Development of a risk assessment for health and environment from the use of metallic additives and a test methodology for that purpose

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Chapter 1: Introduction

The present document is the draft final report of the project managed by BIO Intelligence Service to support the Commission's work in developing a general guidance document for the environmental and health risk assessment of metallic fuel additives. The instructions presented here explain different steps of risk assessment which could be applied to all metallic fuel additives which are or are expected to be on the market in the future.

The application of the risk assessment methodology is not within the scope of this project.

1.1 Context

Metallic fuel additives (MFAs) are the substances intentionally added to fuel (petrol, diesel, and biodiesel) to improve its performance[1]. These additives eventually enter the environment since their metallic portion is not degraded during any stage of their production or use. Thus, they can become a source of exposure for humans and/or biota throughout their life cycle. The health and environmental issues linked to the exposure of humans and the environment to MFAs[2,3,4] justifies the regulation of their use through the adoption of limits values.

Directive 2009/30/EC4, adopted in April 2009 by amending the Fuel Quality Directive (98/70/EC), includes stricter EU air quality targets and future vehicle emission requirements, including limit values for the use of MFAs. During the review process of the Fuel Quality Directive, new limit values for the use of MFAs were introduced. The Directive set limits on Methylcyclopentadienyl Manganese Tricarbonyl (MMT®) at a maximum of 6 mg/litre as of 1 January 2011, and at a maximum of 2 mg/litre after 1 January 2014.

The EU requirements on fuel quality will have an impact on stakeholders in the EU and worldwide, given the global dimension of the fuel market. This includes additive manufacturers, fuel distribution and retail companies, as well as the automobile industry and vehicle and engine manufacturers.

As required by the Directive 2009/30/EC and as a step in the work towards ensuring long-term protection of health and the environment, an assessment should be made regarding the risks for health and the environment from the use of metallic additives in fuel. In order to reach clear, comparable and reproducible conclusions on the risk represented by the use of MFAs, the European Commission has identified the need to develop a standard methodology guidance to collect, produce, and analyse the relevant data in a systematic manner. This guidance must be generic enough to be applicable to all types of metallic fuel additives.

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1 Please note that this is dependent on many other factors such as engine compression, other constituents of fuels, etc.

[2]HEI Special Committee on Emerging Technologies (2011), The Future of Vehicle Fuels and Technologies:Anticipating Health Benefits and Challenges. Communication 16 – Health effect institute. Boston, Massachusetts. p.26

[3]International Council on Clean Transportation (2008). Strategic Plan 2009-2011

[4]Directive 2009/30/EC1. Available at: http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2009:140:0088:0113:FR:PDF

1.2 Objectives

The aim of the project is to serve as a basis for the Health and Environmental Risk Assessment report on fuel metallic additives that the Commission has to deliver by the end of 2012.

1.3 Methodology

The project methodology consists of an extensive literature review on the relevant issues using scientific databases and publications from public authorities and expert groups as well as grey literature and online sources (see Bibliography). In addition, a number of stakeholders and experts have been consulted to gather their comments and opinions on this report. These include the Joint Research Centre (JRC) of the EU, Toyota Motor Europe, European Automobile Manufacturers Association, CONCAWE (the oil companies' European association for environment, health and safety in refining and distribution), and Afton Chemical. This input is of great importance for the study, and the received feedback has been integrated in the report in an appropriate manner. Both interested (stakeholders) and non-interested (independent experts) parties were consulted on a draft version of the report.

1.4 Report structure

In addition to this introductory chapter, this report has been structured into the following chapters:

- Chapter 2: presents background information and rationale for the categorisation of MFA presented in Chapter 3 and for the methodological guidance developed in Chapter 4. This chapter especially aims to help the reader retrieve relevant information throughout the report, by referring to specific sections of the report and the annexes.
- Chapter 3: outlines an approach to group or classify the MFAs for the purpose of facilitating the specific considerations needed in the risk assessment (developed in Chapter 4).
- Chapter 4: presents a draft approach to risk assessment methodology for human health and the environment. The guidance is aimed to be generic and applicable to all MFAs. It will also include specific aspects for different types of MFA. Finally and importantly, it describes the most frequent uncertainties and data gaps in risk assessment.
- Annex 1 provides some additional elements of discussion on the methodology.
- Annex 2 provides an overview of the data identified on the characteristics of metallic additives.
- Annex 3 provides a list of acronyms used in the main text.
- Annex 4 provides a bibliography on metallic fuel additives.

Chapter 2: Background information

2.1 Metallic fuel additives

For the purposes of this document, a metal or metal compound added to gasoline or diesel fuel is termed a metallic fuel additive (MFA)[5]. As used here, the term MFA refers not only to a metal moiety but to the entire product or chemical matrix in which the metal moiety occurs. As such, MFAs are typically complex mixtures of chemical compounds, including diluent oils or solvents that facilitate the production, handling, and use of these additive products[6]. Such additive products are generally intended to enhance vehicle's engine performance, reduce vehicle emissions, and/or serve some other identified functional purpose beyond that of the basic fuel itself. They are generally limited in concentration to no more than 1% by volume[7]. As intentional addition to fuels, MFAs are distinct from trace impurities or contaminants in fuels originating from natural (e.g. geological) or other sources. It is the responsibility of the manufacturer or importer, named "applicant" in the hereby document, to name and characterise a fuel additive with respect to its physicochemical properties and functional purpose(s) and analysed it separately from petroleum products in product registers[8].

The continuous development of new types of vehicle engines and fuels, combined with market, technical and legislative requirements, leads to the development of many different types of fuel additives, which can include MFAs. Because these compounds fulfil different functions, are added to different types of fuel, and have many other respective properties and characteristics, care must be used in making generalisations about such products and their potential impacts on human health and the environment (see section 2.4).

The identification of relevant existing MFAs is a prerequisite to their risk assessment and their categorisation may also help develop specific guidelines relevant to certain groups of MFAs. Chapter 3:, section 3.1 identifies relevant MFAs and summarises key information related to their metallic constituents, CAS numbers, hazard classifications, functions in the fuel, and physicochemical structures. Annex 2 provides further information on each MFA identified through detailed factsheets (including classification and possible hazards, function, emissions, etc.). Section 3.2 brings some insights regarding the interest of grouping MFAs for the risk assessment.

