Health assessment of benzalkonium chloride residues in food

BfR opinion No 032/2012, 13 July 2012

On the occasion of quality controls in food business and during official food surveillance, benzalkonium chloride residues in excess of the currently applicable maximum residue level (MRL) of 0.01 mg/kg were detected in food. The Federal Institute for Risk Assessment (BfR) derived toxicological reference values for benzalkonium chloride and assessed whether the detected residues pose a health risk for consumers.

Benzalkonium chloride is a quaternary ammonium compound belonging to the group of cationic surfactants. The substance is used in disinfectants and detergents.
Benzalkonium chloride is both a biocide and a pesticide active substance. In addition, DDAC is contained in products used as plant strengtheners.

The available data indicate “background” levels of benzalkonium chloride above the currently applicable default maximum residue level for most commodities. Based on the available data the cause can not always be clearly identified. It is noticed, that for large tropical fruit, for example avocado, occasionally especially high residues were reported. It is likely that these fruits received post-harvest treatments with benzalkonium chloride. Residues in milk and ice cream might be due to disinfection of bottling plants, ice cream machines or other equipment.

Based on German and further European consumption data, the BfR estimated the dietary intake of benzalkonium chloride residues from contaminated food. The acceptable daily intake (ADI) was not exceeded. The ADI is the quantity of a substance that can be ingested daily over an entire lifetime without any appreciable health risk. The BfR comes to the conclusion that a chronic risk for consumers is unlikely.
I
n most food commodities, residues also were not in excess of the acute reference dose (ARfD). The ARfD is defined as the quantity of a substance that can be ingested during one or several meals in the course of a day without any appreciable health risk. However, based on the currently available data an acute risk for consumers (both children and adults) can not be ruled out when consuming milk/milk products with residues as high as 6.66 mg/kg (highest concentration reported for milk). The potential adverse effects might include slight reversible clinical symptoms due to irritation in the gastrointestinal tract.

When not taking into account the two by far highest residue values in milk and using the next highest residue in milk (0.95 mg/kg) instead for the assessment, an acute risk for consumers would be unlikely.

Where consumer health protection is concerned, the BfR is of the opinion that peak values of benzalkonium chloride residues, as measured in milk and milk products, should be avoided. This can be achieved through more extensive controls and greater consideration of residue relevance in the guidelines for the disinfection of equipment and subsequent washing and cleaning procedures, especially when the equipment has contact with foods. The first steps in this direction have been taken on EU level, in particular through the preparations for the commencement of the new Biocide Regulation (EC) No. 528/2012, but they are also being implemented by the OECD Task Force on Biocides.

1. Subject of the assessment

On the occasion of quality controls in food business and during official food surveillance, benzalkonium chloride residues in excess of the currently applicable maximum residue level (MRL) of 0.01 mg/kg were detected in food. The current assessment considers all residue data which have been submitted to BfR by 06 July 2012.

The BfR derived toxicological reference values for benzalkonium chloride and assessed whether the detected residues pose a health risk for consumers.

2. Results and conclusions

BfR derived an ADI value of 0.1 mg/kg bw/day and an ARfD of 0.1 mg/kg bw (body weight) for benzalkonium chloride.
The residues in food reported so far are unlikely to pose a chronic health risk for German or further European consumer groups.
In most food commodities, residues also were unlikely to pose an acute health risk for German or further European consumer groups. However, based on the currently available data an acute risk for consumers (both children and adults) can not be ruled out when consuming milk/milk products with residues as high as 6.66 mg/kg (highest concentration reported for milk). The potential adverse effects might include slight reversible clinical symptoms due to irritation in the gastrointestinal tract. When not taking into account the two by far highest residue values in milk and using the next highest residue in milk (0.95 mg/kg) instead for the assessment, an acute risk for consumers would be unlikely.

