Chemicals in Food Hygiene

VOLUME 2

Cleaning agents, sanitisers and disinfectants in food businesses: detection of traces and human risk assessment processes

Foreword

The Global Food Safety Initiative (GFSI) is a non-profit industry association tasked with promoting continuous improvement of food safety management systems to ensure confidence in the delivery of safe food to consumers worldwide. GFSI provides a platform for collaboration between some of the world's leading food safety experts from retailer, producers and food service companies, service providers associated with the food supply chain, international organisations, academia and government.

Since GFSI's inception in 2000, experts from all over the world have been collaborating in numerous Technical Working Groups (TWG) to tackle current food safety issues defined by GFSI stakeholders. In 2017 a TWG was established to determine best practices in relation to biocides (defined as the residues from cleaning agents, sanitisers and disinfectants) in the food supply chain. The objective of the work of the group was to ensure consumer protection through the appropriate application of cleaning agents, sanitisers and disinfectants from farm to fork, balancing the risks and benefits of their use whilst facilitating the global trade of food.

The TWG:

- Mapped and evaluated the current and pending global regulatory landscape in respect to cleaning agents, sanitisers and disinfectants and their traces in food;
- Established criteria and approaches for risk assessment in the procurement, application and use of cleaning agents, sanitisers and disinfectants to enable food businesses and primary producers to take risk management decisions;
- Developed guidance on the intended optimal usage of cleaning agents, sanitisers and disinfectants to ensure chemical and microbiological food safety considering carry-over risks of traces in foods;
- Reviewed and identified gaps in the suitability of existing methods for detection of traces at relevant points in the food production process;
- Developed the GFSI position on the use of cleaning agents, sanitisers and disinfectants and the relationship with microbial resistance.

The TWG produced 2 volumes within one document:

- Volume one of this document provides a high-level overview of the considerations that a food business operator needs to consider in relation to ensuring appropriate hygienic practices. This volume is aimed at a variety of readers from the food truck operator or farmer through to the global producer of consumer goods. This guidance focuses on the responsible and effective use of chemicals in food hygiene cleaning and disinfection especially of food equipment and other food contact surfaces including hands. The aim of the document is to ensure that the risk of traces in food is minimised whilst ensuring microbiological efficacy;
- Volume two provides a more in-depth understanding of risk assessment processes. It includes an overview of existing methods for detection of traces at relevant points in the food production process. Criteria and approaches for risk assessment in relation to the procurement, application and use of chemicals in food hygiene for food businesses and primary producers are provided for use as a guideline along with a number of tools to support the risk assessment process.

Global regulatory environment

With respect to the global regulatory environment, mapping of the related regulations showed differences of approach and a lack of harmonisation between jurisdictions. Whilst the correct use of cleaning agents, sanitisers and disinfectants during production, processing and retail is not usually intended to expose food to substances contained in these chemicals, it is

acknowledged that they may lead to the presence of traces in food.

A primary principle of food and related regulation is to ensure the protection of consumers. However, in the case of cleaning chemicals, food business operators have the responsibility of meeting two objectives:

- Limiting consumer exposure to traces of active substances contained in cleaning agents, sanitisers and disinfectants, and;
- Ensuring microbiological safety by having effective tools to control organisms to the extent that they cannot cause harm to human or animal health.

The TWG's opinion is that hazard-based management is not appropriate. Every substance and chemical should be assessed in the specific context of the food production, considering a risk / benefit approach.

A human health risk-based risk assessment principle should be the basis for internal risk management and global regulations. The assessment should focus on traces in food and risks associated with food intake.

It will be necessary to follow the principle of a risk / benefit analysis, a case by case decision based on scientific health risk assessment and depending on food type, chemical and microbial results, recommended condition of use and specificity of installations.

As some traces are technically unavoidable, it is not appropriate to attempt a step to ensure zero traces in food. Every substance and chemical should be assessed in the specific context of food production. It is important to implement proportionate measures to mitigate the risks of significant consumer exposure to traces derived from chemical use.

To ensure compliance with regulations, and in the absence of a harmonised regulatory approach, food companies must seek information about local / national legislation in the countries where they sell their product when developing and implementing onsite cleaning, sanitising and disinfection processes.

GFSI TWG position on the use of cleaning agents, sanitisers and disinfectants, and the relationship with microbial resistance.

Cleaning agents, sanitisers and disinfectants are vital to food hygiene and are a global public health protection measure. Limiting microbial antibiotic resistance is also a public health priority. Although many factors contribute to the incidence of antimicrobial resistance, the use of antibiotic compounds in human clinical settings and food-producing animals are primary contributors.

At the time of publication of this document GFSI are in the process of publishing a review on the relationship of the use of cleaning agents, sanitisers and disinfectants on microbial resistance. This review provides an overview, summary and discussion of the current available information and research on the use of chemicals in food hygiene and the development of anti-microbial resistance. The review identified no evidence of causality between appropriate usage of food hygiene chemicals and co-selection, or of antibiotic resistance. The paper makes a number of recommendations related to reducing the risk of anti-microbial resistance which are covered in the recommendations and guidance sections in volume 1 and volume 2 of this document.

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Executive summary

Cleaning in the food industry is a complex process. Physical, chemical and (micro)biological cleanliness are a prerequisite for food safety. This document provides an overview of existing methods for the detection of traces at relevant points in the food production process and establishes criteria and approaches for risk assessment concerning the procurement and application of chemicals in food hygiene. Food businesses and primary producers (including small entities) may use these criteria as a guideline.

Good Manufacturing Practices and HACCP are generally effective approaches to produce safe food. This document supports food business operators along the supply chain to identify risks and critical control steps depending on the cleaning methods (e.g. wet cleaning) and chemicals in use (e.g. sanitisers or disinfectants). A standardised process for cleaning is of great importance.

A risk assessment is needed to determine whether an activity that introduces cleaning agents, sanitisers and disinfectants represents a known or reasonably foreseeable chemical hazard. Therefore, this document includes a questionnaire to help businesses and primary producers navigate the process of risk assessment. The objectives of any preliminary risk assessment are (1) to identify the need for cleaning, disinfecting or sanitising, (2) to define the best technique and (3) to identify where, why and how sanitisers, disinfectants and cleaning agents are introduced to the food manufacturing process. When necessary, a human risk assessment may be needed to support any risk management decision.

Additionally, validation, monitoring and verification are critical components of food safety and quality management programmes; this guideline therefore includes information on these components. The need for analytical methods for chemical residues or markers was evaluated. A decision tree was developed to support the search for the fitting analytical method in the context of a risk assessment approach.

In summary, this document provides helpful tools for implementing risk assessments of chemical hazards in the food industry, applying several questionnaires and decision trees to this end.

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1 - Scope

The present report is a working document developed by the GFSI Chemicals in Food Hygiene Technical Working Group (TWG), providing general information on risk assessment in the procurement, application and use of cleaning agents, sanitisers and disinfectants to enable food business operators of all sectors (e.g. primary, processing, retail) to take risk management decisions.

As risk is a function of a hazard and an exposure, this document gives particular focus to:

- Human health risk assessment for chemicals, and
- Suitability of existing methods for detection of traces at relevant points in the food production process (related to an exposure assessment).

The TWG also produced "Volume 1: usage guidance to producers: the optimal usage of cleaning agents, sanitisers and disinfectants to minimise the risk of traces in food", which contains more practical information on the responsible and effective use of chemicals in food hygiene.

2 - Food safety system

National and international legislation requires the food industry to put safe food on the market (European Commission 2002[i]). Physical, chemical and (micro)biological cleanliness are prerequisites for food safety. A variety of hazards, including microorganisms and their toxins, previous products and ingredients, colourants, allergens, residues from cleaning agents, sanitisers, disinfectants and lubricants can (cross-) contaminate food during production with food safety or quality consequences.

Many stakeholders in the food production chain, from agriculture production to food service, have adopted the Hazard Analysis and Critical Control Points (HACCP) Principles[ii] as a tool to identify where hazards (physical, chemical, biological) might occur in the production process. Once the hazards are identified, actions to monitor and control different steps of the process are implemented to significantly mitigate those hazards. Pre-Requisite Programmes (PRPs)[iii] and preventative controls (US FDA 2018[iv]) support the implementation of a HACCP-based food safety system.

Previously, three types of food safety measures were used:

- Activities required by regulation on food, ingredients additives, processing aids, biocides, etc.
- Activities stated in the codes of Good Manufacturing Practices (GMP) or Good Hygienic Practices (GHP). These activities relate to processing, transportation, etc.
- Activities performed to verify food safety after production (e.g. finished food testing).

Currently, these measures have been improved by a combination of compliance approaches with food safety regulations, GMP, GHP, the use of an appropriate HACCP system and risk assessment procedures. This is to ensure that all potential hazards to the food and production process are identified and controlled.
Hierarchy of the different activities is presented in Figure 1.

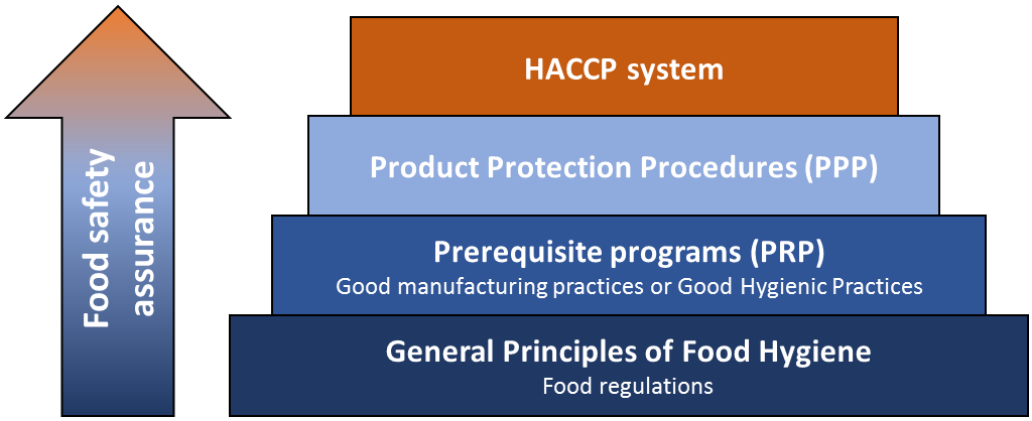


Figure 1. Food safety activities (from Lang et al. 2017 [v])

Good Manufacturing Practices (GMP)

GMP ensure products are consistently produced and controlled according to quality standards. GMP are required before any advanced programmes like HACCP can be implemented. They are designed in the form of detailed programmes and procedures that include guidelines to instruct employees on proper practices to prevent, eliminate or reduce food safety hazards.

