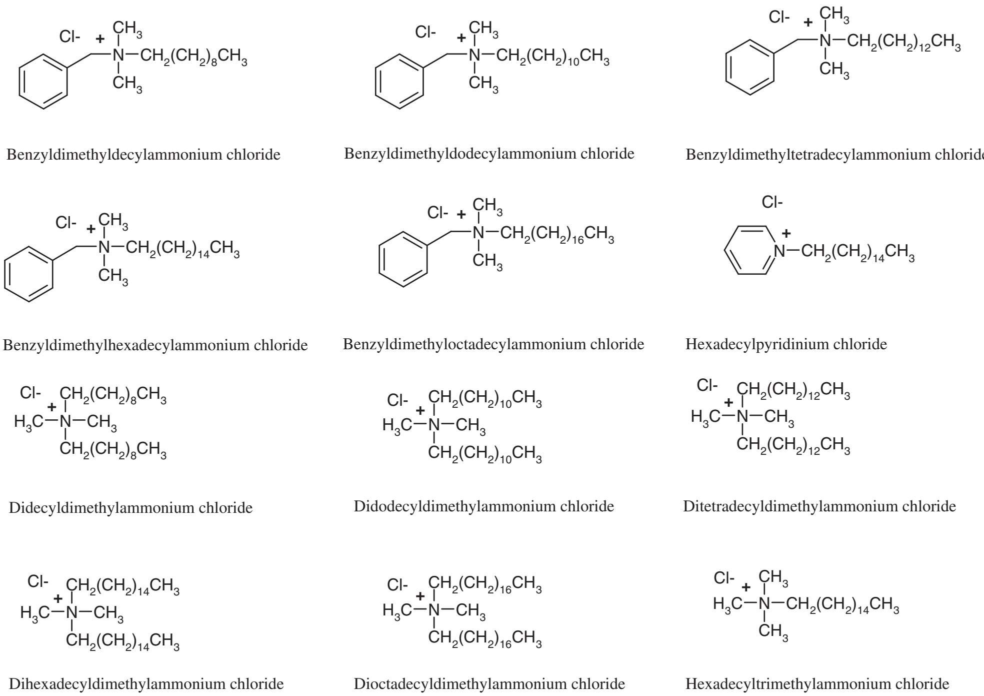

Figure 1. Chemical structures of quaternary ammonium compounds.

Phthalates

Phthalates are one of world's most used groups of plasticisers. They are added to plastic polymers (e.g. polyvinylchloride [PVC]) to enhance flexibility and can be present in printing inks and lacquers to improve surface adhesion, flexibility and wrinkle resistance (Latini, De Felice and Verrotti 2004). Phthalates are not chemically bonded to PVC and leach out over time. As a result, phthalates are considered to be a ubiquitous environmental contaminant. Human exposure to phthalates can occur via ingestion, inhalation, medical intravenous interventions or via dermal contact (Schettler 2006). However, the main route of phthalate exposure is through food ingestion (Cao 2010). Since some phthalates are suspected to cause detrimental effects to human health, e.g. di(2-ethylhexyl) phthalate (DEHP) can disrupt the human endocrine system, it is important to know how and to what extent food products are contaminated with phthalates (Latini *et al.* 2004). Cao (2010) recently carried out a comprehensive review on phthalate esters and their occurrence in food. They report the following phthalates have been found in milk and dairy products – di-2-ethylhexyl adipate (DEHA), DEHP, di-n-butyl phthalate (DBP), di-isodecyl phthalate (DiDP), di-iso-nonyl phthalate (DiNP) and butylbenzyl phthalate (BBzP) (Figure 2). Cao (2010) reported that the likely source of phthalate contamination was from PVC tubing during the milking process or the bulk milk transfer between tankers and storage tanks. They also proposed that the addition of nutritional ingredients to infant formula could also contribute contamination. Phthalates can also migrate into dairy products from packaging materials such as cartons, bottles, tubs, tins and wrapping films.

