BfR recommendations on how to perform the consumer risk assessment for perchlorate residues in food

BfR Opinion No. 015/2013, 6 June 2013

On the occasion of quality controls in food industry and during official food surveillance, perchlorate residues were detected in fruit and vegetables.

Perchlorates are the salts of perchloric acid. Their occurrence in the environment is mainly due to anthropogenic, i.e. man-made, sources. In paleogeochemical deposits of certain countries perchlorates may also occur naturally. Perchlorates are currently neither registered as pesticide nor as biocide active substances. Currently it is not completely clear how perchlorate could have reached food. Together with other federal authorities, the Federal Institute for Risk Assessment (BfR) investigated possible exposure pathways.

No maximum residue levels are currently applicable for perchlorate residues in food. Food placed on the market should not pose an unacceptable risk for consumers. BfR compiled recommendations based on current knowledge on how to perform the consumer risk assessment for perchlorate residues in food.

BfR recommends the usage of the assessment methodology that is implemented for the assessment of pesticide residues as long as the investigation of possible exposure pathways has not been finalized. When further residue data and more comprehensive information on the origin of residues and on the toxicological properties of perchlorate become available, this recommendation will be updated accordingly.

1   Subject of the assessment

The Federal Institute for Risk Assessment (BfR) has been asked by the Federal Ministry of Food, Agriculture and Consumer Protection (BMELV), to give recommendations on how to perform the consumer risk assessment for perchlorate residues in food.

2   Results and Conclusions

Since perchlorate has not been assessed in the framework of the EU active substances programme and currently no toxicological studies on perchlorate are available to BfR, use was made of assessments conducted by the National Academy of Sciences (NAS), the Joint FAO/WHO Expert Committee on Food Additives (JECFA) and the United States Environmental Protection Agency (US EPA).

BfR recommends basing the acute risk assessment for consumers on the PMTDI value (provisional maximum tolerable daily intake) derived by JECFA which is 0.01 mg/kg body weight.

Due to high uncertainties in the underlying data base and in order to sufficiently protect sensitive subpopulations, it is further recommended basing the acute risk assessment on the consumption data and variability factors laid down in the Pesticide Residue Intake Model (PRIMo) which is provided by the European Food Safety Authority (EFSA).

If the calculated intake remains below the PMTDI (i.e. IESTI < 100 %), an undesirable effect on consumer health caused by perchlorate is unlikely. If the calculated intake exceeds the PMTDI (i.e. IESTI > 100 %), an undesirable effect on consumer health cannot be fully excluded. Data for refinement of the assessment (processing factors, pulp/peel ratios, further toxicological data) are currently not available for perchlorate.

The assessment of perchlorate residue data, the origin of residues and toxicological properties of perchlorate are not finalized yet. When the assessment proceeds, this recommendation will be updated accordingly.

3. Rationale/Risk Assessment

3.1 Introduction

The BfR recommends the assessment of samples with perchlorate residues with respect to the acute risk for consumers and to make use of the assessment methodology usually applied for the assessment of pesticide residues as long as the investigation of possible exposure pathways has not been finalized. The chronic risk for consumers should not be assessed based on single findings, because these do not provide a representative picture of mean residue levels in food. The risk that might be related to the long-term intake of perchlorate residues will be assessed based on the whole residue data set for perchlorate. This is currently being done by BfR in the framework of the overall assessment of submitted residue data for perchlorate.

3.2 Toxicological Reference Value

The ingestion of perchlorate induces a reversible inhibition of iodide uptake by the thyroid. The inhibition of iodide uptake may cause changes of thyroid hormone levels and thus is considered to be the key precursor event to the adverse effect of hypothyroidism (NAS, 2005).

Perchlorate has not been assessed in the framework of the EU active substances programme. Since no toxicological studies on perchlorate are currently available to BfR, assessments conducted by the NAS, JECFA and the US EPA were used. (NAS, 2005; EPA, 2005; JECFA, 2011).