3. Rationale/Risk Assessment

The active substance benzalkonium chloride is listed in the European Commission's pesticide database. With Commission Regulation (EC) No 2076/2002 of 20 November 2002 the non-inclusion of benzalkonium chloride in Annex I to Council Directive 91/414/EEC was decided on. Authorisations for benzalkonium chloride containing plant protection products consequently had to be withdrawn in the EU. Since benzalkonium chloride is listed as a pesticide, its residues are under the scope of Regulation (EC) No 396/2005. As long as no specific MRLs have been set for benzalkonium chloride, the default MRL of 0.01 mg/kg applies for all food commodities of plant and animal origin.

In addition, benzalkonium chloride is contained in a plant strengthener/additive. As a consequence of the residues detected in food, this plant strengthener/additive has immediately been withdrawn from the market.

Further sources of exposure in agriculture might be related to fertilizers containing benzalkonium chloride or to plant protection products containing benzalkonium chloride as co-formulants.

Benzalkonium chloride is currently also being evaluated and peer reviewed on EU level in the framework of the biocide active substances review programme. Benzalkonium chloride is a varying mixture of benzyl-C_{12-16}-alkyl-dimethylammonium chlorides. In the course of biocide evaluations, the active substances ADBAC (CAS 68424-85-1, C_{12}: 39-75 %, C_{14}: 20-52 %, C_{16}: <12 %) and BKC (CAS 68424-85-1, C_{12}: 68 %, C_{14}: 29%, C_{16}: 3 %) are distinguished.

The inclusion of ADBAC in Annex I of Dir. 98/8/EC (now Reg. (EC) No 528/2012) has recently been discussed during the 47th meeting of the Competent Authorities (CA, 04-06 July

2012) for the product type 8 (PT 8, wood preservatives). The outcome has not yet been reported to BfR. Discussions were based on the draft Assessment Report and the CA-Report submitted by Italy, which was already peer reviewed in 2007 by the other EU Member States. For BKC also Italy had provided a draft CA-Report for the product type 8. The peer review started in 2011. ADBAC and BKC are also under evaluation for PT 1, 2, 3, 4, 10, 11 and 12 (i.e. including disinfectants), but the draft CA-Reports to be prepared by Italy are not yet available to the BfR.

3.1 Toxikological assessment of benzalkonium chloride

For a detailed toxicological assessment it is referred to:

- the draft CA-Reports (Competent Authority Reports) submitted by Italy in the EU active substances programme for biocides PT 8 for ADBAC (2007) and for BKC (2010)
- the Reregistration Eligibility Decision for Alkyl Dimethyl Benzyl Ammonium Chloride (ADBAC) published by US-EPA (Docket EPA-HQ-OPP-2006-0339 at http://www.regulations.gov)

Toxicological reference values

In the following table the toxicological reference values relevant for consumer risk assessment as derived for benzalkonium chloride (ADBAC, BKC) by different bodies and in different contexts are summarized.

To derive suitable ADI and ARfD values, BfR relied on the EU data package for BKC and ADBAC. However, up to now only study summaries and summary evaluations by the RMS Italy were available to BfR, not the original studies.

Table 1: Toxicological reference values derived for benzalkonium chloride, BKC and ADBAC by different bodies

Reference value	Body	Value	Study	Safety factor
ADI (ADBAC, BKC, benzalkonium chloride)	BfR	**0.1 mg/kg bw**	52 weeks dog	100
ARfD (ADBAC, BKC, benzalkonium chloride)	BfR	**0.1 mg/kg bw**	52 weeks dog (acute effects)	100
Chronic RfD, cPAD (ADBAC)	EPA (US)	0.44 mg/kg bw	Chronic toxicity/ carcinogenicity rat	100
Acute RfD, aPAD (ADBAC)	EPA (US)	Not required		
AEL (ADBAC, biocides PT 8)	IT	0.13 mg/kg bw (proposal only, not yet harmonized, procedure currently ongoing)	52 weeks dog	100
AEL (BKC, biocides PT 8)	IT	0.45 mg/kg bw (proposal only, not yet harmonized, procedure currently ongoing)	90 days dog	100
ADI (ADBAC, biocides PT 8)	IT	Not required for this PT (proposal only, not yet harmonized, procedure		

Reference value	Body	Value	Study	Safety factor
		currently ongoing)		
ARfD (ADBAC, biocides PT 8)	IT	Not required for this PT (proposal only, not yet harmonized, procedure currently ongoing)		

ADI: Acceptable Daily Intake
(A)RfD: (Acute) Reference Dose
AEL: Acceptable Exposure Level
aPAd: Acute Population Adjusted Dose
cPAD: Chronic Population Adjusted Dose

In the context of the EU biocides evaluation the RMS Italy proposed an AEL of 0.45 mg/kg bw (based on the 90 days dog study) for BKC and an AEL of 0.13 mg/kg bw (based on the 52 weeks dog study) for ADBAC, while no reference values for consumer risk assessment were derived.