In recent years, several food safety management certification programmes have been recognised by GFSI[vi] and meet internationally recognised food safety requirements.

Hazard Analysis and Critical Control Points (HACCP)

Hazard Analysis Critical Control Point (HACCP) is recognised as one of the most effective approaches to safe food production. It is a proactive and prevention-based system that complements regulatory compliance and GMP and provides additional assurances.

Due to its systematic approach, it has gained widespread acceptance from regulation (e.g. in the European Union, Directive 93/43 (EEC)[vii] and / or Hygiene Regulation (EC) No 853/2004[viii]), governmental agencies (e.g. in the United States of America: National Advisory Committee on Microbiological Criteria for Foods 1997 [ix] and U.S. Food & Drugs Administration Food Safety Modernization Act[x]), and other organisations such as Codex Alimentarius[xi] and GFSI.

Rather than relying on finished food testing to detect failures, HACCP applies control measures at identified stages of the production process. This serves to prevent, reduce or eliminate hazards before they occur. When well implemented, HACCP will meet the requirements of an effective food safety system.

A HACCP system includes both prerequisite or underlying programmes and HACCP plans (see figure 2). Prerequisite programmes are the foundation of a HACCP system and include the procedures and practices that provide the basic environmental and operational conditions needed to produce safe food. Once a facility documents and implements these environmental controls, it can begin the development of HACCP plans.

HACCP plans outline how the hazards associated with incoming materials (ingredients) and process steps are controlled. They also identify the processes that are critical to ensuring food safety (e.g. the critical control points).

Figure 2. Interrelationships in an HACCP system (from Lang et al. [xii])

The HACCP system is built following seven principles. Each principle is designed to develop the level of understanding of hazards, their identification and implementation of controls. The principles are defined by Codex Alimentarius (2003)[xiii] as follows:

Principle 1: Conduct a hazard analysis

Identify the potential hazard(s) associated with food production at all stages, from primary production, processing, manufacture and distribution until the point of consumption. Assess the likelihood of occurrence of the hazard(s) and identify the measures for their control.

Principle 2: Determine the Critical Control Points (CCPs)

Determine the points, procedures or operational steps that can be controlled to eliminate the hazards or minimise their likelihood of occurrence. A 'step' means any stage in food production and / or manufacture including the receipt and / or production of raw materials, harvesting, transport, formulation, processing, storage, etc.

Principle 3: Establish critical limit(s)

Establish critical limit(s) which must be met to ensure the CCP is under control.

Principle 4: Establish a system to monitor control of the CCP

Establish a system to monitor control of the CCP by scheduled testing or observations.

Principle 5: Establish the corrective action to be taken when monitoring indicates that a particular CCP is not under control.

Principle 6: Establish procedures for verification to confirm that the HACCP system is working effectively.

Principle 7: Establish documentation concerning all procedures and records appropriate to these principles and their application.

Prerequisite programmes

Many identified hazards may be common to several stages of the process.

Prerequisite programmes are the Standard Operating Procedures (SOPs) and environmental conditions necessary for safe food production and packing and found in any comprehensive food safety system.

Prerequisite programmes must provide all the information that is needed to ensure a safe environment to produce food.

Prerequisite programmes with trusted controls will reduce the number of critical control points (CCP) needed in a HACCP system. Reducing this number allows food business operators to focus on where food safety is most likely threatened.

HACCP plans should not control hazards that are normally controlled through the prerequisite programmes. According to Lang et al. 2017 [xii], the required standard procedures are grouped in eight prerequisite programmes:

- Premises;
- Transportation and Storage;
- Equipment;
- Personnel/Training;
- Sanitation and Pest Control;
- Recall;
- Allergen Control;
- Supplier Food Safety Assurance.

Box 1

Prerequisite programmes (PRP) are called **Good Manufacturing Procedures (GMP)** or **Good Hygienic Practices (GHP)** in the United States. They are called **Standard Operating Procedures (SOPs)** in many other countries.

Case of small entities

For small entities, specific guidance documents exist such as:

- The FAO / WHO guidelines for small businesses[xiv] , or
- The FDA Food Safety Modernization Act[xv].

3 - Cleaning / disinfection / sanitation

A critical step

Cleaning is a critical step within the food production industry to maintain and further ensure food safety and quality standards. As mentioned above, it is generally considered as part of the Pre-Requisite Programmes (PRPs) or preventative controls. Cleaning can include the use of detergents and can be combined with disinfectants / sanitisers (see Box 2 and glossary). Various methods of cleaning, with or without disinfection / sanitation are typically practiced (see Box 3).

Box 2

Cleaning
Process of removing unwanted soil (fats, proteins, sugars, scaling, etc.) from equipment and/or manufacturing facilities, by application of an effective procedure, either manual or automated.

Sanitisation
Process of reducing microbiological contamination on an effectively cleaned surface by means of a bactericidal treatment such as heat or chemicals, to a level that is acceptable to local health regulations. For effectiveness, this must be preceded by cleaning.

Disinfection
Process that eliminates many or all microorganisms, except bacterial spores, on inanimate objects. Some disinfectant chemicals also have sporicidal activity.

Box 3

Dry cleaning
Process of removing unwanted soil, using an effective procedure, from equipment and/or manufacturing facilities, without use of water (including aqueous solutions or steam).

Wet cleaning
Process of removing unwanted soil, using an effective procedure, from equipment and/or manufacturing facilities, with the use of unrestricted quantities of water. This includes cleaning in place (CIP), cleaning out of place (COP) and other forms of cleaning using unrestricted amounts of water. Wet cleaning can be combined with disinfection/sanitation.

Controlled wet cleaning
Process of removing unwanted soil, using an effective procedure, from equipment and/or manufacturing facilities with limited amounts of water, applied with strict control or by use of humid cloths. Controlled wet cleaning is followed by immediate active drying of cleaned surfaces. In order to comply with this definition, this type of cleaning is often limited to small surfaces or occasional application on individual pieces of equipment. Controlled wet cleaning can be combined with disinfection/sanitation.

Cleaning in Place (CIP)
CIP is a method for cleaning the production lines without dismantling the installation by circulating cleaning solutions according to defined protocols, combining physical, mechanical and chemical energies.

Cleaning out of Place (COP)
COP is a method of cleaning whereby equipment or parts of equipment are removed from their normal place of use in a food processing operation specifically for purposes of cleaning.

Objective of cleaning / disinfection / sanitation

For all cleaning /disinfection/sanitation activities, the objectives of the cleaning should be clearly defined, e.g.:

- To control hazardous microorganisms;
- To control food chemical contamination;
- To control foreign body contamination;
- To control allergen cross contact;
- To control ingredient / residue / colour / flavour at product changeover;
- To avoid pest infestation;
- To control chemical residues from cleaning / sanitation regimes;
- To assure mechanical operations of equipment
- To improve process efficiency (e.g. heat transfer efficiency);
- To assure occupational safety;
- To satisfy local regulatory requirements;
- To meet specific customer requirements;
- To meet GFSI requirements.

Cleaning procedures - Standard Sanitation Operating Procedure (SSOP / SOP)

Cleaning is a complex process. A defined and systematic approach is required to ensure it is conducted correctly. This approach takes the form of Standard Sanitation Operating Procedure (SSOP), usually a legal requirement and a fundamental GFSI requirement. The collection of these cleaning procedures forms a Cleaning Plan or Programme which is specific to a facility.

A typical SSOP includes the following:

- Cleaning frequency / duration / sequence;
- Cleaning agents, sanitisers and disinfectants used (ensuring they are food-grade and fit-for-purpose);
- Cleaning process parameters (equipment used, concentration of chemicals, time, temperature, physical parameters);
- Safety requirements (assembled / disassembled equipment list, requirements to protect adjacent lines / products);
- Responsibilities, documentation, visual aids, training / qualification requirements;
- Necessary monitoring or verification activities.

Note that establishing SSOPs require training of cleaning personnel to limit variation between operators.

Additionally, validation procedures are needed to determine the ability of the SSOP to achieve the desired outcome. This consists in microbiological, allergen, cleaning agent / disinfectant residues analyses after each cleaning trail or other tests required on food contact surfaces and other sample points. Details are given in section 6 – Cleaning Validation, Monitoring and Verification.

Acceptance criteria

For all cleaning objectives with or without disinfection / sanitation activities, a standard level of cleanliness / disinfection should be set.

Steps should be clearly defined to control the process when conditions pose the greatest chance of product or process failure.

The acceptance criteria should rely on qualitative (e.g. visual criteria) and / or quantitative (limits for microbiological, chemical, allergens or their appropriate markers) techniques.

Acceptance criteria should be set to comply with finished food specifications and existing regulatory limits. In absence of specified acceptance criteria, acceptable limits may be

set according to the type of residue or contaminant (see section 5 – Assessing the risks of cleaning / disinfection productions: proposed approach and decision tree).