[5] Many types of fuel additive exist and the majority contain no metallic elements, instead comprising the elements carbon, hydrogen, nitrogen, oxygen and sulphur. (ATC informal communication).
[6] ATC (2007). An internationally recognized nomenclature system for petroleum additives, ATC document 31
7 JRC (2012), Protocol for the evaluation of the effects of metallic fuel additives on the emissions performance of vehicles – Final draft

[8] Videncenter for jordforurening, (Denmark) (2006). Fuel additives: A risk screening of additives to gasoline and diesel. Contamination of soil, soil air and groundwater. Teknik og Administration Nr. 3.

2.2 Sources of emissions

MFAs may enter the environment during any stage of their life-cycle, from their production/manufacturing to disposal. Such emissions can result in the direct or indirect exposure of humans and biota to either the MFAs, related emitted compounds or their transformation products and, as such, contribute to the possible risk these substances may raise for human health and the environment. It is thus important to both identify the sources of these emissions and quantify these emissions. The methodological guidance presented in section 4.4 provides insights on how to estimate emissions at each step of their life-cycle. For informative purposes, other existing guidance on characterisation of emissions and relevant publications are listed in Annex 4. As an illustration, Annex 1.1 also presents a template to report these estimated emissions as well as further qualitative information regarding different groups of MFA, from the distribution and trade step, and for the use step. To assess the potential impacts of MFAs on the compounds produced during fuel combustion and/or remaining in the exhaust, one needs to compare the emissions produced with and without using MFAs.

In this context, the Joint Research Centre (JRC) has developed a test protocol[9] for monitoring and calculating the emission data with regard to MFAs for the purpose of risk assessments, focusing on the use stage of their life cycle. In this protocol, measurements are made at tailpipe and the emissions are compared for a metallic additive-containing fuel with the same fuel without the additive. The test design includes a car fleet representing the EU situation. The protocol aims to:

- evaluate the short-term effects of a metallic additive on regulated emissions as mentioned in the JRC protocol (namely HC, CO, NO_x, PM, PN and CO_2);
- measure the mass of the metallic emissions produced by the combustion of the fuel containing metallic additive[10], and determine the speciation of the combustion products as well as particle size distribution of particle-bound metals ; and
- evaluate the effects of the additive on the long-term emission performance of the vehicle's engine and emission control system.

Pre-defined pass/fail criteria have not been set in the JRC draft protocol.

There may be additional (unregulated) emissions and complex pollutant interactions that are not necessarily covered by the JRC protocol but are of interest in the context of a health and environmental risk assessment.

[9] Joint Research Center (2011), Protocol For The Evaluation Of Effects Of Metallic Fuel-Additives On The Emissions Performance Of Vehicles, Final Draft

[10] Emission measurements should be carried out according to the European type approval procedure, in which: "The exhaust gases are diluted and a proportional sample is collected in one or more bags. The exhaust gases contained in the bag(s) shall be analysed as soon as possible after the end of the test cycle". The whole procedure is described in the UNECE Regulation 83, revision 4, 26 April 2011: "Uniform provisions concerning the approval of vehicles with regard to the emissions of pollutants according to engine fuel requirements".

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2.3 Possible exposure pathways

After entering the environment, MFAs or their transformation products eventually become a source of exposure for humans and/or biota. The predominant routes of exposure throughout the life-cycle of the MFA are presented in Annex 1.3 and the exposure section in Chapter 4.

Once combusted with fuels in vehicle's engines, the MFAs can modify the nature of emitted substances both in terms of quantity and quality. MFAs the compounds emitted following their combustion in fuel and transformation products, can thus enter the environment at different stages in their life cycle, in different forms, and through different contamination pathways. These considerations raise the issue of a potential exposure of both humans and environment following a range of exposure pathways, with inhalation being one of the main pathways for humans. Furthermore, once in the environment and/or human body, MFAs and/or emitted compounds after combustion products may undergo various biological, physical and chemical processes which have the potential to modify their properties and related impacts on human health and the environment. The fate and behaviour of MFAs and related substances in the environment and the body are further discussed in Annex 1.3 section C. In this context, several scenarios of exposure can be developed (see Chapter 4, section 4.6.1) that must take into account exposure pathways as well as susceptibility of different sub-populations.

After developing scenarios, exposure can be quantified through bio-monitoring methods and/or epidemiological studies (that are still lacking within the community for MFAs).Methodological guidance to assess environmental and human exposure is developed in Chapter 4, sections 4.6.2 and 4.6.3. For illustrative purposes, Annex 1.3 presents a template to report these estimated emissions. For informative purposes, other existing guidance documents on quantification of exposure and relevant publications are specified in Annex 4.

In the REACH framework, which partly inspired the guidance proposed in Chapter 4, an exposure assessment of a MFA or its transformation products would not be required should the chemical already be judged not to be dangerous following the hazard assessment. The present guidance makes the exposure assessment a mandatory step and ensures that the decision tree for doing an exposure assessment does not truncate if the fuel additive is not classified as hazardous. One has indeed to consider the possibility that even a low toxicity chemical could have significant impacts under certain exposure conditions, such as very high exposure levels (e.g. accidents), widespread population exposures (which would include sensitive sub-groups), and chronic exposures. Further considerations on the importance to include a mandatory step for exposure assessment in the risk assessment methodology are developed in Annex 1.3.

2.4 Possible impacts on the environment and health

In the past, the health concerns associated with the use of some metallic fuel additives such as lead led to their phasing out through regulations[11]. MFAs have metallic components which could

[11]Directive 98/70/EC sets the environmental specifications to be applied (with effect from 1st January 2000 and 1st January 2005) to fuels for vehicles equipped with positive ignition engines (petrol) and with compression ignition engines (diesel). www.biofuels-platform.ch/en/infos/eu-directive199870.php [Accessed online 04/04/2012]

themselves be a hazard for both humans and the environment due to their intrinsic reactivity, toxicity in some cases and their possible capacity to accumulate within living organisms.