BfR recommends to derive reference values for consumer risk assessment (ADI and ARfD) for benzalkonium chloride (ADBAC, BKC) from the 52 weeks dog study. ADBAC has been administered via feed in this study. The NOAEL (no observed adverse effects level) was 13 mg/kg bw/day, while at a dose of 34 mg/kg bw/day reductions of feed intake and body weight gain were observed. Employing a safety factor of 100, BfR proposes an ADI value of 0.1 mg/kg bw/day and an ARfD of 0.1 mg/kg bw (body weight) based on the available data.

3.2 Dietary intake assessment for benzalkonium chloride

3.2.1 Available information on benzalkonium chloride residues in food

When quite recently easy-to-use analytical methods became available for quaternary ammonium compounds such as benzalkonium chloride (see e.g. publication by the European Union Reference Laboratory for Residues of Pesticides[1]), an extensive generation of monitoring/surveillance data started. It has to be noted however that *representative* monitoring data covering all kinds of food of plant and animal origin is not available up to now.

Data were made available by quality control institutions in food business and by German Federal States' (Länder) Authorities which are responsible for official food surveillance/monitoring.

Results were sometimes reported as „benzalkonium chloride", sometimes separately for single compounds with different alkyl chain lengths making up the mixture „benzalkonium chloride", namely benzyl-C_{12}-alkyl-dimethylammonium chloride up to benzyl-C_{18}-alkyl-dimethylammonium chloride (the latter however has never been found). Since the toxicological assessment is also based on (different) mixtures of these compounds, the findings reported for single compounds were aggregated accordingly. This was done as follows: If residues >LOQ had been detected for single components, only those "real values" were added, not also residues at LOQ level for all other (not detected) compounds. This is considered as being justified, since benzalkonium chloride containing biocidal products on the market normally contain few main components leading to quite specific analytical results. Furthermore,

1.1.1.1 [1] http://www.eurl-pesticides.eu/library/docs/srm/meth_QAC_ShortMethod_EurlSRM.PDF

an addition of LOQs ist not reasonable because LOQs differ very much. The following example is supposed to illustrate the approach taken:

C_{12}: 0.1 mg/kg; C_{14}: 0.2 mg/kg; C_{16}: <0.015 mg/kg; C_{18}: <0.15 mg/kg → total: 0.3 mg/kg

LOQs differed between single components and between laboratories and were not specified in all cases. The evaluation of the data (mean, median, OECD Calculator results) and the subsequent risk assessment were therefore based on "real values" only, i.e. on residues >LOQ.

Food of plant origin

The following table summarizes all benzalkonium chloride findings in plant commodities which were made available to BfR until 06 July 2012. Figures marked **bold** have been used in the risk assessment described later on.

Table 2: Available monitoring/surveillance data on benzalkonium chloride residues in food of plant origin

Code number*	Commodity group	Number of samples Residues (mg/kg)		
0110000	Citrus fruit	N	>LOQ	14
			<LOQ	92
		Mean (only values >LOQ)		0.04
		Median (only values >LOQ)		**0.035**
		Maximum		**0.11**
		OECD Calculator result (only values >LOQ)		0.15
processed	Juice (Orange)	N	>LOQ	0
			<LOQ	19
		OECD Calculator result (only values >LOQ)		-
0130000	Pome fruit	N	>LOQ	5
			<LOQ	75
		Mean (only values >LOQ)		0.17
		Median (only values >LOQ)		**0.024**
		Maximum		**0.76**
		OECD Calculator result (only values >LOQ)		1.5
0140000	Stone fruit	N	>LOQ	4
			<LOQ	43
		Mean (only values >LOQ)		0.017
		Median (only values >LOQ)		**0.018**
		Maximum		**0.02**
		OECD Calculator result (only values >LOQ)		0.05