Controlling chemical residue(s) as a cleaning / sanitation objective

Based on a targeted risk assessment (see section 5 – Assessing the risks of cleaning / disinfection productions: proposed approach and decision tree) and practicality, food business operators might opt to use the HACCP approach to evaluate chemical hazards that can be introduced to finished food through the application of sanitisers, disinfectants and cleaning agents on Food Contact Surfaces (FCS). For example, it may be set as one of the objectives for the cleaning / sanitation regime. Multiple cleaning objectives (for food safety or quality attributes) may be combined.

Although the cleaning methods may vary depending on the type of soil to be removed from FCS, and the cleaning objectives, completely removing the detergent from the surface by rinsing at least once is an expectation, often driven by regulatory requirements.

When the cleaning agent / sanitiser / disinfectant can degrade to form residues (e.g. hypochlorite disintegration to (per)chlorate), the residues should be appropriately managed. This includes following specification instructions, proper storage, handling and dosage at the facility. Residues may also be left on an FCS due to the physico-chemical properties of the substance (e.g. more fat-soluble and less likely to be completely removed during a water rinse). The occurrence of unacceptable levels of such residues in foodstuffs or amounts above any existing legislative limits must be avoided.

Where regulatory requirements (i.e. Maximum Residue Levels (MRLs)) exist for used disinfectants / sanitisers or their active substances, regulatory compliance for finished food specifications must be ensured, i.e. demonstrating that residues in the final foodstuff are below the MRL. Regulatory compliance may also be ensured by limiting the amount of chemicals in a cleaning agent / sanitiser / disinfectant use solution based on the potential residue left behind, which is calculated using standard exposure models relevant for the application or use pattern (e.g. by models used for no-rinse cleaning and sanitising on hard surfaces or direct food treatments).

4 - Human health risk assessment principles

Definitions

The following definitions are acknowledged internationally (OECD 2003[xvi], International Programme on Chemical Safety 2004[xvii]).

Hazard is 'The inherent property of an agent or situation having the potential to cause adverse effects when an organism, system or (sub) population is exposed to that agent.'

Hazard assessment is 'A process designed to determine the possible adverse effects of an agent or situation to which an organism, system or (sub) population could be exposed. The process includes hazard identification and hazard characterization. The process focuses on the hazard in contrast to risk assessment where exposure assessment is a distinct additional step.'

Hazard identification is 'The identification of the type and nature of adverse effects that an agent has as inherent capacity to cause in an organism, system or (sub) population.'

Hazard characterisation / Dose Response Assessment is 'The qualitative and, wherever possible, quantitative description of the inherent properties of an agent or situation having the potential to cause adverse effects. This inherent hazard can also be referred to as the potency of the substance. This should, where possible, include a dose–response assessment and its attendant uncertainties.' Hazard characterisation is also known as dose–response assessment. At this step, the No-Observed-Adverse-Effect Level (NOAEL), the Lowest-Observed-Adverse-Effect Level (LOAEL) or Benchmark Doses (BMD) are derived for the observed effects, where possible and appropriate.

Exposure Assessment is 'Evaluation of the exposure of an organism, system or (sub) population to an agent (and its derivatives).'

Risk characterisation is 'The qualitative and, wherever possible, quantitative determination, including attendant uncertainties and variability of data and/or populations being evaluated, of the probability of occurrence of known and potential adverse effects of an agent in a given organism, system or (sub)population, under defined exposure conditions.'

Principles of chemical risk assessment

According to FAO/WHO[xviii], a health risk assessment is the scientific evaluation of whether a chemical poses a hazard or adverse health effect independent of exposure, whether the chemical results in exposure independent of hazard, and characterisation of the risk if the chemical poses both an adverse health effect and will result in human exposure. A dietary risk assessment is intended to evaluate known or potential adverse health effects resulting from human exposure to foodborne hazards, or hazards introduced into the food during the food production process. Health risk assessment consists of four steps (Figure 3).

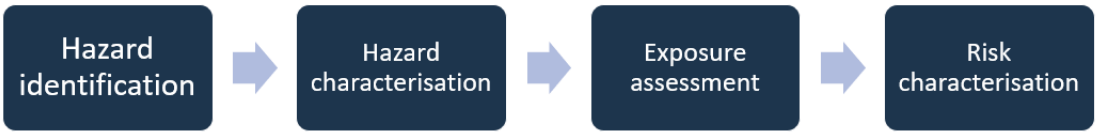


Figure 3. The four steps of the risk assessment process

Box 4

The risk assessment process incorporates the risk paradigm which demonstrates that if there is no hazard (hazard = 0) or no exposure (exposure = 0), there is no safety concern.

Hazard identification

This step consists in listing the anticipated chemicals to be found on food contact surfaces that could transfer to food. The chemicals included in a hazard identification should be those that have the potential to cause an adverse health effect.

For this purpose, it is helpful to consult several databases, such as regulations on chemicals in food, risk assessments from food safety agencies (e.g. European Food Safety Authority (EFSA), U.S. Food & Drug Administration (US FDA)), the opinion of other agencies (e.g. European Chemicals Agency (ECHA), U.S. Environmental Protection Agency (US EPA)) and / or to refer to the published toxicology literature to determine the hazard(s) posed by each substance from oral (dietary) exposure.

Note as indicated in section 5 – Assessing the risks of cleaning / disinfection productions: proposed approach and decision tree: If the

hazard identification step concludes to the absence of chemicals, impurities or degradation products that will pose an adverse effect, then there is an absence of a hazard. That means the chemical will not pose a health risk and a full risk assessment will not be needed.

Hazard characterisation:
This step describes the relationship between the administered dose of a chemical and the incidence of an adverse health effect. For a dietary risk assessment, hazard characterisation would usually be limited to adverse effects from studies that administered the substance orally.

Hazard characterisation involves the following steps:

1. Determining the doses at which adverse effects are caused;
2. Identifying the most relevant adverse effect or endpoint and whether the effect has a toxicity threshold or whether it is a non-threshold toxicant and / or carcinogen;
3. If the substance exhibits a threshold effect, identifying the lowest dose at which that effect occurs as well as the dose that no adverse effect occurs (LOAEL and NOAEL);
4. Identifying uncertainty and safety factors that account for animal and human differences (interspecies extrapolation), life-stage sensitivities (safety factors), human variability (intra-species variability) or data gaps.

The derivation of Health-Based Guidance Values (HBGV) can be referred to as an Acceptable Daily Intake (ADI), Tolerable Daily Intake (TDI), Reference Dose (RfD) or Benchmark Dose (BMD).

A HBGV may already be established by a regulatory body. Several HBGV databases are available and should be consulted:

- European Chemicals Agency: https://echa.europa.eu/information-on-chemicals/registered-substances;
- The OpenFoodTox database of the European Food Safety Authority (EFSA): https://echa.europa.eu/information-on-chemicals/registered-substances;
- US Integrated Risk Information System (IRIS) from the US Environmental Protection Agency (US EPA): https://www.epa.gov/iris
- US Environmental Protection Agency Office of Pesticides, Registration Eligibility Decisions (REDs): https://archive.epa.gov/pesticides/reregistration/web/html/status.html
- Agence Nationale de Sécurité Sanitaire de l'alimentation, de l'environnement et du travail (ANSES): https://www.anses.fr/fr/content/liste-des-valeurs-toxicologiques-de-r%C3%A9f%C3%A9rence-vtr-construites-par-l%E2%80%99anses

When no HBGV is available, the hazard characterisation steps above should be followed to derive a value with adequate data. If there is limited data, it may also possible to use alternative approaches such as those outlined below to derive a value:

- To consider cut-off values from the Threshold of Toxicological Concern (TTC) approach (see the paragraph 'Threshold of Toxicological Concern approach');
- Validated Quantitative Structure Activity Relationship (QSAR), read-across and docking techniques are now available and should also be used (in addition/complement to the TTC) in evaluating toxicologically non-characterised chemicals (see paragraphs 'Threshold of Toxicological Concern approach' and 'Quantitative structure activity relationship (QSAR)'). It is worth noting the significant progress in computational / in silico toxicology over the past years.

Further guidance is expected through the outcome of the current Codex Electronic working group (eWG) on 'Guidelines for Risk Analysis of Chemicals inadvertently present in food' [xix] in this context.

Exposure assessment
Preamble

Exposure assessment is the process of estimating human dietary intakes for the

chemical of concern. It takes into consideration the occurrence and concentrations of the chemical in the diet, the consumption patterns of the food containing the chemical, the likelihood of consumers eating large amounts of the food in question (high consumers: p95) and of the chemical being present in this food at high levels.

Intake estimates are usually performed on population subgroups (e.g. infants, children, adults) and for mean and high consumers.

The general equation for exposure assessment is:

Equation 1 EDI = C1/FI

With

- EDI = Estimated Dietary Daily Intake (mg FCS/kg body weight/day)
- C1 = concentration of chemical in food (mg/kg)
- FI = food consumption level (mg food/kg body weight)

When it proves difficult to measure trace levels (C1) in food from a FCS, due to very low levels and analytical hurdles, a model may be chosen and used to estimate the potential level that could transfer to food from a surface. These models are typically health protective and over-estimate the trace levels that could get into food.

Types of models for FCS are:

a) FCS used on hard non-porous surfaces – restaurants and/or food processing;
b) FCS used on porous surfaces;
c) Process water substances;
d) Direct food antimicrobials;
e) Other potential models may be needed for certain applications.

The US EPA proposes models for hard-surface Food Contact Sanitising Solutions (FCSS) [xx]. The tier 1 model is mainly dedicated to Public Eating establishments, while the Tier 2 model applies to food processing facilities.