JECFA has derived a PMTDI of 0.01 mg/kg body weight (bw) based on a study of human volunteers (Greer et al., 2002) and a safety factor of 10. In this study on 16 male and 21 female volunteers (healthy, non-pregnant adults), perchlorate was given with the drinking water at doses of 0.007, 0.02, 0.1 or 0.5 mg/kg bw per day for 14 days. The uptake of radiolabelled iodide into the thyroid was measured at baseline before administration of perchlorate on days 2 and 14 of administration and 15 days after cessation of perchlorate administration. Uptake was measured at 8 and 24 h after administration. The inhibition was not significantly different from baseline at the lowest dose of 0.007 mg/kg bw per day, but was significantly increased with the perchlorate dose in all other dose groups (ca. 16-18%, 40-45% und 67-69% in the 0.02, 0.1 and 0.5 mg/kg bw per day groups). The uptake did not differ between day 2 and day 14 of perchlorate administration. At 15 days after cessation of perchlorate administration, the effect was fully reversible. There were no effects at any dose on serum levels of thyroid hormones thyroxine (T4) and triiodothyronine (T3). With the highest dose tested (0.5 mg/kg bw per day), a marginal but significant decrease of TSH levels (thyroid-stimulating hormone)

was observed in morning blood samples during perchlorate administration, with recovery by 15 days after cessation of perchlorate administration.

The No Observed Effect Level (NOEL) for the inhibition of iodide uptake into the thyroid (0.007 mg/kg bw per day) was chosen by NAS (NAS, 2005) as basis for deriving the reference dose (RfD). Opposed to that, JECFA selected a critical effect size of 50% inhibition of iodide uptake as the benchmark response (the lower of two calculated BMDL50 values: 0.11 mg/kg bw per day). This was used as the point of departure for derivation of a PMTDI, because human clinical data from healthy adults following both short-term and chronic exposure to perchlorate have shown that such a level of inhibition is not associated with any changes in TSH or thyroid hormone (T3, T4) levels (JECFA, 2011).

The study by Greer et al., 2002 involved healthy adults with normal thyroid function. No respective studies are currently available for potentially vulnerable subgroups such as people with clinical or subclinical hypothyroidism, those with iodine-deficient diets, neonates and young infants. A further vulnerable subgroup is the group of pregnant women with clinical or subclinical hypothyroidism. Thyroid hormones play a critical role in early life developmental processes, especially brain development. During this phase, thyroid disruption, including transient disruption, may cause permanent adverse effect on neurodevelopment. Especially in the first two trimesters of pregnancy, fetuses are dependent on maternal supply with thyroid hormones. The amount of thyroid hormone stored in the colloid in late-gestation fetuses and neonates is estimated to be sufficient for less than 1 day only. Since perchlorate is transferred to breast milk, thyroid hormone synthesis of nursing infants and - as a consequence - neurodevelopment of infants may be adversely affected. It is also unclear whether nursing infants may be additionally at risk if perchlorate were to reduce the passage of iodine into breast milk (NAS, 2005; JECFA, 2011).

A sufficient iodide supply cannot necessarily be assumed for Germany. About one third of the German population suffers from a more or less distinct undersupply (Hampel et al., 2005; Thamm et al., 2007). Therefore the occurrence of undesirable effects cannot be ruled out even after a single occasion of perchlorate uptake.

The inhibition of iodide uptake into the thyroid, which is already observed upon acute exposure of both animals and humans to perchlorate, is considered to be the key issue for possible undesirable effects of perchlorate (NAS, 2005; EPA, 2005; JECFA, 2011). As discussed above, this was chosen as the point of departure for derivation of a PMTDI by JECFA (JECFA, 2011). BfR therefore recommends basing the acute risk assessment for consumers on this PMTDI value of 0.01 mg/kg body weight. This approach is considered by BfR to be very conservative for subpopulations with normal thyroid function.

3.3 Estimation of the acute dietary intake (IESTI)

It is recommended to conduct the acute risk assessment with the EFSA model PRIMo rev. 2_0 based on the already implemented IESTI equation (International Estimated Short-term Intake) and the default variability factors in the model. Though this methodology was originally developed for the assessment of pesticide residues, it generally allows consumer exposure calculations under the consideration of unit-to-unit variations of residues in single food items. BfR therefore recommends using this model for the assessment of perchlorate residues in food as well. The model is provided on the EFSA webpage as an EXCEL sheet with implemented macros (EFSA, 2008). EFSA PRIMo contains a comprehensive set of consumption data for both adults and children from several EU Member states, including consumption data for German children.