Fierens *et al.* (2012) investigated the occurrence of eight phthalates including dimethyl phthalate (DMP), diethyl phthalate (DEP), di-iso-butyl phthalate (DiBP), DiNP, DnBP, BzBP, DEHP and dicyclohexyl phthalate (DCHP) in Belgian milk at farm level. They showed that BzBP and DEHP migrated into raw cow's milk during the mechanical milking process. Ingestion of contaminated feed additionally contaminated this raw milk with DiBP and DEHP. A separate study by the same group showed that no additional phthalate contamination was observed between the farm and the processing facility (Fierens *et al.* 2013). In this separate study, milk and dairy product samples were collected at farm, industry and retail level. At the processing facility, food contact materials including packaging materials increased the levels of DiBP, DnBP, BzBP and DEHP in milk and powder. Analysis of retail products revealed

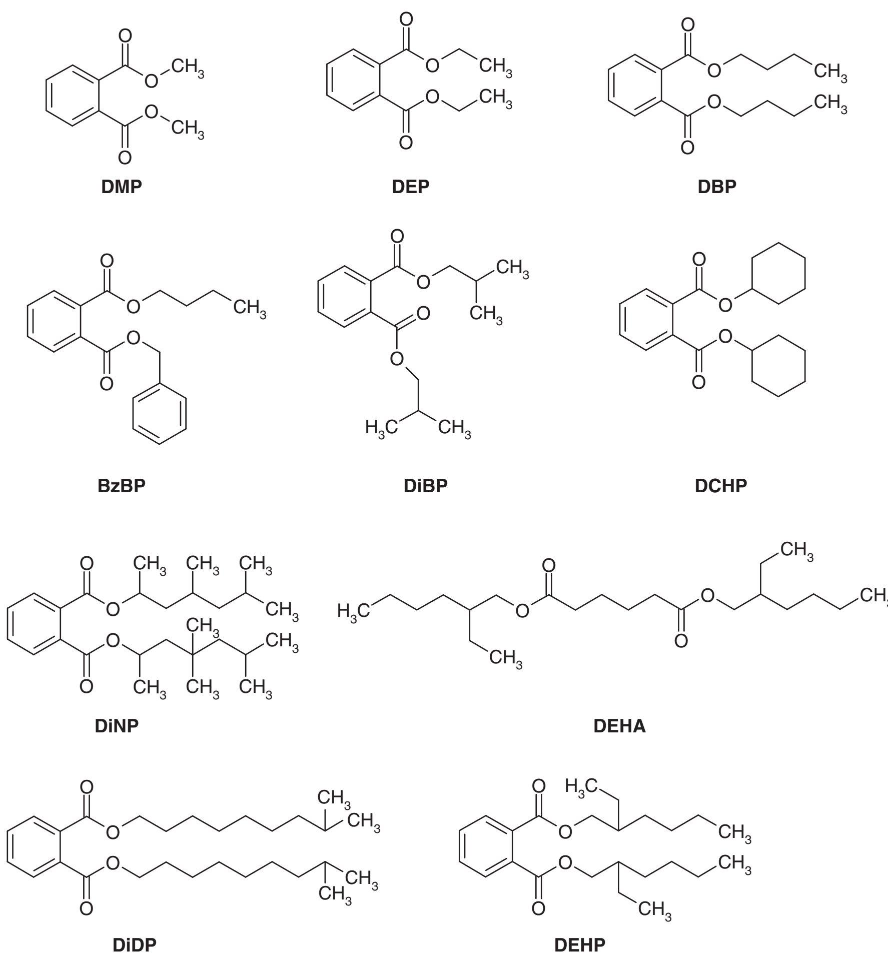

Figure 2. Chemical structures of phthalates.

that milk and cheese were further contaminated along the chain with DiBP and DnBP. Other studies report that levels of phthalates in retail products vary considerably. In addition, differences in phthalate contamination can be attributed to differences in licensing in different countries or continents (Yano *et al.* 2005). It has also been shown that the type of packaging materials used can also influence phthalate exposure, e.g. it has been reported that milk seemed to contain more DnBP and DEHP when it is packed in plastic than in Tetra Brik (Casajuana and Lacorte 2004; Farajzadeh *et al.* 2012).

Future Perspectives

Future research in the area of chemical contaminants should focus on more efficient and comprehensive strategies to detect and measure residues in milk and dairy products. In particular, the focus should be on contamination issues that may affect Irish exports and disadvantage the competitiveness of the Irish agri-food industry. Quaternary ammonium compounds, phthalates, cephalosporins and flukicides are residues of concern. Quaternary ammonium compounds are an issue of particular concern to the dairy industry due to reports of residue positive samples internationally. In addition, there are no data available at present concerning the fate of QACs during infant formula manufacture. The following technological and knowledge gaps exist: i) the need for validated and robust methodologies to measure QAC residues in dairy products and ii) knowledge on causes of QAC contamination in dairy products during manufacture. Research is also needed in the area of phthalates in milk and dairy products but should build on the existing research that has already been carried out to date internationally. In order to proceed with this research, analytical capabilities need to be developed for measuring phthalate residues in food. In the area of veterinary drugs, extensive surveillance of milk is carried out by regulatory and industry laboratories. However, analytical support should be developed in the area of antibiotic analysis, particularly for cephalosporin residues in milk.

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