The calculation of exposure becomes:

Equation 2 EDI = (FCS x T)/FI

With

- EDI = Estimated Dietary Daily Intake (mg FCS/kg body weight/day)
- FCS = level of chemical on food contact surface (mg/dm²)
- T = transfer ratio from food contact surface to food (dm²/kg)
- FI = food consumption level (mg food/kg body weight)

Default value vs databases on food intakes

Selection of dietary intake levels of food is a complex issue for which results of food intake surveys must be available. Results of food intake surveys may be viewed at the following sources:

- In Europe, the EFSA is managing a food intake database available at: http://www.efsa.europa.eu/en/food-consumption/comprehensive-database;
- At the international level, WHO is running the GEMsFood database: https://extranet.who.int/sree/Reports?op=vs&path=/WHO_HQ_Reports/G7/PROD/EXT/GEMS_cluster_diets_2012&userid=G7_ro&password=inetsoft123;
- In the USA, there are a few sources of food consumption and intake that may be used in dietary risk assessments depending on the use, including the National Health and Nutrition Examination Survey (NHANES)[xxi]. The US EPA Office of Pesticide Programs may also use the Dietary Exposure Evaluation Model (DEEM)[xxii] or the Indirect Residential Exposure Assessment Model (IDREAM)[xxiii], which have food consumption rates built into the models, or they may use a default intake rate.

Considering adults with a mean body weight of 60 to 70 kg, a worst-case scenario can be used considering intakes of 2 kg of solid food per day and 2 L of liquids per day (for both Europe [xxviii] and the USA[xxiv, xxv]).

Another scenario may be to use default levels based, for example, on recommendations from the EFSA (EFSA 2016[xxvi]) on default dietary intakes for packed food. Indeed, food contact material can be assimilated to processed food. These default levels address the whole population; they are based on the highest intake levels observed for specific class of age such as infants and toddlers

(EFSA 2016[xxvii]). These food intakes can be easily extrapolated to other populations' subgroups by using the default values set by the EFSA (EFSA 2012a[xxvii]).

Estimated Dietary Daily Intake calculation

Steps to estimate the dietary daily intake of a cleaning agent / sanitiser / disinfectant include:

1. Asking supplier for the composition of the used cleaning agent / sanitiser / disinfectant;
2. Monitoring amounts of cleaning agent / sanitiser / disinfectant used for a full cleaning operation;
3. When there is a water rinse, monitoring amounts of water used for rinsing:
   a. Evaluating the physical and chemical properties of a FCS to help determine whether a water rinse will be effective in removing the residue or if some residue may remain, or
   b. Setting a default trace level in the assessment;
4. If traces could remain on a FCS and transfer into food:
   a. Determining trace levels in food using validated analytical methods (see paragraphs 'Sampling procedures' and 'Typical analytical procedures'), or
   b. Determining the appropriate exposure model for estimating exposure (estimated dietary daily intake (EDI)) to the FCS. (Note: If a FCS from a cleaning agent / sanitiser / disinfectant will not transfer into food, then the exposure assessment and risk assessment does not need to proceed (see Box 4).);
5. Monitoring amounts of food prepared after the cleaning operation;
6. Calculating the estimated dietary daily intake of a FCS using the appropriate exposure model based on the use pattern:
   a. FCS used on hard non-porous surfaces – restaurants and/or food processing (food intakes are included in the model);
   b. FCS used on porous surfaces (food intakes could be included as part of model);
   c. Process water substances;
   d. Direct food antimicrobials;
   e. Other potential models may be needed for certain applications.

The General Equation will be:

- When analytical measurements of residues in food exist:

Equation 3 $EDI = (C1/FI) \times 10^{-6}$

With

- EDI = Estimated Dietary Daily Intake (mg FCS/kg body weight/day)
- C1 = concentration of chemical in food (mg/kg)
- FI = food consumption level (mg food/kg body weight)
- 10^{-6} = adjustment factor kg/mg

- When measures of residues in food are not available, but it is possible to estimate a transfer rate of a residue from a surface:

Equation 4 $EDI = [(C1 \times Q1)/(D \times Q2)] \times T \times FI \times 10^{-6}$

With

- EDI = Estimated Dietary Daily Intake (mg FCS/kg body weight/day)
- C1 = concentration of chemical in product (mg/L)
- Q1 = quantity of chemical used on food contact surface(L)
- D = coefficient of dilution with rinsing water (no Unit)
- Q2 = quantity of food produced (Kg)
- T = transfer rate from food contact surface to food (no Unit)
- FI = food consumption level (mg food/kg body weight)
- 10^{-6} = adjustment factor kg/mg

Equation 4 presents a realistic case.

- When measures of residues in food are not available, and it is assumed 100% of a residue will transfer into food:

Equation 5 $EDI = [(C1 \times Q1)/(D \times Q2)] \times 100\% \times 2$

With

- EDI = Estimated Dietary Daily Intake (mg FCS/kg body weight/day)
- C1 = concentration of chemical in product (mg/L)
- Q1 = quantity of chemical used on food contact surface(L)

- D = coefficient of dilution with rinsing water (no Unit)
- Q2 = quantity of food produced (Kg)
- 100% = default transfer rate from food contact surface to food
- 2 = default food consumption level (mg food/kg body weight)

Equation 5 presents a worst case.

Risk characterisation

This is the fourth and final step of the risk assessment process, integrating information from the hazard characterisation and the exposure assessment to produce scientific advice for risk managers.

Different approaches must be used to characterise the risk depending on whether toxic effects have a threshold or not:

- Health-based guidance values are set for substances that produce threshold effects. When comparing dietary intakes with HBGV, a Margin of Safety (MoS) below 1 indicated that intakes are of low concern for human health. A level of 1 is considered sufficient as safety factors were used to set the HBGV;
- a NOAEL or LOAEL can be used for risk characterisation purposes for substances showing threshold effects but where no HBGV has been derived. In this case, a Margin of Safety of 100 is indicative of a low concern for human health depending on the toxicity profile of the chemical (EFSA 2012[xxviii]).
- the Margin of Exposure (MoE) must be at least 10,000 in the EU, (EFSA 2005[xxviii], 2006[xxix], 2012b[xxx]) for substances that are both genotoxic and carcinogenic (not having a threshold dose).

Note that other regions may have different approaches for cancer risk characterisation. As an example, in the US, the assessment is based on setting an acceptable likelihood of increased cancer risk. Some regulatory bodies will accept a ≥1/10,000 increased risk, others target ≥1/1,000,000 increased risk. In 2005, the US EPA published a document titled *Guidelines for Carcinogen Risk Assessment* that highlight the cancer / non-threshold toxicant risk assessment framework used by the agency[xxxi]. Additionally, the US EPA considers early life susceptibility when conducting cancer risk assessments and that approach is described in a separate supplemental guidance document[xxxii].

Threshold of Toxicological Concern (TTC) approach

The TTC approach is a pragmatic risk assessment tool establishing human exposure threshold values for chemicals below which there is a very low probability of adverse effects to human health. According to the TTC concept, a 'safe' level of exposure can be identified for many chemicals based on their chemical structure and the known toxicity of chemicals that share similar structural characteristics. The TTC approach is exclusively designed as a substitute for substance-specific information in situations where there is limited or no information on the toxicity of the compound and information on exposure indicates that human exposure is very low.

The use of the TTC is accepted worldwide today (i.e. FDA[xxxiii], WHO[xxxiv], EC Commission[xxxv]…) for impurities in several products like cosmetics, pharmaceuticals, food additives and food contact materials, etc.

In Europe, the TTC is not a general threshold (as applied by the FDA under the so-called Threshold of Regulation for Food contact materials) but several thresholds depending on the nature of the substance, the structural information and / or the toxicological data. These conditions are evaluated using the Cramer classification scheme included in software like Toxtree[xxxvi], the OECD QSAR Toolbox[xxxvii], the Danish (Q)SAR Database[xxxviii] or the Vega suite[xxxix].

As indicated above, the result of the Cramer decision tree or of these softwares is the classification of chemicals into 3 classes depending on their presumptive toxicity:

- Class I substances are those with structures and related data suggesting a low order of oral toxicity. They have simple chemical structures and are efficiently metabolised by high capacity pathways;

- Class II substances are simply 'intermediate' substances with less clearly innocuous structures than those of Class I substances, but without structural features suggestive of toxicity;
- Class III substances are those that have chemical structures that permit no strong initial presumptions of safety, or that may even suggest significant toxicity. They thus deserve the highest priority for investigation.

We should point out that the TTC approach does not apply to several chemical families (EFSA 2012c[xl], EFSA 2018[xli]) such as:

- High potency carcinogens (i.e. aflatoxin-like, azoxy- or N-nitroso-compounds, benzidines, hydrazines);
- Inorganic substances;
- Metals and organometallics;
- Proteins;
- Steroids;
- Substances that are known or predicted to bioaccumulate;
- Nanomaterials;
- Radioactive substances.

Depending on toxicity potential, the structure or the Cramer class, the TTC showed in Table 1 can be applied.

Table 1. TTC values

Type of TTC value	TTC value in µg/person per day	TTC value in µg/kg bw per day
Potential DNA-reactive mutagens and / or carcinogens	0.15	0.0025
Organo-phosphorous compounds and carbamates	18	0.3
Cramer Class III	90	1.5
Cramer Class II	540	9
Cramer Class I	1800	30

Quantitative structure activity relationship (QSAR)

A Structure–Activity Relationship (SAR) is the relationship of the molecular structure of a chemical with a physico-chemical property, environmental fate attribute, and / or specific effect on human health or an environmental species. These correlations may be qualitative (simple SAR) or quantitative (QSAR) (OECD 2002[xlii]).

When data does not exist or is limited for a given toxicological endpoint, the use of SARs may be considered in the hazard assessment. The potential toxicity of a substance may sometimes be evaluated by read-across from structurally or mechanistically related substances for which experimental data exist. The read-across approach is based on the principle that structurally and / or mechanistically related substances may have similar toxicological properties.