3.4 Explanatory notes concerning the unit-to-unit variability of residues in food

Residues are not equally distributed among single units of food commodities. They differ to a considerable extent even within one lot, e.g. within one box of apples. The single units (e.g. individual apples) might have received very different exposure levels during spray application, e.g. due to partial coverage by canopy. High variabilities are also observed after soil applications and subsequent uptake by plants or in rotational crops planted into previously treated soil. These two situations might occur for pesticides, but also for fertilizer application and uptake. Even post-harvest dipping applications of food, for which equal distributions might be assumed, lead to variabilities of ca. factor 3 – depending on the kind of food and chemical. Variabilities might be due to natural variations such as differences in plant growth, fruit size or water content, but might also be a consequence of blending products from different growers within agricultural cooperatives.

Variability factors are required to account for the fact that residue analyses are normally conducted with composite samples (the sample is composed of several single units for reasons of feasibility und to achieve a robust estimation of the mean residue), while on the other hand consumers may be exposed to single units with higher individual residues. To check compliance of the samples with legal requirements such as established maximum residue levels, the measured residue of the composite sample is used (representing a mean of the single unit residues), while for risk assessment the most critical, but still realistic situation needs to be considered: in all cases where the ingested portion might contain higher residues than the composite sample, the measured value needs to be "corrected" by a variability factor (factors between 3 and 7 are used, depending on the commodity). Variability factors are not required (factor 1 in EFSA PRIMo) if single units are very small (<25 g each, e.g. strawberries) or for commodities which are usually blended before consumption (e.g. cereal grain, oilseeds) or which are blended and processed before consumption (e.g. fruit juice). In these cases the residue in the composite sample corresponds to the residue in the ingested portion. All required variability factors have already been implemented in the EFSA model PRIMo rev. 2_0 and the user does not normally need to make any changes to these default settings. The only exception is head cabbage and head lettuce: in agreement with the pesticide risk assessment it is recommended to use the alternative variability factor of 3 rather than the default value of 5, because for these food commodities extensive empiric data from unit-to-unit variability studies was available for a lot of different substances (BfR, 2010). BfR therefore considers the variability factor of 3 to also be appropriate for perchlorate residues in these commodities.

The BfR is aware of the fact that the use of variability factors in the acute risk assessment of perchlorate residues is discussed controversially and that for example The Netherlands did not consider variability factors in their otherwise comparable perchlorate assessment (NL, 2013), because perchlorate is not a pesticide for which this approach would have been appropriate. Since the observed variability is mainly due to natural variations of plants/commodities or to blending and since it is no inherent property of the chemical in question, the BfR recommends for the time being the usage of variability factors as implemented in EFSA PRIMo in the acute consumer risk assessment for perchlorate.

When further residue data become available, and the entry pathways of perchlorate into food commodities have been further elucidated or if unit-to-unit studies on perchlorate become available, this recommendation will be updated accordingly.

3.3 Technical advice on how to use the model PRIMo rev. 2-0

In the sheet titled „Report", the toxicological reference value of 0.01 (unit is mg/kg bw) is entered in the cell „ARfD". Afterwards the respective residue value in mg/kg is entered in the sheet titled „acute_overview_children" in the column accented with light green colour. Residue values for different commodities might be processed in parallel. The food commodities accented with dark or light blue colour represent commodity groups (e.g. „Citrus fruit"). Residue values entered here will automatically be copied to all commodities belonging to this group. However, the residue value is not normally entered in the cell for the commodity group, but in the cell belonging to the particular commodity for which this residue has been measured (e.g. "Oranges").

In case of food commodities consisting of an edible and a non-edible portion, preferably those residue data which refer to the edible portion (if available) are entered into the model. For example, residue data in orange pulp are to be preferred over residue data in whole oranges including the peel. However, in most cases, residue data will not be available for the edible portion und then the available whole fruit data have to be entered.