Code number*	Commodity group	Number of samples Residues (mg/kg)		
0150000	Berries & small fruit	N	>LOQ	3
			<LOQ	151
		Mean (only values >LOQ)		0.08
		Median (only values >LOQ)		**0.078**
		Maximum		**0.132**
		OECD Calculator result (only values >LOQ)		0.3
0161000	Miscellaneous fruit with edible peel (all reported data referring to sharon/kaki)	N	>LOQ	0
			<LOQ	7
		OECD Calculator result (only values >LOQ)		-
0162000	Miscellaneous fruit with inedible peel (small), includes kiwi	N	>LOQ	0
			<LOQ	15
		OECD Calculator result (only values >LOQ)		-
0163000	Miscellaneous fruit with inedible peel (large), includes e.g. banana, mango, avocado	N	>LOQ	13
			<LOQ	105
		Mean (only values >LOQ)		0.315
		Median (only values >LOQ)		**0.24**
		Maximum		**1**
		OECD Calculator result (only values >LOQ)		1.5
0210000	Root and tuber vegeta-bles	N	>LOQ	0
			<LOQ	29
		OECD Calculator result (only values >LOQ)		-
0231000	Solanacea	N	>LOQ	2
			<LOQ	236
		Mean (only values >LOQ)		0.71
		Median (only values >LOQ)		**0.71**
		Maximum		**0.78**
		OECD Calculator result (only values >LOQ)		-
0232000 0233000	Cucurbits	N	>LOQ	2
			<LOQ	62
		Mean (only values >LOQ)		0.025
		Median (only values >LOQ)		**0.025**
		Maximum		**0.03**
		OECD Calculator result (only values >LOQ)		-
0240000	Brassica vegetables	N	>LOQ	1
			<LOQ	39
		Maximum		**0.11**
		OECD Calculator result (only values		-

Code number*	Commodity group	Number of samples Residues (mg/kg)		
		>LOQ)		
0251000-0255000	Leaf vegetables without fresh herbs	N	>LOQ	0
			<LOQ	115
		OECD Calculator result (only values >LOQ)		-
0256000	Fresh herbs	N	>LOQ	22
			<LOQ	288
		Mean (only values >LOQ)		0.174
		Median (only values >LOQ)		**0.092**
		Maximum		**0.61**
		OECD Calculator result (only values >LOQ)		1
0260000	Legume vegetables (fresh)	N	>LOQ	7
			<LOQ	55
		Mean (only values >LOQ)		0.166
		Median (only values >LOQ)		**0.1**
		Maximum		**0.56**
		OECD Calculator result (only values >LOQ)		1
0270000	Stem vegetables	N	>LOQ	1
			<LOQ	37
		Maximum		0.01
		OECD Calculator result (only values >LOQ)		-
0280000	Fungi	N	>LOQ	0
			<LOQ	9
		OECD Calculator result (only values >LOQ)		-
0402000	Oilfruits (Olive oil)	N	>LOQ	0
			<LOQ	20
		OECD Calculator result (only values >LOQ)		-
0500000	Cereals	N	>LOQ	0
			<LOQ	20
		OECD Calculator result (only values >LOQ)		-

* according to Annex I of Reg. (EC) No 396/2005
N: indicates number of analysed samples

Food of animal origin

In a publication by a German Federal States' (Länder) Authority[2] benzalkonium chloride residues in ice cream have been reported. The cleaning procedure subsequent to the disinfection of the equipment was found to strongly influence the residue level. Levels of 1 mg/kg and more in ice cream could be reduced to below 0.1 mg/kg by adequate cleaning with hot water after the disinfection. Though not clearly stated in the publication, the residues might still have exceeded 0.01 mg/kg.