New substances are being developed for which the available health and environmental data are limited and for which little is known about their eco-toxicity and toxicity. Yet, determining the toxicity and ecotoxicity of MFAs and their related substances is a prerequisite to assessing their actual impacts on the environment and human health.

Chapter 4, section 4.5.2 develops a guidance to determine the physical and chemical hazards as well as bioaccumulation potential and persistence of the substances of interest. Chapter 4, Sections 4.5.3 and 4.5.4 help determine human health and environmental hazards respectively. Examples of toxicological endpoints for Cerium compounds are provided for illustrative purposes in Annex 1.2, section A. For informative purposes, other existing guidance documents on hazard assessment and relevant publications are specified in Chapter 4, section 4.2.2.

Once the exposure to different substances and their hazard properties is determined, the aim is to ultimately reach conclusions on whether the uses of such MFAs pose a risk (see Chapter 4 section 4.7), and whether further risk reduction measures are required (see Chapter 4 section 4.8). For information purposes, other existing guidance documents on risk assessment and relevant publications are indicated in Annex 4. It has to be noted that the project team took inspiration from REACH, which already proposes some guidance to assess the risk posed by chemical substances. However, not all the MFAs are registered under REACH. The REACH framework focuses on the product itself and substances resulting from chemical reactions (i.e. combustion products during the use phase) are excluded from the assessment. Moreover, REACH does not include a comparative approach (i.e. among fuel with and without MFAs) as promoted by the JRC protocol and does not require exposure assessment if the substance considered did not pass the hazard criteria. The project team proposed an adaptation of this framework relevant to the specificities of MFAs. Key steps of the draft methodological guidance proposed are summarised in Chapter 4, section 4.9.

Chapter 3: Categorisation of metallic fuel additives

3.1 Identified metallic fuel additives

Fuels can contain several additives. Most fuel additives are added in order to help the fuel meet the required production specification; the remainder are designed to improve the performance of the fuel in the engine and to provide marketable claims for retailing companies. The majority of fuel additives are comprised only of carbon, hydrogen, nitrogen, oxygen and sulphur - only a small proportion, predominantly those intended as octane or combustion improvers contain metallic elements.

Annex 2 presents a list of metallic fuel additives, based on the compilation of information from existing literature.

3.2 Grouping of metallic fuel additives

In this section possible ways to group MFAs are presented. It should be kept in mind that different possible categorisations may concern different steps of the life cycle, and can be useful at the different steps of the risk assessment. The grouping is presented according to fuel type, addition stage, hazard and risk categories used in product registers, function and physicochemical structure.

3.2.1 Fuel type

MFAs can be added to gasoline, diesel and biofuels. They can be used for both on-road and off-road applications for both automotive and mobile machinery use. Metals may also be present in lubricants and engine components, but these are not considered MFAs. In EU, diesel powered vehicles account for over 50% of the passenger vehicle market, though the percentage varies depending on the country[12].

3.2.2 Addition stage

This grouping is based on the stage at which the fuel additive is put into the fuel[13]. MFAs can be added to fuel in a variety of ways and locations:

- additives used to ensure a fuel meets the specification required by regulatory authorities, such as gasoline octane improvers, are typically added at the refinery - these are typically referred to as Refinery or Functional Additives[14];

[12]Kozak M and Merkisz J (2007).Some considerations on the oxygenated fuels for diesel engines. TEKA Kom Mot Energ Roln – OL PAN 7: 129-136

[13]Gerlofs- Nijland, M.E. Groenewegen, L. Cassee F.R., (2008). Health effects of addition and combustion of fuel additives. Quick scan and deepening of a selective additive set. RIVM Letter Report 630160001/2008

- additives used to improve engine performance, create specific marketing claims or to protect older vehicles from damage, such as combustion improvers or valve seat recession additives, are typically added at fuel depots, terminals or by additive injection equipped delivery tankers - these are typically referred to as **Performance Additives**[14];
- additive mixtures sold for use by consumer, thus inserted after the fuel has been purchased, are referred to as **after-market products**. These products are sold for example in gas stations or via internet, and allow for the consumer to add the product directly into the fuel, e.g. from a bottle with a dosage cap. They are not part of this assessment since they are not within the scope of the Fuel Quality Directive.

3.2.3 Hazard and risk categories used in product registries

A categorisation could be made following the categories used by national or international product registries. However, due to confidentiality requirements, the information underlying these classifications and being accessible might be limited[14].

In the EU, MFAs are registered under REACH[15] and notified in the Classification Labelling Packaging (CLP)[16] system. This is namely the case for MMT, pentacarbonyl iron, cerium dioxide and tetraethyl lead. Information on the substances to be provided for registration and evaluation purposes by the registrant is specified Annex VI to REACH. Information requirements will differ, according to tonnage, use and exposure. The registrant must report overall manufactured quantities and quantities used for production of an article that is subject to registration, and/or imports in tonnes per registrant per year. Information on exposure (main routes and patterns) is required only for substances registered in quantities between 1 and 10 tonnes per year per manufacturer or importer. Moreover, the supplier of a dangerous compound or product in the EU is required under REACH to provide a chemical safety data sheet (SDS) describing its properties (technical, environmental, hazards). This SDS namely includes a section highlighting exposure scenarios of the concerned substance. A compound in a product (or the product itself) may be classified as dangerous based on a number of different criteria, and in a number of different categories (irritant, allergenic, etc.). However, components below specified volume or weight limits will generally not be declared in the product SDS[14].

This data was used in the ATC Classification and user labelling information concerning the health effects of major petroleum additive components[17].

In the United States, the Globally Harmonized System of Classification and Labelling of Chemicals (GHS) were adopted in 2003[18]. In this classification, safety phrases are provided for

[14]Videncenter for jordforurening, (Denmark) (2006). Fuel additives: A risk screening of additives to gasoline and diesel. Contamination of soil, soil air and groundwater. Teknik og Administration Nr. 3.
[15] Text available at: ec.europa.eu/enterprise/sectors/chemicals/reach/index_en.htm
[16] Text available at:ec.europa.eu/enterprise/sectors/chemicals/classification/index_en.htm
[17]ATC. Classification and user labelling information concerning the health effects of major petroleum additive components. ATC Document 43, revision3. 2000. www.atc-europe.org/public/Doc43.REV.pdf [Accessed online 02/04/2012]

each chemical substance and help to define the hazard (e.g. H228 = Flammable solid; H302 = Harmful, if swallowed).