As soon as the residue value has been entered, the result of the intake calculation appears in the column titled „IESTI 1" and the result of the comparison with the toxicological reference value in the neighbouring column titled „% ARfD".

The calculation result is always based on that consumer group (in this sheet: children) with the highest intake of the respective commodity per kg body weight. Detailed informations concerning the input data for the intake calculation can be found in the columns left of „IESTI 1". The columns titled „alternative variability factor" and „IESTI 2" (and related to those the column titled „ARfD for calculation with alternative variability factor") do not need to be considered for most food commodities. Only for the commodities head lettuce and head cabbage it is recommended to use the variability factor of 3 instead of the default factor of 5. For these two commodities the result of the IESTI calculation is then obtained from the columns titled „IESTI 2" and „ARfD for calculation with alternative variability factor" (the respective cell indicating the alternative variability factor has been accented with blue colour in the model).

In all cases in which the calculation reveals an intake exceeding the toxicological reference value („> 100 % ARfD"), the cell is automatically accented with orange colour and an additional information is given in the column titled „Threshold MRL IESTI 1": here the highest residue value is mentioned which does not exceed the toxicological reference value (the title of this column is somewhat misleading but has historical reasons). All residue data that have been entered in the sheet titled „acute_overview_children" are automatically copied by the model to the sheet titled „acute_overview_adults". This sheet provides the results of the intake calculation and the comparison of the intake with the toxicological reference value as described above, but for adult consumer groups. Again, the calculation result is always based on that consumer group (in this sheet: adults) with the highest intake of the respective commodity per kg body weight.

In the sheet titled „Report", all food commodities are listed for which the residue data entered into the model led to an intake higher than the toxicological reference value (i.e. IESTI > 100 %). In those cases an undesirable effect on consumer health cannot be fully excluded. If the calculated intake does not exceed the toxicological reference value (i.e. IESTI < 100 %), an undesirable effect on consumer health caused by perchlorate is unlikely. Data for refinement of the assessment (processing factors, pulp/peel ratios, further toxicological data) are currently not available for perchlorate.

4. References

BfR, 2010:
http://www.bfr.bund.de/cm/343/variabilitaetsfaktoren_fuer_die_abschaetzung_der_kurzzeitex
position_von_verbrauchern_gegenueber_pflanzenschutzmittelrueckstaenden.pdf

EFSA, 2008: http://www.efsa.europa.eu/en/mrls/docs/calculationacutechronic_2.xls

EPA, 2005: Perchlorate treatment technology update. Federal facilities forum issues paper
542-R-05-015 www.epa.gov/tio/tsp

Greer MA, Goodman G, Pleus RC, Greer SE, 2002: Health effects assessment for environ-
mental perchlorate contamination: The dose response for inhibition of thyroidal radioiodine
uptake in humans. Environm. Health Perspectives 110: 927-937

Hampel R, Bennöhr G, Gordalla A, Below H, 2007: Jodidurie bei Ewachsenen in Deutsch-
land 2005 im WHO-Zielbereich. Medizinische Klinik 104: 425-428; zitiert nach Abstract

JECFA, 2010: Safety evaluation of certain contaminants in food, prepared by the Seventy-
second meeting of the Joint FAO/WHO Expert Committee on Food Additives (JECFA), WHO
food additives series; 63. FAO JECFA monographs; 8. FAO & WHO, 685-762, 2011 sowie
WHO technical report series 959: 64-73

NAS 2005: Committee to Assess the Health Implications of Perchlorate Ingestion: Health
Implications of Perchlorate Ingestion. National Research Council

NL, 2013:
http://www.vwa.nl/actueel/mededelingen-
voedselveiligheid/nieuwsbericht/2032921/actielimieten-voor-perchloraat-in-groente-en-fruit-
vastgesteld dated 06.05.2013

Thamm M, Ellert U, Thierfelder W, Liesenkötter KP, Völzke H, 2007: Jodversorgung in
Deutschland. Ergebnisse des Jodmonitorings im Kinder- und Jugendgesundheitssurvey
(KiGGS). Bundesgesundheitsbl - Gesundheitsforsch - Gesundheitsschutz 50:744–749