In a poster presentation at the 9th European Pesticide Residue Workshop (Vienna, 25-28 June 2012)[3] the following information was given: "322 dairy products were checked for QAC (quaternary ammonium compounds; this includes both benzalkonium chloride and DDAC) and 78 % of them showed positive results (258 samples). Whereas milk samples presented an average level of QAC of 0.20 mg/kg, yoghurts, Tzatziki samples and farmers cheese samples showed levels across a wide concentration range: 0.01 mg/kg up to 17.9 mg/kg." Most of the findings were related to benzalkonium chloride.

Monitoring/surveillance data has been submitted by German Federal States' (Länder) Authorities which are responsible for official food surveillance/monitoring. The following table summarizes all findings in milk and milk products which were made available to BfR until 06 July 2012. Figures marked **bold** have been used in the risk assessment described later on.

Table 3: Available monitoring/surveillance data on benzalkonium chloride residues in milk and milk products

Code number*	Commodity group	Number of samples Residue (mg/kg)		
1020000	Milk	N	>LOQ	17
			<LOQ	21
		Mean (only values >LOQ)		0.952
		Median (only values >LOQ)		0.15
		Maximum		**6.66**
		OECD Calculator result (only values >LOQ)		10
processed	Milk product (cheese incl. farmers cheese)	N	>LOQ	41
			<LOQ	7
		Mean (only values >LOQ)		0.312
		Median (only values >LOQ)		0.24
		Maximum		0.87
		OECD Calculator result (only values >LOQ)		1
processed	Milk product (yoghurt)	N	>LOQ	4

1.1.1.2 [2] H. Knapp, P. Fecher, K. Werkmeister, Bayerisches Landesamt für Gesundheit und Lebensmittelsicherheit, Erlangen, „Desinfektionsmittelrückstände in Lebensmitteln", Lebensmittelchemie 65, 1-16 (2011). The publication is available in German language only.

1.1.1.3 [3] A. Friedle, A. Nitsopoulos, G. Lach and S. Bruns, "Determination of Quaternary Ammonium Compounds (QAC) in Food Products", 9. EPRW, Wien, 2012

Code number*	Commodity group	Number of samples Residue (mg/kg)		
			<LOQ	6
		Mean (only values >LOQ)		0.06
		Median (only values >LOQ)		0.05
		Maximum		0.11
		OECD Calculator result (only values >LOQ)		0.2
processed	Milk product (cream)	N	>LOQ	32
			<LOQ	3
		Mean (only values >LOQ)		0.573
		Median (only values >LOQ)		**0.31**
		Maximum		6.76
		OECD Calculator result (only values >LOQ)		7
processed	Milk product (ice cream)	N	>LOQ	49
			<LOQ	73
		Mean (only values >LOQ)		1.213
		Median (only values >LOQ)		0.22
		Maximum		21.67
		OECD Calculator result (only values >LOQ)		30

* according to Annex I of Reg. (EC) No 396/2005
N: indicates number of analysed samples

3.2.2 Estimation of the chronic dietary intake

Though knowing that the currently available data were not collected within representative national monitoring programmes, they meanwhile cover most crop groups and were therefore used for chronic risk assessment.

Calculations have been performed with the German NVS II model[4] (DE, 2011; NVS = National Consumption Survey) and additionally with the EFSA PRIMo[5] (rev. 2_0, EFSA, 2008, PRIMO = Pesticide Residue Intake Model) which includes a comprehensive set of European and WHO diets for children and adults. The ADI value of 0.1 mg/kg bw/d is used in the calculation.

To provide a worst case calculation, a couple of rules/assumptions were followed:

- It was assumed that all food commodities contain DDAC residues.
- Limits of quantifications (LOQs) were different in the laboratories and were not always specified. Therefore the chronic intake calculation was based on the median residue of all

1.1.1.4 [4] http://www.bfr.bund.de/cm/343/bfr-berechnungsmodell-zur-aufnahme-von-pflanzenschutzmittel-rueckstaenden-nvs2.zip
1.1.1.5 [5] http://www.efsa.europa.eu/en/mrls/docs/calculationacutechronic_2.xls
1.1.1.6

positive samples within a group disregarding the whole number of samples below the LOQ.