3.2.4 Function

Metallic fuel additives may be used for a number of purposes[14], including for instance:

- improving engine performance;
- improving fuel combustion properties;
- reducing emissions from the fuel combustion;
- etc.

It should be noted, however, when considering this type of categorisation that a single additive may be used for a number of different purposes and thus claim multiple benefits (i.e. improves combustion, increases octane, reduces valve wear, etc.) which may render the placing of each additive into a specific functional group difficult. Also, the function may be different depending on the additive concentration used[14].

For informative purposes, in the following, a brief overview is given of the categories identified through literature reviews. It needs to be noted that the use of additives varies in response to differences in market requirements, market supplies, product prices and supplier availabilities. The types of additives actually used within the EU, and within certain countries or regions may not be reflected in this brief overview. Metallic additives are not used necessarily included in each of these function categories.

Functional categories for gasoline and diesel metallic fuel additives might include[19]:

- Antistatics
- Anti-valve seat recession
- Anti-knock agents
- Antioxidants
- Demulsifiers
- Antioxidants
- Fuel-born catalysts and octane improvers

3.2.5 Physicochemical structure of the fuel and metallic element

A grouping based on physic-chemical properties which might be relevant for the risk assessment (e.g. iron based additives, nanoparticulate-containing additives, alkyl leads) could be used.

[18] Text available at:www.osha.gov/dsg/hazcom/ghs.html#1.1; www.epa.gov/oppfead1/labeling/lrm/chap-03.pdf
[19] ATC (2004). Fuel additives and the environment. www.atc-europe.org/publications.asp[Available online 02/04/2012]

The chemical and structural properties of fuel additives differ compared to the fuel itself in terms of molecular weight and/or polarity. Most additives contain a few main structural groups[14]. Some organic material chelated to the metal within the metallic additive can still be present in the exhaust after combustion (albeit now separated from the metal) and new material could also be formed during the process, depending on the engine performance and emission control technologies[20].

A categorisation could also be made based on the metal included in the additive major component or functional group (e.g. lead), since some metallic compounds are known to have a toxic potential for both health and the environment.

[20]Subhasis Biswas, Vishal Verma, James J. Schauer, Flemming R. Cassee, Arthur K. Cho and Constantinos Sioutas (2009), Oxidative Potential of Semi-Volatile and Non Volatile Particulate Matter (PM) from Heavy-Duty Vehicles Retrofitted with Emission Control Technologies. *Environ. Sci. Technol.*, **2009**, *43* (10), pp 3905–3912

Chapter 4: Risk Assessment Methodology for Health and Environment

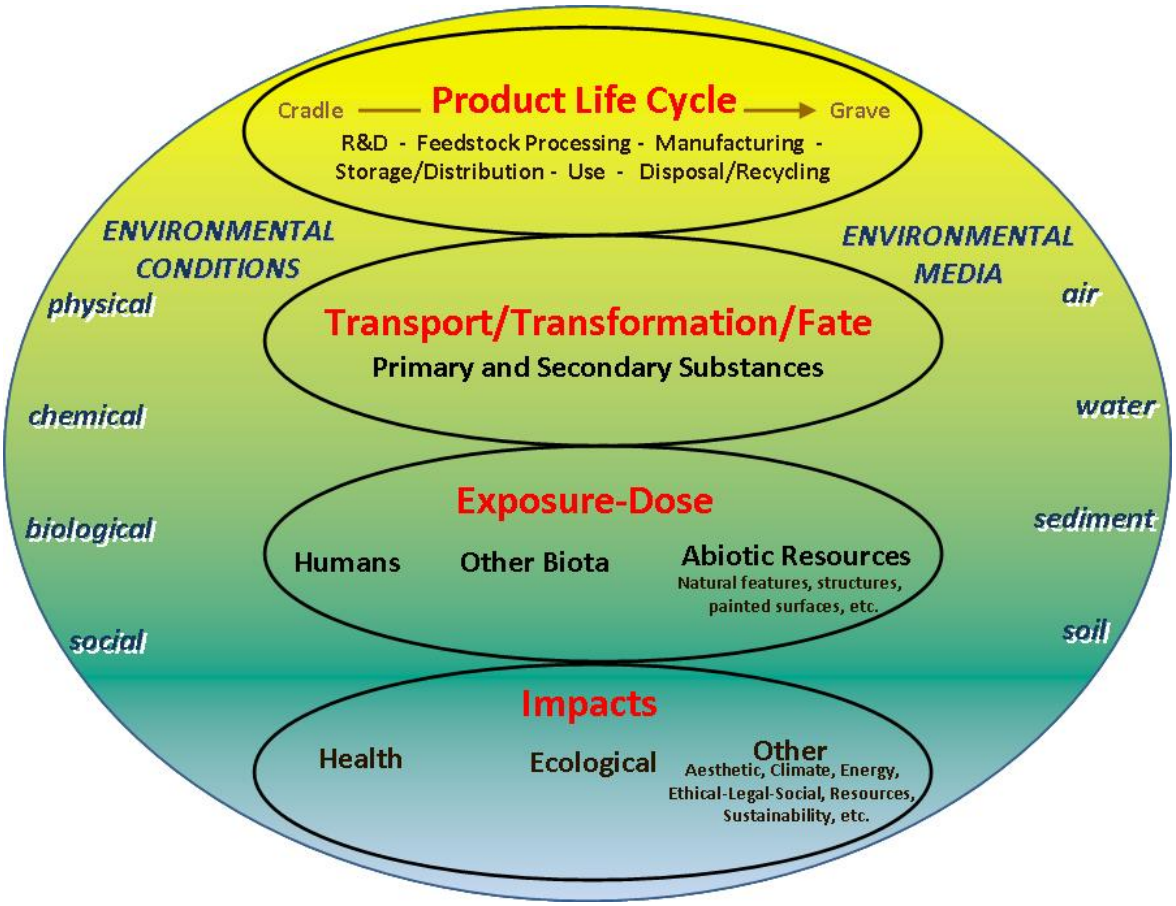
4.1 Introduction

In this chapter, a guidance to perform the environmental and health risk assessment for metallic fuel additives is presented. This methodology considers the product itself, emitted compounds and transformation products during the use phase. Some emissions and/or exposure pathways may be regulated in the context of other EU legislation (e.g. rules for occupational exposure, or manufacturing plants).