Quantitative Structure–Activity Relationships (QSARs) are estimation methods developed and used to predict certain effects or properties of chemical substances, which are primarily based on the structure of the substance. They have been developed based on experimental data on model substances. Quantitative predictions are usually in the form of a regression equation and would thus predict dose–response data as part of a QSAR assessment.

OECD[xliii] and ECHA[xliv] provide information on validation of QSARs and their recommended use in risk assessment.

5 - Assessing the risks

of cleaning / disinfection products: proposed approach and decision tree

Obtain information from your cleaning agent, sanitiser and disinfectant supplier

Suppliers of cleaning agents, sanitisers and disinfectants intended to be used on surfaces that may come into contact with food (FCS) will have evaluated the safety of those chemicals. In most countries this is required by law.

Suppliers recommend conditions of effective and safe use in standard product information documents. This will describe how chemicals are best used, e.g. recommended dilution, exposure duration and often whether to rinse food contact surfaces with potable water at the end of the cleaning process. These use instructions are typically general in nature and need to be validated for the specific use in the food processing facility in question. Suppliers can assist in this evaluation.

Components of interest may be:

- Active ingredients that are intentionally added to the cleaning agents, sanitisers and disinfectants such as quaternary ammonium compounds to control hazardous microorganisms or acids like citric acid to decalcify surfaces. Specific food contamination limits may have been set by regulators like MRLs. These ingredients may also taint the food;
- Unintentional contaminants in cleaning agents, sanitisers and disinfectants that are typically used in the production process of the intentional ingredients, like dioxane in ethoxylated surfactants, but may also be environmental contaminants like heavy metals. They are usually only present at very low levels. They may be relevant in cases where cleaning agents, sanitisers and disinfectants are not sufficiently rinsed and large amounts of cleaning agents, sanitisers and disinfectants contaminate the food. In those cases, special ingredient qualities may be needed. In most cases suppliers will communicate this in their product documentation;
- Unintentional contaminants originating from or increasing upon improper storage or use. An example is Sodium Chlorate in Sodium Hypochlorate based disinfectants. Storage requirements are indicated in the Material Safety Data Sheet (MSDS) or in the product information;
- Ingredients reacting with specific natural components of food. This is very food specific and food business operators have most knowledge about this. Cleaning agents, sanitisers and disinfectants suppliers will help to understand new cases.

Material Safety Data Sheets provide information on the potentially harmful ingredients of cleaning agents, sanitisers and disinfectants and their properties. They are intended to ensure the safe handling and storage of cleaning agents, sanitisers and disinfectants as supplied by their supplier, and the contents are usually required by law. Product use instructions are typically provided separately.

Conducting a risk assessment for cleaning agents, sanitisers and disinfectants

The primary objective of conducting a hazard analysis and targeted risk assessment is to determine whether an activity that introduces cleaning agents, sanitisers and disinfectants represents a known or reasonably foreseeable chemical hazard causing serious adverse health consequences to humans.

This risk assessment approach is intended to facilitate the identification with respect to where, why and how cleaning agents, sanitisers and disinfectants are introduced to FCS. It should enable the development of mitigation strategies including validation, monitoring and verification activities (see below).

Prerequisites to any targeted risk assessment for chemical hazards introduced through cleaning agents, sanitisers and disinfectants are that:

- All cleaning agents, sanitisers and disinfectants must be stored, handled and used according to the suppliers' instructions;
- Chemicals should be 'fit for purpose' and must not introduce food safety, compliance or quality hazards when used according to the validated cleaning program.

Is it possible to simplify the risk assessment?
A logical process helps to determine when a risk assessment is necessary (see paragraph 'Full process of risk assessment'). Steps 1 and 2 below allow to limit the risk assessment.

Step 1: Assess the presence or absence of traces in food

This step is dedicated to clearly describing how the cleaning agents, sanitisers and disinfectants are used and on what kind of material and equipment.

Some questions to consider may be:

- Will the chemical be applied to a hard, non-porous surface (e.g. tanks, countertops, tabletops, dishes or utensils), a softer, more porous surface (e.g. conveyor belts or membranes); will it be applied to process water in contact with food (e.g. boiler additives or direct food contact antimicrobials such as vegetable washes), or directly to food (e.g. food tissue treatments)?
- Is there a water rinse following the application of the chemical or not (no-rinse chemicals)?
- What is the likelihood that traces stay on the FCS after rinsing with water?

Step 2: Estimate the level of FCS traces in food

This can be done by theoretical calculation (see paragraph 'exposure assessment') or by quantification from chemical analysis (see paragraph 'Typical analytical procedures').

When regulatory limits exist, such as MRL, a compliance check allows to conclude on the absence of risk.

Otherwise, the limit of detection (LOD) must be considered.

Step 3: Perform a full risk assessment

When trace levels are above the LOD and no official MRL are set, a complete risk assessment could be performed (see paragraph '4 – Human health risk assessment principles').

We should point out that assessing risks to humans from dietary exposures is only dedicated to specialists in:

- Exposure assessment (selection of scenarios, exposure models, definition of food categories, targeting vulnerable populations and / or high consumers, consideration of exposure duration related to the incidental food contamination …);
- Toxicology (Selection of relevant and robust toxicological studies, setting HBGV such as TDI, RfD, NOAEL, LOAEL or Benchmark Dose (lower confidence limit) – BMDLs, determining the mode of action (threshold non-cancer effect or non-threshold cancer effect));
- Risk characterisation (evaluation of whether the combined exposure to a potential FCS residue and the hazard presented by the FCS pose a human health risk and needs to be addressed).

Full process of risk assessment
The risk assessment processes for cleaning agents, sanitisers and disinfectants used in

food hygiene are summarised in the following decision tree.

This decision tree was built to assess risks in a simple manner (adapted for small and medium entities) and to point out when expert judgment is needed.

In our opinion, a full risk assessment (involving experts) is only needed in two cases:

- For qualification of the cleaning / disinfection strategy and procedures (a priori assessment);
- In the case of an incident leading to food contamination (a posteriori assessment).

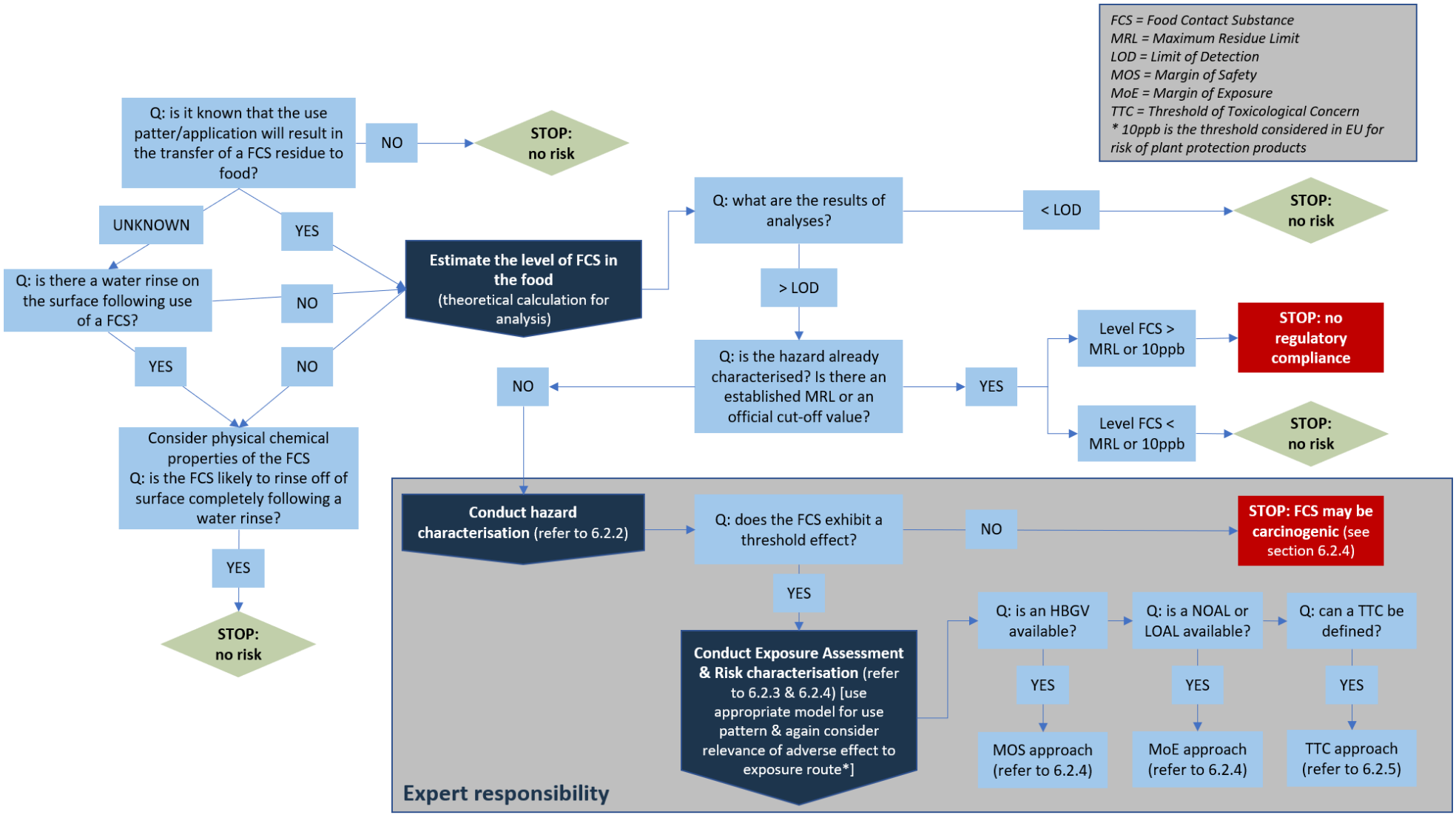


Figure 4. Decision tree on risk assessment of cleaning / disinfection / sanitation products

Prioritisation of chemicals in cleaning agents to support Quality Management

As chemicals used in food hygiene are typically formulations involving multiple substances, prioritisation may be a useful approach to narrow down the substances that pose food safety risks.