- If all values within a commodity group were below the LOQ or if the commodity group was not investigated at all, a benzalkonium chloride residue of 0.1 mg/kg was assumed for all commodities in the group.

- If only one value >LOQ was reported for the commodity group and this value was between 0.01 and 0.1 mg/kg, a benzalkonium chloride residue of 0.1 mg/kg was assumed for the whole group (higher values were used unchanged in the calculation).

- Concerning milk and milk products, the highest median (0.31 mg/kg) reported for any of the sub-groups was used for the whole group “milk and milk products”.

The theoretical maximum daily intake (TMDI, PRIMo rev. 2_0) based on the assumptions/ rules listed above results in a utilization of 15 % of the ADI (0.1 mg/kg bw) for UK infants, which were identified as the most critical among European consumer groups.
The by far highest contributor was milk and milk products (with the worst case assumption of ubiquitous residues at a level of 0.31 mg/kg). A utilization of 7 % of the ADI value was calculated for the Swedish general population and for WHO Cluster diet B, which were identified as the most critical among adult European consumer groups.

The national theoretical maximum daily intake (NTMDI, NVS II model) based on the assumptions/rules listed above results in a utilization of 10 % of the ADI (0.1 mg/kg bw) for German children aged 2-4 years and 6 % for the German general population aged 14-80 years.

Since the calculated chronic intake is below the ADI value for all European consumer groups for which consumption data was available (both children and adults), the long-term dietary intake of benzalkonium chloride residues is unlikely to present a public health concern.

3.2.3 Estimation of the acute dietary intake (IESTI)

Calculations have been performed with the German NVS II model (DE, 2011; NVS = National Consumption Survey) and additionally with the EFSA PRIMo (rev. 2_0, EFSA, 2008, PRIMO = Pesticide Residue Intake Model), both including consumption data for children and adults. The ARfD of 0.1 mg/kg bw which has been derived by the BfR is used in the calculation.

The following was considered in the acute risk assessment:

- If all values within a commodity group were below the limit of quantification (LOQ) or if the commodity group was not investigated at all, a residue of 0.1 mg/kg was assumed for all commodities in the group.

- If only one value >LOQ was reported for the commodity group and this value was between 0.01 and 0.1 mg/kg, a benzalkonium chloride residue of 0.1 mg/kg was assumed for the whole group (higher values were used unchanged in the calculation).

- In all other cases the maximum reported for the commodity group was used for the assessment of all single commodities in this group.

- The maximum residue value in milk was used to assess the whole group of milk and milk products (6.66 mg/kg). The highest residues reported for cream were comparable to those in milk (6.76 mg/kg). However the highest reported residues in ice cream (up to 21.67 mg/kg) have not been used in the assessment. They have predominantly been taken from ice cream machines and are considered being unrealistic with respect to milk (which makes up the largest part of the large portion).

The international estimate of short term intake (IESTI, PRIMo rev. 2_0) results in a utilization of less than 100 % of the ARfD for all European consumer groups (children and adults) und all food commodities except milk and pineapple. For milk/milk products the highest residue (HR 6.66 mg/kg) exceeded the ARfD by far, while this exceedance was marginal for pineapples:

- Milk/milk products: 827 % of the ARfD of 0.1 mg/kg bw for UK infants (8.7 kg body weight) and 115 % of the ARfD for adults from the Netherlands (63 kg body weight), which were identified as the most critical among European consumer groups (children and adults, respectively).

- Pineapple: 101 % of the ARfD of 0.1 mg/kg bw for 4-6 years old UK children (20.5 kg body weight) and 23 % for UK adults (76 kg body weight), which were identified as the most critical among European consumer groups (children and adults, respectively).