It has to be noted that a comprehensive assessment of human and environmental exposure and associated risks in relation to MFAs across the product life cycle entails numerous considerations and scoping exercises, the relative importance of each of which may vary depending on the specific MFA in question. Given that a general methodology is presented for the assessment of MFAs, some issues could apply broadly to various MFAs, whereas other issues might be unique or limited in relevance to only one or two MFAs. For this reason the scope defined in this document has been set to be large enough to tackle specific situations. Determining the relative importance of these issues will require initial expert judgments about their potential relevance to a given MFA, followed by efforts to compile available information (or identify information gaps) for that specific MFA.

Before the assessment, a holistic approach for evaluating the environmental implications of various choices among chemicals, products, and technologies might be needed to identify and prioritize research to support future assessment efforts and/or to provide input to risk managers to enable better targeted decisions. An example is given Figure 1. This holistic, *meta-assessment* approach[21] incorporates and builds on other assessment and analytical methods, including conventional life cycle analysis, exposure assessment, hazard analysis, and risk characterization. It aims to avert any unintended consequences by first taking a broad view of potential environmental impacts associated with a MFA, and then using a careful process to arrive at a judgment about which impacts warrant highest priority/attention.

[21]U.S. EPA (2011) Comprehensive Environmental Assessment (CEA): A Meta-Assessment Approach to Increase Effectiveness of Risk Management and Research Planning. Available at: www.epa.gov/nanoscience/files/CEAPrecis.pdf); Powers, C.; Dana, G.; Gillespie, P.; Gwinn, M.; Ogilvie Hendren, C.; Long, T.; Wang, A.; Davis, J.M. Comprehensive environmental assessment: a meta-assessment approach. Environmental Science & Technology, 46 (17): 9802-9208, 2012. Available at: http://pubs.acs.org/doi/full/10.1021/es3023072; DOI: 10.1021/es3023072)



Source: adapted from U.S. EPA (2011)[22]

Figure 1: Example of holistic approach for risk assessment of chemicals[21]

Based on this holistic perspective, pragmatic scoping choices can be made. It will be crucial to state them clearly, along with their rationale, in order to ensure the transparency and the relevance of the assessment.

Figure 2 presents the main steps of the assessment. For each step, the key aspects are summarised at the beginning of the section in a dedicated figure.

The process presented here is generic enough to be applied to any metallic fuel additive. However, specific examples and case-by case considerations are provided in the footnotes and might be of help for the applicant in orienting the assessment development as well as the discussions and the bibliography provided in the Annexes, notably for additives containing nano-scale materials since these materials can exhibit very different behaviour from chemically identical materials at a larger scale.

[22]US EPA (2011), Comprehensive Environmental Assessment (CEA): A Meta-Assessment Approach to Increase Effectiveness of Risk Management and Research Planning. Available at: www.epa.gov/nanoscience/files/CEAPrecis.pdf). See also Powers, C.; Dana, G.; Gillespie, P.; Gwinn, M.; Ogilvie Hendren, C.; Long, T.; Wang, A.; Davis, J.M. Comprehensive environmental assessment: a meta-assessment approach. Environmental Science & Technology, 46 (17): 9802-9208, 2012. Available at: http://pubs.acs.org/doi/full/10.1021/es3023072; DOI: 10.1021/es3023072)