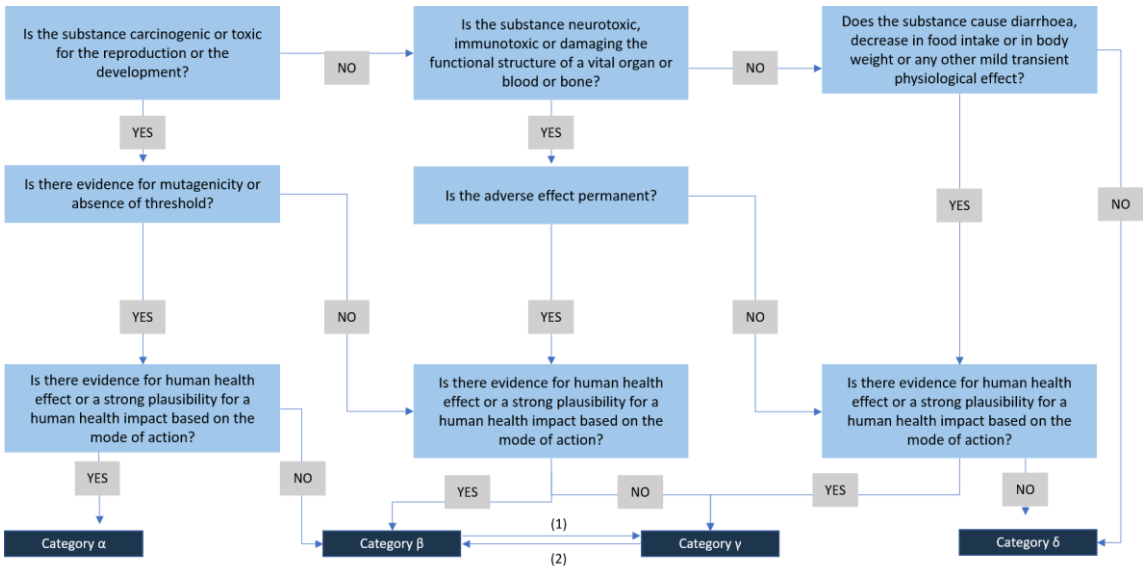
There may be different approaches to carry out a prioritisation. The following example introduces a 3-step strategy for setting prioritisation to the chemicals of concern:

- determine the severity of toxicological effect for each chemical using available toxicological information,
- predict occurrence based on usage / functionality of the chemicals,
- set a priority based on a matrix concerning those two criteria: severity and the estimated likelihood of occurrence.

Criteria for prioritisation

1) Severity setting: T. Stroheker et al. (2017)[xlv] defined a severity setting of chemicals based on types of toxicity (see figure 5). Briefly, carcinogenicity, reproductive and developmental toxicity were denoted as the most severe types of toxicity. Mutagenicity, absence of threshold and irreversibility for toxic effects were then considered in determining toxicity. Lastly, the human relevance was considered.

Based on available information and an estimation of toxicity by computational toxicology in case of the absence of toxicological information, severities of toxicity can be designated to chemicals of concern.



(1) For substances with ration LOAEL/NOAEL ≤ 3 or substances with toxicity data of low quality, e.g. missing chronic studies

(2) For substances with good toxicological database that suggests the severity is overestimated

Figure 5. Decision tree for the severity grading of toxic effects (Stroheker et al. 2017).

2) Occurrence estimation: chemicals with high potential occurrence can be differentiated from those with low potential occurrence by checking if any of the chemicals are used in cleaning agents on food contact surfaces in the manufacturing process. If used intentionally in a product, chemicals are marked as high occurrence potential; if not, as low occurrence potential. Then, the functionality of the chemicals needs to be considered as 1) main components, 2) additives, and 3)

contaminants / impurities, in order to separate the contribution to likelihood of occurrence scenario. Depending on the functionalities (e.g. usage in hand soap, or potential use in processing line), the likelihood of occurrence can be estimated and designated as:

- High (e.g. active components in cleaning agents for food production lines);
- Medium (e.g. additives);
- Low (e.g. contaminants or impurities, use in hand soap).

Prioritisation

Based on levels of severity identified and estimated likelihood of occurrence, the chemical of concern can be prioritised by ranking as shown in figure 6.

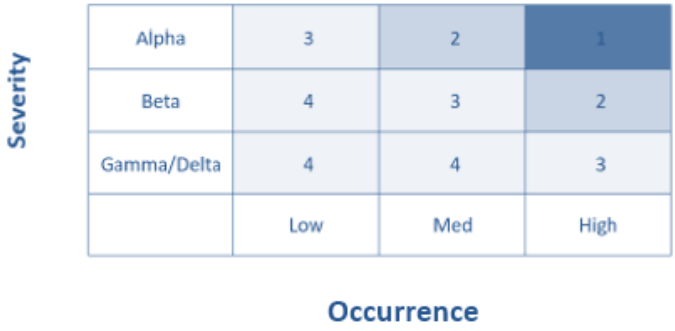


Figure 6. Prioritisation grid based on severity and likelihood of occurrence

A classification of 1 indicates a chemical is of high concern due to an alpha classification of severity combined with a potentially high likelihood of occurrence. Chemicals with low potential likelihood of occurrence and having a low severity rating (gamma/delta) are of low concern.

Case of small entities

Maintaining high hygiene standards is important for all food facilities. The use of cleaning agents, sanitisers and disinfectants are usually essential to achieve this. Suppliers will provide instructions on the safe and effective use of the chemical on the label. This is often supplemented by more detailed instructions in product information sheets.

Cleaning agents, sanitisers and disinfectants are highly regulated in most countries. Any use instruction meets these regulatory requirements and needs to be followed to be compliant.

Performing a full toxicological risk assessment including an assessment of potential food contamination levels of any residue is not usually practical for small scale operations.

It is good practice to rinse food contact surfaces with potable water after they have been cleaned, sanitised and disinfected. Cleaning agents, sanitisers and disinfectants are designed to facilitate easy rinsing. Contact the supplier for any guidance or suggestions on how to validate that the rinsing procedure is sufficient. However, in some regions, a few cleaning agents uses are authorised without any rinsing step. In such a case, every chemical in the product should have been evaluated for safety by the regulatory body that registered it.

6 - Cleaning validation, monitoring and verification

Validation, monitoring and verification are critical components of food safety and quality management programmes. ISO/TS 22003:2013[xlvi] provides recognised definitions (Box 4).

Box 4

Validation:
Obtaining evidence that the control measures managed by the HACCP plan and by the operational PRPs are capable of being effective.

Monitoring:
Conducting a planned sequence of observations or measurements to assess whether control measures are operating as intended.

Verification:
Confirmation, through the provision of objective evidence, that specified requirements have been fulfilled.

Validation

Hazard analysis, as part of the HACCP approach, should determine when cleaning validation is required. Cleaning / sanitation procedures should be validated where they are designed to control hazards identified in the HACCP study (see paragraph 'Determining the need for analytical methods for chemical residues or markers').

Cleaning validation is not necessarily required for low risk or non-critical surfaces such as floors, walls or exterior surfaces of equipment; nevertheless the development of an SSOP and subsequent monitoring / verification should be considered within the cleaning program.

A robust cleaning validation should take into consideration, for example, the nature of raw materials, the previous and following steps in the processing chain, the process itself, the expected shelf-life and intended use of the food / ingredients, the chemicals used for cleaning and the duration of the operations (EHEDG 2016[xlvii]). Among others, the equipment supplier (if possible), the chemical supplier and the cleaning contractor (if applicable), should be involved in the cleaning validation.

Analytical methods used to detect residuals or contaminants (chemical, microbiological, allergenic, etc.) should be specific for the substance or class of substance to be analysed (e.g. detergent or sanitiser). The method should have supporting validation data, and its limit of detection and quantification, its specificity, sensitivity and reproducibility should be known and should be sufficiently sensitive to detect the established acceptable limit of the residue or contaminant.

Monitoring

Monitoring activities should provide an indication of the state of control and

effectiveness of cleaning in real time, with the frequency adapted according to the type of cleaning, e.g.

- continuous monitoring of cleaning cycles, cleaning fluids, rinse water, etc. during cleaning in place (CIP) versus
- sporadic monitoring during cleaning out of place (COP).

Generally, complex analytical methods are not required for monitoring.

Verification

Appropriate verification methods (e.g. visual, sensory, analytical – microbial / hygiene, allergenic, chemical residue) and frequencies should be established for all cleaning and / or disinfection procedures similar to the validation methods.

Verification methods should be applied either immediately after the cleaning or at a later retrospective stage. For disinfectants / sanitisers or their active substances / by-products having Maximum Residual Levels (MRL) in food, verification of compliance to regulations should be performed through periodic testing; e.g. MRL = 0.1 mg / kg for quaternary ammonium compounds (QACs, benzalkonium chloride and didecyldimethylammonium chloride) in the EU.

Determining the need for analytical methods for chemical residues or markers

The decision tree (Figure 7) indicates circumstances whereby analytical methods for chemical agents / residues or appropriate markers may be required in the context of a HACCP approach.