The national estimated short term intake (NESTI, NVS II model) results in a utilization of less than 100 % of the ARfD for German consumers (children and adults) for all commodities except for milk/milk products. For this commodity group an exceedance of the ARfD was calculated based on the highest reported residue in milk (HR 6.66 mg/kg):

- Milk/milk products:
  310 % of the ARfD of 0.1 mg/kg bw for bovine milk and 121 % for goat's milk for 2-4 years old German children
  164 % of the ARfD of 0.1 mg/kg bw for bovine milk processed into butter and 131 % for bovine milk (1-3.5 % fat content) for the German general population aged 14-80 years

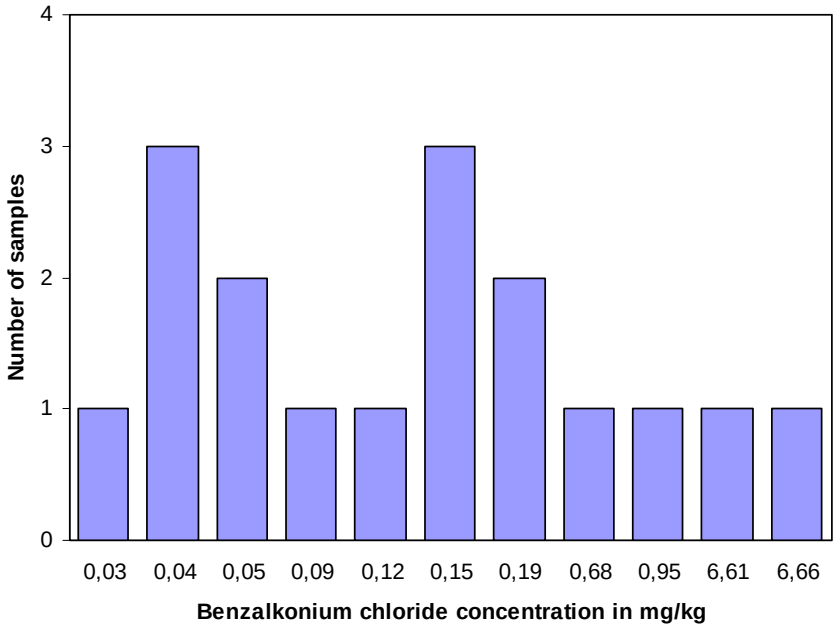
The slight exceedance of the ARfD for pineapple is considered being negligible. Although no information was available for benzalkonium chloride concerning the pulp/peel distribution of residues, respective data for the structurally related and physico-chemically comparable DDAC were available for citrus fruits. These data indicate that residues in the edible portion (pulp) were clearly lower than in peel (mean processing factor for DDAC in peeled citrus fruit was 0.11). A comparable behaviour could be expected for benzalkonium chloride and at least qualitatively the results might be extrapolated from citrus to pineapple. In fact the highest residue of benzalkonium chloride in the edible portion of pineapple (and in other large tropical fruits with inedible peel) is expected to be below the ARfD.

Since the calculated intake for milk and milk products clearly exceeds the ARfD for German and further European consumer groups, an acute risk for consumers (both children and adults) can not be ruled out when consuming milk/milk products with residues as high as 6.66 mg/kg (highest concentration reported for milk). See also the health risk assessment in chapter 3.3.

Out of the 17 milk samples reported to BfR to contain benzalkonium chloride residues >LOQ (38 milk samples had been investigated in total) 15 exhibited residues $\leq$ 0.95 mg/kg while in

2 samples residues amounted to 6.66 and 6.61 mg/kg, respectively. The following figure gives an overview of the positive findings in milk:

Figure 1: Benzalkonium chloride concentrations in milk samples



For all other commodities and all other European consumer groups (children and adults), for which consumption data are available, the calculated acute intake does not exceed the ARfD and an acute health risk consequent to benzalkonium chloride residues in these food commodities is unlikely.

3.2.4 Discussion

The available data indicate “background” levels of benzalkonium chloride above the currently applicable default MRL (Maximum Residue Level) of 0.01 mg/kg for most commodities.

In most commodities of plant origin residues of benzalkonium chloride were lower than those reported for DDAC. This might be due to different uses of DDAC- and benzalkonium chloride containing products.

High residues were again observed in large tropical fruit with inedible peel, especially avocado: the highest residue was 1 mg/kg. It is likely that these fruits received post-harvest treatments with benzalkonium chloride. A respective application for import tolerance has not yet been submitted.