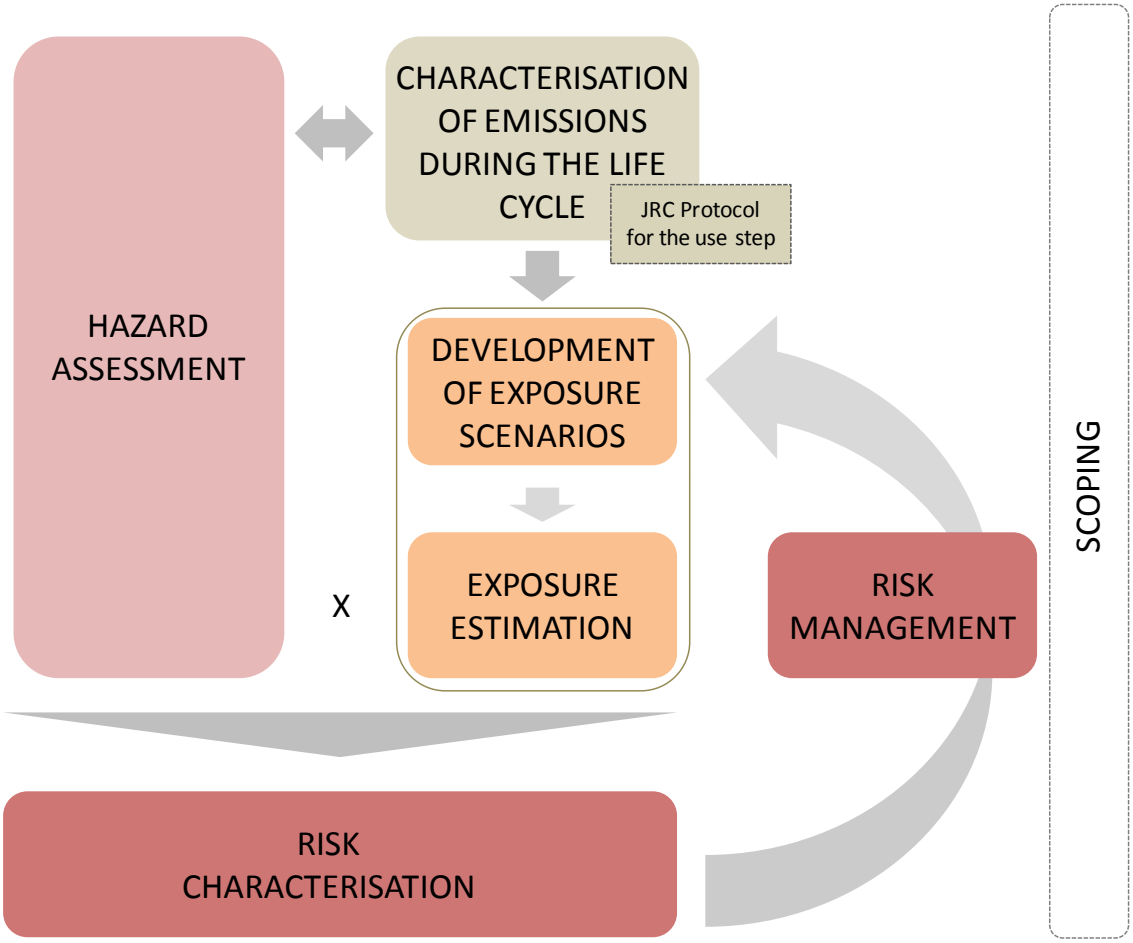


Figure 2: Main steps of risk assessment

4.2 Role of advisory boards established by the applicants

An advisory board is to be established to assist in and advise during the preparation and performance of the assessment. It is to be nominated by the applicant, from the beginning of the process. This advisory board should include members recognized as impartial and objective authorities in various technical disciplines, including fields such as vehicle and fuels technology, exposure analysis, health and ecological effects, and risk assessment/management. It should consist of no fewer than five and up to nine recognised experts with documented credentials. All individuals serving in the advisory board should attest to their independence from the applicant and an absence of competing interests, financial or otherwise, in the outcome of the assessment. The applicant is required to inform the European Commission about the composition of the advisory board. The European Commission is entitled to require further clarifications if the choice made is not considered satisfactory.

This advisory board will have as primary purpose to validate decisions regarding the assessment scope, conduct, and conclusions as well as provide guidance, review, and feedback on all aspects of the assessment. In particular, it will review the conclusions of the assessment regarding the

comparative risks and benefits of a given MFA in relation to its use versus non-use in fuels, as well as the maximum concentration or range of acceptable concentrations at which the MFA in question is judged to be without appreciable risk of adverse impacts on the environment or public health. In helping to ensure the quality of an assessment, the advisory board should also oversee the selection and interpretation of existing data to be incorporated in the assessment with regard to its scientific adequacy, consistency, applicability, and reproducibility, including considerations such as the source, type, age, geographical representativeness, temporal relevance, and other features of the data in question. Given that uncertainties, inconsistencies, and gaps in information should be identified as part of any assessment, it is also important that the advisory board reviews and elaborates, as appropriate, such uncertainties and data gaps, as well as prioritises their relative importance as a guide for risk managers and future assessment efforts.

The advisory board should be consulted on especially complex or contentious technical issues. All written feedback and review comments from the advisory board should be recorded and included as part of an annex to the assessment dossier, including the respective views of individual members regarding any issues on which the advisory board does not reach a consensus judgment.

In situations where existing data are inadequate for assessment purposes and where new data need to be generated, the advisory board may be used to help establish a separate Expert group, the purpose of which is to provide guidance on the design, conduct, and analysis of specific efforts to develop new or additional empirical data that could be used in preparing an assessment. Such efforts might include environmental monitoring studies, population exposure studies, toxicological effects studies, and other investigations.

4.3 Risk assessment guidance and examples

Several guidance documents and papers in the scientific literature discuss or illustrate methodological and other issues that are pertinent to assessments of MFAs. These include testing and measurement methods prescribed by regulatory authorities. A non-exhaustive list of examples is provided in Annex 4 to help applicants in compiling information needed to assess the potential impacts of MFAs.

4.4 Emissions during the life cycle

4.4.1 General aspects

- **Objectives**

Emissions can take place throughout the life cycle of the MFAs (illustrated in Figure 3). The purpose of this section is to provide guidance on the estimation of emissions to the environment (i.e. into water, soil and air) of MFAs, including combusted compounds and transformation products in the use phase.

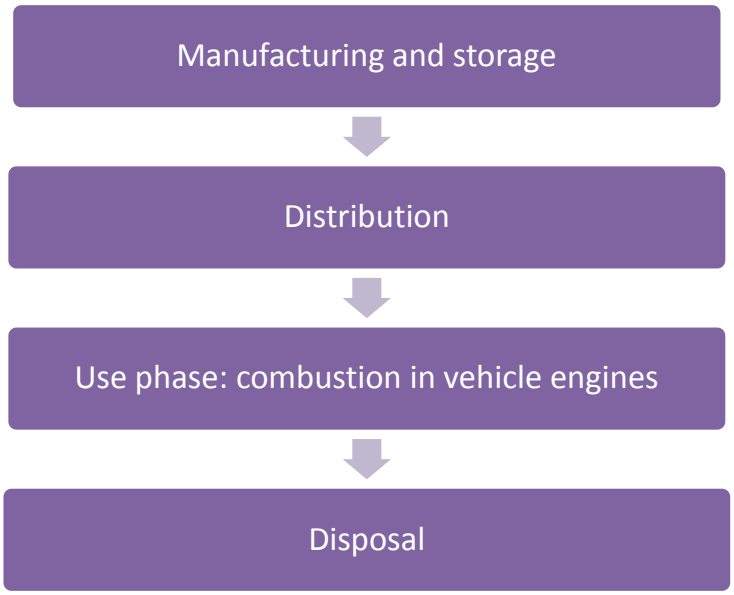


Figure 3: Life-cycle stages for MFAs

Figure 4 highlights the key steps to consider for assessing the emissions of MFA and related substances throughout the MFA life-cycle.