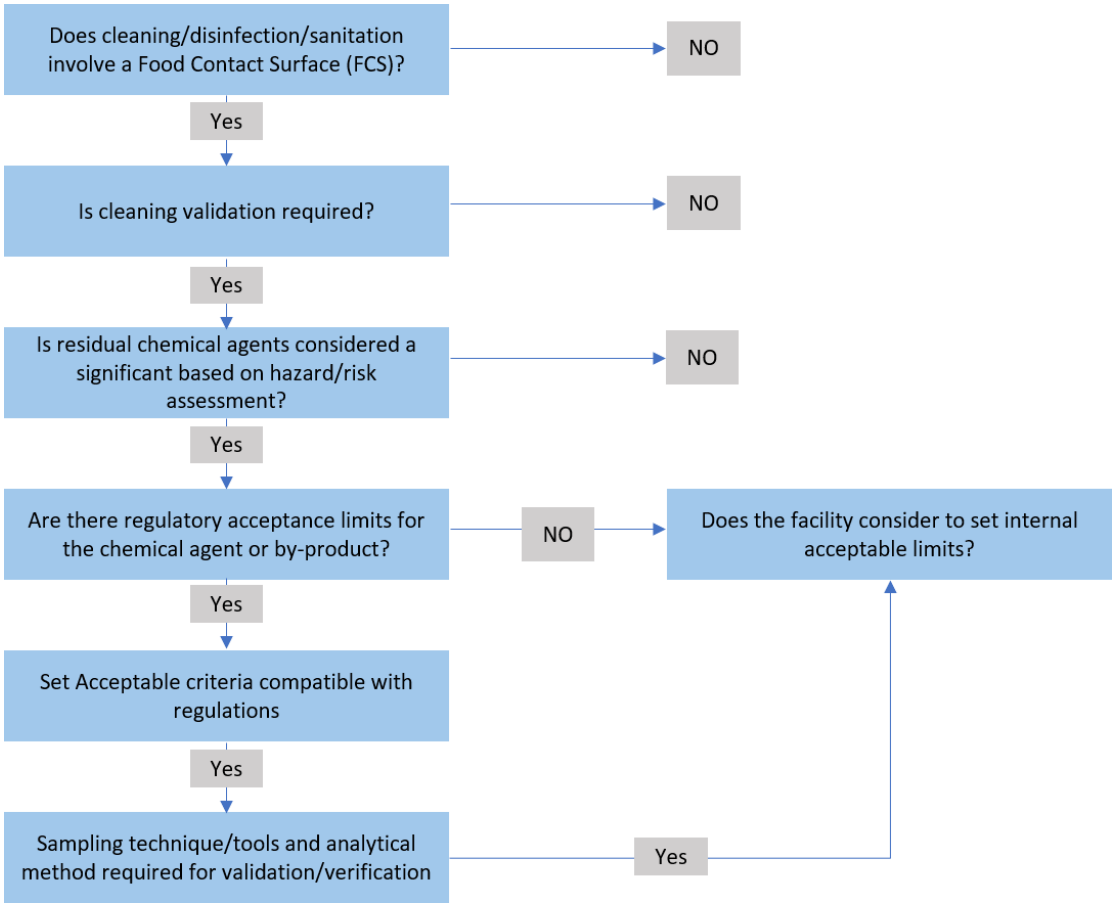


Figure 7. Determination of needs for trace analyses

Target compounds

The chemical suppliers know the composition of the individual formulation and must notify any critical changes in the formulation to the food business operator.

Detergents

A detergent solution may contain multiple components, blended carefully to specification.

Detergent suppliers normally have a range of detergents to be employed in varying and specific circumstances. Box 5 shows a list of general ingredients and related examples[xlviii].

Box 5

- Alkalis: caustic soda, silicate, phosphate
- Acids: Glycolic, phosphoric, nitric, citric
- Chelates: EDTA, NTA, citrate,
- Solvents: Isopropanol, propylene, butyl diglycol, ethers
- Surfactants: Anionic, cationic, non-ionic, amphoteric
- Inhibitors: Organic, inorganic
- Enzymes: protease, lipase, amylase
- Oxidisers: hypochlorite; isocyanurates
- Stabilisers
- Viscosity modifiers

Disinfectants
Most disinfectants are oxidising agents, including chlorine, hypochlorite, iodophors and peracetic acid. Non-oxidising disinfectants are typically based on quaternary ammonium compounds, amphoterics, alcohols and aldehydes[li].

Sampling procedures

The selection of a sampling technique should be scientifically justified and fulfill the aim of the cleaning validation / verification study, which is to demonstrate that the amount of residual material on a FCS has been reduced to an acceptable level. In this context, meaningful sampling locations should be clearly defined; for instance, the most difficult to clean equipment usually requires the most intensive monitoring schedule. Sampling procedures should be validated, and the employees carrying out the sampling be fully trained to avoid errors (Murthy and Chitra 2013[xlix], Asgharian et al. 2014[l]).

Rinse sampling
Two different procedures can be utilised as a suitable method for rinse sampling.

a) A test which measures the amount of traces in the liquid used for final rinsing of equipment. This method is suitable for systems that cannot easily be disassembled, such as CIP (clean-in-place) equipment and narrow tubing. However, sampling may be difficult if the traces are not soluble in water.

b) A test for the additional rinse volume used on clean equipment after the final rinse.

Rinse sampling does not employ mechanical action on the surface: either the sample is collected from the water used in the final rinse of the surface, or water is applied to the surface specifically to collect a rinse sample.

Advantages

- Adaptable to online monitoring;
- Easy to sample;
- Non-intrusive;
- Less technique dependent than swabs;
- Allows sampling of a large surface area;
- Allows sampling of a unique (e.g. porous) surfaces and inaccessible areas of equipment that cannot be routinely disassembled.

Limitations (Murthy and Chitra 2013[liii], Asgharian et al. 2014[liv]):

- Limited information about actual surface cleanliness in some cases;
- May lower test sensitivity;
- Inability to detect location of residues;
- Rinse volume is critical to ensure accurate interpretation of results;
- May be difficult to accurately define and control the areas sampled, therefore usually used for rinsing an entire piece of equipment, such as a vessel.

Swab sampling
This procedure is based on wiping the inside surface of the production apparatus with a fibrous swab material, extracting the adhering material, and conducting a measurement of the extract solution. Alternatively, the swab material can be tested directly using a direct combustion carbon measurement system.

Advantages:

- Dissolves and physically removes sample;
- Adaptable to a wide variety of surfaces;
- Economically and widely available;
- May allow sampling of a defined area.

Limitations:

- An invasive technique that may introduce fibers;
- Results may be technique dependent;
- Swab material and design may inhibit recovery and specificity of the method;
- Evaluation of large, complex and hard to reach areas is difficult.

Steam condensation sampling
Hot steam can penetrate all parts of equipment. The amount of residue can be measured in the collected steam condensates.

Spray Desorption Collection (SDC)
This procedure allows for much larger areas of surfaces to be sampled compared to traditional swabbing techniques, providing a valuable pre-concentration advantage. Analytes from the sample surface are collected onto a selected collection surface, which in a second step can be analysed directly e.g. when coupled with paper spray mass spectrometry (PS-MS) (Jain et al. (2011)[li]).

Direct sampling
The advantage of direct sampling techniques is that sampling and analysis will take place in one step, and there will be no real loss of the sampling system.

Near InfraRed Chemical Imaging (NIR-CI) represents an attractive alternative to the current methodologies for cleaning verification since it represents a direct, rapid and sensitive technology; however, its application seems so far to have only been demonstrated for the analysis of active pharmaceutical ingredients in the frame of line cleaning validations (Alvarez-Jubete et al. 2013[lii]).

Typical analytical procedures

Many analytical techniques are available that can be applied in cleaning validation, monitoring and verification. The selection of the appropriate analytical tool depends on a variety of factors that should be considered prior to selection, such as:

- The testing matrix (e.g. rinse water, food sample, swab sample);
- The parameters to be measured (e.g. pH, individual surfactants);
- Defined acceptance levels;
- Application e.g. whether the method is used for validation purposes (which may require the detection of specific compounds at low level) or for verification purposes (where relatively non-specific methods are preferred).

Analytical methods should be validated to demonstrate their robustness to measure traces at the established limit and in the matrix of interest.

In general, in the frame of a line cleaning validation, data on recovery studies must be collected where appropriate to determine the amount that can be recovered from a surface.

Table 2 gives a non-exhaustive listing of appropriate analytical procedures and their applicability for cleaning validation and verifications purposes. Specific and non-specific methods are mentioned. While a specific method detects unique compounds (e.g. HPLC-MS), non-specific methods detect any compounds that trigger a certain response (e.g. Total organic carbon).