In the group legume vegetables (fresh) occasionally higher residues were observed in beans (with pods, fresh) from Kenya. The origin of those residues is not clear. Apart from single findings, benzalkonium chloride residues in commodities of plant origin were below 0.1 mg/kg (except for large tropical fruit with inedible peel).

Benzalkonium chloride residues in milk and milk products however are considered as critical. High residues were not only observed in cream and ice cream samples taken from respective machines, but also in milk samples. They might be due to disinfection of bottling plants

or other equipment used during milk processing. The “unavoidable” level of residues in milk arising from such biocide uses following good practice can not be derived from the data. Such a level might serve as basis for MRL setting. It is however very clear that every effort needs to be made to considerably reduce benzalkonium chloride residues in milk/milk products, because the highest residue levels reported exceed the ARfD by far and might pose an acute risk to consumers.

BfR recommends to establish clear guidance on adequate cleaning/washing procedures to be followed after disinfection of equipment that gets in contact with food. Residues arising from disinfectant uses need to be restricted to a level which is unlikely to pose an acute risk for consumers (both children and adults).

3.3 Health risk assessment

For the assessment of potential adverse health effects the Margin of Safety (MOS) has been considered. It is defined as the quotient of the NOAEL (no observed adverse effect level) and the calculated dietary intake.
Toxicological reference values are usually derived from the NOAEL of the respective animal study by employing a safety factor of 100. This is supposed to ensure an MOS of (at least) 100 between the NOAEL and the maximum acceptable consumer exposure. The safety factor of 100 consists of to sub-factors of 10 each. One accounts for the inter-species differences (i.e. between animals and humans) and one for the intra-species differences (i.e. between individuals) when extrapolating from animal studies to humans.

For the calculated dietary intake through milk and milk products (based on the highest residue in milk of 6.66 mg/kg and the highest ARfD utilization calculated for any of the commodities in the group of milk/milk products) for which ARfD exceedance was observed, the consumer risk is characterized as follows:

Table 4: Risk characterization for children and adults exposed to benzalkonium chloride following consumption of a large portion of milk/milk products (residue 6.66 mg/kg, only most critical commodity considered)

Consumer group	Calculated intake (mg/kg bw/d)	NOAEL (mg/kg bw/d)	ARfD(mg/kg bw)	MOS	% ARfD
Children	NVS II: 0.3104	13	0.1	**42**	310 %
	EFSA PRIMo: 0.8273			**16**	827 %
Adults	NVS II: 0.1642	13	0.1	**79**	164 %
	EFSA PRIMo: 0.1148			113	115 %

For children the calculated dietary intake led to a utilization of the ARfD of 310 % and 827 %, respectively, and to an MOS of 42 and 16, respectively (see Table 4), which is far below the required MOS of 100.

For adults the calculated dietary intake (NVS II model) led to a utilization of the ARfD of 164 % also resulting in an MOS below 100 (79). Based on the intake calculated with EFSA PRIMo the utilization of the ARfD was 115 % and the respective MOS 113 (which would be acceptable).

When not taking into account the two by far highest residue values in milk and using the next highest residue in milk (0.95 mg/kg) instead for the assessment, the required MOS von 100 is met for both children and adults (see Table 5).

Tabelle 5: Risk characterization for children and adults exposed to benzalkonium chloride following consumption of a large portion of milk/milk products (residue 0.95 mg/kg, only most critical commodity considered)

Consumer group	Calculated intake (mg/kg bw/d)	NOAEL (mg/kg bw/d)	ARfD(mg/kg bw)	MOS	% ARfD
Children	NVS II: 0.0443	13	0.1	293	44 %
	EFSA PRIMo: 0.1180			110	118 %
Adults	NVS II: 0.0234	13	0.1	556	23 %
	EFSA PRIMo: 0.0164			793	16 %

Based on the currently available data an acute risk for consumers (both children and adults) can not be ruled out when consuming milk/milk products with residues as high as 6.66 mg/kg. The potential adverse effects might include slight reversible clinical symptoms due to irritation in the gastrointestinal tract.

However an acute risk for consumers (both children and adults) would be unlikely for milk/milk products containing benzalkonium chloride residues of up to 0.95 mg/kg.