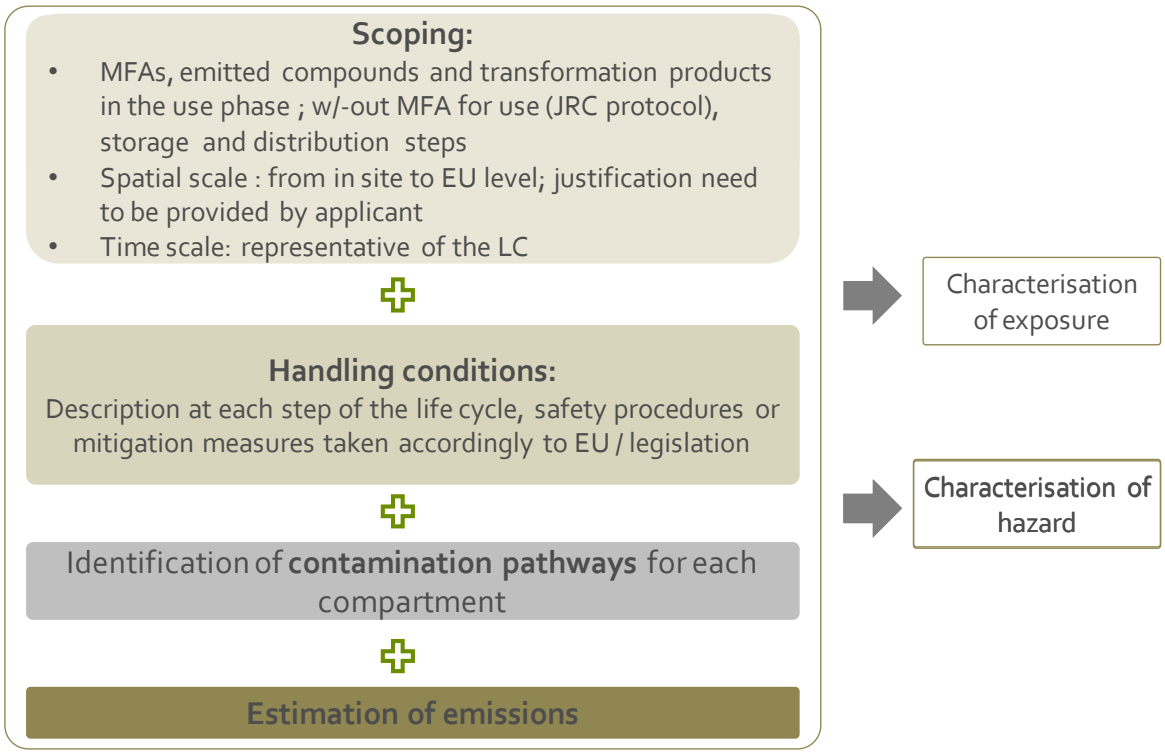


Figure 4: Key steps in assessing emissions throughout the substance life cycle

- **Scope**
  - The applicant must consider emissions at each life-cycle stage of MFA, emitted compounds[23] and transformation products using fuel with and without MFA in use (according to the JRC protocol), distribution and storage steps. The spatial scale can vary from in site to EU level depending on the specific MFA, its behaviour in the environment and the life cycle step considered. The applicant needs to justify the choice of spatial scale.
  - The time scale needs to include at least one whole life cycle of the MFA. When developing exposure scenarios in a later step, the applicant will need to consider present and future emissions trends.
  - For the use, the storage and transport phase, emissions using the fuel containing additive must be compared with emissions on the same fuel without additive. In the use phase, special attention must be put on characterising the nature of the exhaust, including the mass of particle-bound metal, speciation of combustion products and distribution of particle sizes.

- **Nature of data to be retrieved or produced**
  - The type and extent of emissions expected (and the exposure, as described in the following sections) may vary depending on the category or the type of fuel additive, notably if a functional product (added at the refineries), performance product (added at depots and terminals)or an after-market product (added by the consumer) is considered (Cf. Annex 1.1.A).
  - The emissions during the life cycle may be partly covered by existing EU legislation. The applicant must identify the existing legislation and/or safety and mitigation procedures which allow reducing the emissions throughout their life cycle[24].

[23] Most of the metal in a fuel additive is altered during combustion of the fuel and some percentage of the primary metal in an MFA can combine with other elements and form new compounds. These combustion products can then be released as such into the air; they can also attach to or be incorporated into other small particles in the atmosphere.

[24] For example, the control of emissions in the manufacturing phase is covered by the IPPC and SEVESO Regulations which include permit requirements for new plants. This means that there is already a mechanism for protecting human health and the environment from emissions taking place during this part of the life cycle of fuel additives. Similarly the immediate risks associated with transports may be partly considered through other legislation (e.g. ADR).
Council Directive 96/82/EC of 9 December 1996 on the control of major-accident hazards involving dangerous substances, available online at: eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:1997:010:0013:0033:EN:PDF [Accessed online 02/04/2012]
The European Agreement concerning the International Carriage of Dangerous Goods by Road governs transnational transport of hazardous materials, available online at UNECE website: www.unece.org/trans/danger/publi/adr/adr2011/11ContentsE.html [Accessed online 04/05/2012]

- Identification of emissions sources: at each step of the life cycle, the applicant will be asked to identify the possible emissions sources, and contamination pathways including among others:
  - leakages from storage/tanks;
  - spillage during the handling and use phase;
  - air emissions through combustion or evaporation[25];
  - emissions to water through wastewater management[26]; and
  - emissions to soil and surface waters through surface runoff/wind drift, with an eventual pollution of ground waters.
- The applicant must report the data on emissions in a specific table, or a more complex mass flow tool, along with the underlying assumptions for these estimations (Cf. Annex 1.1 B). The units chosen will need to be fully specified.

Sources of information

- The applicant must prioritise empirical data where possible. Some data may exist since collected under other reporting obligations and/or industrial sources.
- If empirical data are not available, the applicant can have recourse to the use of extrapolations, calculations or models[27]. In any case, the applicant must ensure the transparency of the sources of information used discuss the validity of the provided estimations.

4.4.2 Manufacturing and storage

The manufacturing step includes the production of the MFAs in the form ready for distribution (e.g. possible blending with fuel or other solvent) and its storage.

[25]Evaporation may take place e.g. through spilled fuel and additive into the hard cover (floor) or soil. The vapour pressure of the fuel additive may be of importance here: if the additive vapour pressure is lighter than the fuel, then the fuel additive might be left on the concrete or soil following evaporation of the more volatile fuel components. Subsequently, depending on its sensitivity to sun light, floor cleaning, wind drift, etc. the FA compound will be more or less prone to enter the air, water or soil compartments.