Table 2. Analytical procedures and their applicability for cleaning validation and verifications purposes (non-exhaustive list)

Analytical Technique	General Information	Application	Matrix (Line sample/Food)	Sensitivity (a)	Cost (b)	Speed (c)	Additional information	Ref.
								SPECIFIC METHODS
High Performance Liquid Chromatography (HPLC), Ion chromatography (IC)	Involves application of a liquid probe on a chromatographic column that allows separation of the target species from other components in the sample, and their subsequent measurement by variable detectors including: Mass Spectrometer (MS), ultraviolet/visible (UV/VIS), Fluorescence (FD), Electrochemical (EC), Refractive Index (RI), Conductivity, Evaporate Light Scattering detection (ELSD), charged aerosol detection (CAD)	Surfactants Disinfectants Chelates Alkali Acids	Line samples Food samples	+++	+++/++	+	Detection of compounds produced by degradation possible	(1)
Gas Chromatography (GC)	Volatile components of a sample are separated on a column by a nonreactive 'carrier' gas. Subsequent measurement of the individual components that exit the column can be done through variable detectors such as Electron Capture Detector (ECD) Flame Ionization Detector (FID); Mass Spectrometer (MS); nitrogen/phosphorus detector (NPD)	Surfactants Solvents Disinfectants Chelates	Line samples Food samples	+++	++	+	Limited to volatile compounds Detection of compounds produced by degradation possible	(2)
Atomic Absorption Spectrometry (AAS)	Spectro analytical procedure for the determination of chemical elements using the absorption of optical radiation (light) by free atoms in the gaseous state	Metal ions (e.g. Sodium and potassium) coming from formulations	Line samples	+++	++	+	AAS was used in the 1980s to measure indirectly residues of surfactants in water. AAS has since been replaced with more common analytical techniques such as HPLC-MS/MS in this regard	(3)
								NON-SPECIFIC METHODS
TOC	In an aliquot of sample organic molecules are oxidized to carbon dioxide (CO2) which is measured by any of a variety of techniques expressing the response as carbon concentration.	Total of organic compounds	Line samples	+++	+	++	Verification method; As TOC analysers are not specific enough they may be complemented and used	(4)

							together with pH and conductivity	
Test strips	Available as commercial applications	Disinfectants Acids		+	+	+++	Various commercial applications	See diverse commercial applications
Spectrophotometry	method to measure how much a chemical substance absorbs light by measuring the intensity of light as a beam of light passes through sample solution	Surfactants Disinfectants Alkali (phosphate)	Line samples	+++	+	++	Available as commercial test kits	(5) See also diverse commercial applications
pH		Alkalis Acids	Line samples	+	+	+++		(6)
Conductivity	Measurement of the total ion concentration in a solution.	Alkalis Acids	Line samples	++	+	+++		(7)

[a] Sensitivity	[b] Cost	[c] Speed
+++ Highly sensitive (ppb range)	+++ High investment costs	+++ rapid, no sample preparation, real time applications possible
++ Sensitive (low ppm range)	++ Medium investment costs	++ requires a minimum of sample preparation, simple, fast
+ Less sensitive (higher ppm range)	+ Low investment costs	+ Requires sample preparation, significant time and knowledge for analysis and result interpretation needed

(1) Laine and Matilainen 2005[liii], Zayas et al. 2006[liv], Loos et al. 2007[lv], Resto et al. 2007[lvi], González et al. 2008[lvii], Xie et al. 2010[lviii], Olkowska et al. 2013[lix], Wei et al. 2016[lx], Slimani et al. 2017[lxi], Liu et al. (undated)[lxii]
(2) Kolbe and Andersson 2006[lxiii], Kubota et al. 2010[lxiv], Traverso-Soto et al. 2012[lxv], Asgharian et al. 2014
(3) Crisp et al. 1975[lxvi]; Crisp et al. 1976[lxvii]; Le Bihan et al. 1977[lxviii]; Van Hoof et al. 1985[lxix]; Thermo Fisher Scientific 2016[lxx].
(4) Jenkins et al. 1996[lxxi]; Jin and Woodward 2017[lxxii]; Li et al. 2018[lxxiii];
(5) See also diverse commercial applications
(6) Serra-Mora et al. 2018[lxxiv]
(7) Lelieveld et al. 2016[lxxv]
(8) LeBlanc 2017[lxxvi]

Conclusion

Cleaning and sanitation procedures in food facilities vary greatly. These procedures depend on the cleaning objective, product type, production process, equipment used and regulatory requirements. The cleaning and sanitation programme is an important prerequisite that is fundamental in any HACCP system.

However, a risk assessment is needed to determine whether an activity that introduces cleaning agents, sanitisers and disinfectants represents a known or reasonably foreseeable chemical hazard.

The purpose of any preliminary risk assessment is

(1) to identify the need for cleaning, disinfecting or sanitising,
(2) to define the best technique and validate it (including rinsing if required), and
(3) to identify where, why and how cleaning agents, sanitisers and disinfectants are introduced to the food manufacturing process.

When necessary, a dietary risk assessment could support a risk management decision to ensure the safety of a FCS. Conducting a dietary risk assessment is a scientific process that should be done by a properly trained expert. The steps outlined in this document describe the process such an expert would follow when conducting a dietary risk assessment for cleaning agents, sanitisers and disinfectants.

For small food business operators, it may not be feasible to conduct a complete human risk assessment; alternatively, they could follow a simplified HACCP have been developed by the US FDA or the Codex Alimentarius for smaller organisations.

Much information is required to properly manage the risks of cleaning agents, sanitisers and disinfectants. The Technical Working Group has outlined four key steps (Table 3).

Table 3. Thinking through a cleaning / disinfection procedure

1 Before buying:
• What is the purpose of the procedure? What is the objective? • Are there alternative procedures to chemical treatment providing the same food safety benefits of the cleaning agents, sanitisers or disinfectants? • Are the required information available: certification of the supplier, MSDS, technical sheet, recommended condition of use, compatibility with food contact materials /equipment, regulatory requirements, etc.?
2 When buying:

• Supplier qualification
• Selection of the cleaning product: is it legally approved for food contact materials / equipment? What is the antimicrobial spectrum for biocides?
• Technical information:
  ○ If possible, detailed composition including impurities and by-products if any;
  ○ Conditions of use related to the objectives (SOPs);
  ○ MSDS;
  ○ Is there a recommended method of residues analysis?
  ○ Are HBGV and MRL available?
  ○ Has a dietary risk assessment already been conducted by the supplier or a regulatory body demonstrating safety under normal conditions of use?

3 When storing:
• Does the product degrade with time? • Are there specific conditions of storage (temperature, humidity…)? • Is there a shelf life?

4 When using: case by case, depending on the installation and the food product

- Revise the HACCP and the SSOPs (including training of the operators)
- Search for acceptable limits in food/feed and set levels for validation/control purpose (including by-products)
- Tests for effectiveness of the cleaning/disinfection procedure (validation trials)
- Perform analytical controls for residues
- Conduct a hazard analysis and a health risk assessment based on potential residues levels
- Revise the HACCP and/or hazard analyses

Note: occupational risk and waste management are not addressed here due to being out of the scope of the present report

Glossary

Biocide	Disinfectant or sanitising compounds, including: water disinfectants.
Cleaning	The removal of food residues, dirt, grease and other objectionable matter (Codex).
Cleaning agent	Product to clean.
Consumer	A member of the public who takes possession of food, is not functioning in the capacity of an operator of a food establishment or a food processing plant and does not offer the food for resale.
Detergent	A chemical found in cleaning agents.
Disinfectant	A chemical to reduce bacteria to an acceptable level.
Disinfection	The reduction of the number of microorganisms in the environment, to a level that does not compromise food safety or suitability (Codex).
Food	Raw, cooked or processed edible substance, ice, beverage or ingredient used or intended for use or for sale in whole or part for human consumption (based on FDA food group definition).
Microbial resistance	The development of tolerant populations through adaptation or selection that compromises the effectiveness of cleaning and / or disinfection.
Residue	Refer to definition in relevant regulation.
Sanitiser	A mix of detergent and disinfectant or a disinfectant.
Surfactant	An abbreviation of the phrase ‘surface active agent’. A surfactant is a chemical compound that reduces the interfacial tension between water and other liquids such as fats and oils. Surfactant types are cationic, anionic, non-ionic and amphoteric. An amphoteric surfactant can be either cationic or anionic depending on the pH.
Trace	Low levels of chemicals present in foods but not intentionally added.

Appendices

Source of toxicological information

European Chemicals Agency (ECHA) - Registered substances (https://echa.europa.eu/information-on-chemicals/registered-substances)
US EPA Integrated Risk Information System (IRIS) (https://www.epa.gov/iris)
Hera Project - Human and Environmental Risk Assessments on ingredients of household cleaning products (http://www.heraproject.com/RiskAssessment.cfm)
American Cleaning Institute - Cleaning Product Ingredient Safety Initiative (CPISI) (https://www.cleaninginstitute.org/science/ingredients_and_assessments.aspx)
The Agency for Toxic Substances and Disease Registry (ATSDR) (http://www.atsdr.cdc.gov/)
The WHO International Programme on Chemical Safety (http://www.who.int/ipcs/en/)
IUCLID and SIDS reports (data and hazards OECD evaluations of specific chemicals) (http://webnet.oecd.org/hpv/ui/Search.aspx).

Acronyms

ADI: Acceptable Daily Intake
ANSES: Agence nationale de sécurité sanitaire de l'alimentation, de l'environnement et du travail
ARfD: Acute Reference Dose
BRC: British Retail Consortium (https://brc.org.uk/)
CCP: Critical Control Points
CIP: Cleaning In Place
COP: Cleaning Out of Place
CP: Control Points
DNEL: Derived No-Effect Level
EChA : European Chemicals Agency
BMDL: Benchmark Dose (Lower Confidence Limit)
EDI: Estimated Daily Intake
EFSA: European Food Safety Authority
EU: European Union
FSSC: Food Safety System Certification
FCS: Food Contact Surface
GFSI: Global Food Safety Initiative (http://www.mygfsi.com/)
GHP: Good Hygienic Practices
GMP: Good Manufacturing Practices
HACCP: Hazard Analysis and Critical Control Point
HBGV: Health-Based Guidance Value
IFS: International Featured Standard
IPCS: International Programme on Chemical Safety
IRIS: US Integrated Risk Information System
LOAEL: Lowest Observed Adverse Effect Level
LOD: Limit f Detection
MRL: Maximum Residue Limit
MRL: Maximum Risk Limit
NOAEL: No Observed Adverse Effect Level
OECD: Organisation for Economic Co-operation and Development
PRPs: Pre-Requisite Programmes
QACs: Quaternary Ammonium Compounds
QSAR: Quantitative Structure Activity Relationship
RfD: Reference Dose
SOP: Standard Operating Procedure
SQF: Safe Quality Food
SSOP: Standard Sanitising Operating Procedure
TTC: Threshold of Toxicological Concern
TWG: Technical Working Groups

US EPA: US Environmental Protection Agency
US FDA:US Food and Drug Administration
WHO: World Health Organization

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