[26] Emissions may occur from different sources depending on whether the waste water is treated on site oris pumped into the municipal wastewater treatment plant.

[27]Examples of such models include the models for industrial release and consumer release in terms of mass flow calculations that were used for MFAs by the Canadian environmental and health agencies: Environment Canada, Health Canada, (2010). Screening Assessment for the Challenge Zinc, bis[O,O-bis(1,3-dimethylbutyl) phosphorodithioato-S,S']-, (T-4)-. Chemical Abstracts Service Registry Number 2215-35-2.
Note: Zinc is not a fuel additive. It is a lubricant additive.

Objectives

The applicant is required to estimate the possible MFA, emitted compounds and transformation products from the manufacturing and storage step. Note that storage occurs at multiple stages of the life cycle (i.e. after distribution).

Nature of data to be retrieved or produced

- The applicant must carefully evaluate the specific conditions at the manufacturing site which could result in emissions, answering the following questions:
  - Is the process closed?
  - Is the temperature controlled?
  - Is the final product diluted? If yes, what are the final concentration and the nature of the solvent?
  - How the product is stored within the manufacturing site (e.g. steel tanks and vessels, above/underground location[28], type of construction materials, the presence of lining)
  - How is it transported within the manufacturing site?
  - Is the manufacturing site controlled under some type of legislation (i.e. IPPC or SEVESO), which would allow or require (fully or partially) controlling emissions?
  - Is the product classified as e.g. dangerous goods, requiring specific (storage) conditions?
  - How are by-products and waste water originating from the manufacturing process treated?
  - What volumes are stored in tanks?
  - What types of tanks are used for storage (e.g. ISO-tanks)?
  - What is the average duration of storage?
  - What are the fittings/pipes and environmental conditions surrounding the tank?
  - Are there eventual regular replacement programs?
- Particular attention must be paid to the positive and/or negative effects of MFA on possible emissions through leaking and evaporation (e.g. Roos et al. (2002) [29]show lower evaporative emissions from fuel storage containers when MFAs were used).

[28]Fuel additives or diluted fuel additives are typically stored in underground storage tanks.
[29] Roos, Joseph W., Grande, Doni G., Hollrah Don P. and Cunningham, Larry J.(2002) Reformulating Gasoline for Lower Emissions Using the Fuel Additive MMT, Society of Automotive Engineers, 2002-01-2893

- **Output**

Based on the consideration of the aspects mentioned above, the applicant is required to design a strategy to quantify the total loss of MFA from the manufacture and storage site per time unit (day/year), through measurements and/or modelling. For illustrative purposes, an example of how to display this information is provided in Annex 1.1. B.

4.4.3 Distribution and trade

- **Objectives**

The applicant is required to estimate the emissions of MFA and by-products from the distribution and trade stages. Annex 1.1.C provides a brief description of the fate of various MFAs during distribution and trade as well as of the possible contamination pathways.

- **Nature of data to be retrieved or produced**
  - The applicant must carefully evaluate the specific conditions during product transportation and handling at the distribution site which could result in emissions. The applicant must answer the following questions:
    - Are the MFA produced domestically or are they imported within the EU? In the latter case, from where and what are the import transport conditions? Likewise, are the products exported within the EU? Where and what are the export transport conditions?
    - What are the type of containers (e.g. pipes, tanks, steel barrels) and means of transport?
    - How the content is discharged into storage containers, refuelling containers and/or vehicle tanks (e.g. gravity, pumping into customer storage tanks)?
    - Is the MFA mixed/diluted with fuel before distribution or is it sold as an after-market product?
    - In which types of facilities (e.g. gas stations) are the MFA distributed?
    - What are the existing licenses/legislative requirements applying to the fuels that may allow controlling emissions during the distribution step?
    - In the case of after-market fuel additives, is the packaging adapted to avoid emissions and spill over?
  - Particular attention must be paid to the positive and/or negative effects of MFA on possible emissions through leaking and evaporation. In this context, the potential for metal exposure from evaporative emissions must be considered.

- **Output**

Based on the consideration of the aspects mentioned above, the applicant is required to design a strategy to quantify the total loss of MFA from the distribution and trade step per time unit (day/year), through measurements and/or modelling.

4.4.4 Use

- **Objectives**

The applicant is required to measure or estimate the nature and the quantity of the emissions in the combusted exhaust[30] (both regulated[31] and non-regulated) in the use phase, using fuel with and without MFA following the JRC protocol[32]. However, additional (unregulated) emissions may be of interest, which are not necessarily covered by the JRC protocol but relevant in the context of a health and environmental risk assessment. Unregulated pollutants as well as complex pollutant interactions altered through use of metallic additives could then be considered in the assessment if relevant for the risk assessment. Particular interest must be paid to metallic compounds and their binding with particles, which are present in the MFA and in the fuel before the combustion and/or formed during combustion.

This is a key step which the applicant must focus on when assessing emissions, since the release of metallic additive combustion products is expected to be linked to the major exposure pathway for the general public.

[30] During combustion, the alkyl groups that are chelated to the metal will be fully combusted in the engine and the metal will in general be converted to a metallic oxide. It is the metallic oxide that will ultimately appear in the vehicle exhaust and then in the environment. Some metals could be adsorbed on soot (e.g. carbonaceous) particles. For example, upon combustion, MMT® produces a variety of inorganic salts and oxides of Mn (Mn phosphate predominating, the rest in the form of Mn sulphate and Mn oxides). On average, less than 15% of the manganese added to the fuel is emitted from the tailpipe regardless of vehicle type.
Wood, G., Egyed, M., (1994) Risk assessment for the combustion products of methylcyclopentadienyl manganese tricarbonyl (MMT) in gasoline. Environmental Health Directorate Health Canada. Part 1, December.
Pfeifer G.D. Roper, J.M. Dorman, D. Lynam D.R. (2004) Health and environmental testing of manganese exhaust products from use of methylcyclopentadienyl manganese tricarbonyl in gasoline Science of the Total Environment 334– 335, 397–408

[31] The regulated emissions in EU (Directive 2005/78/EC) include CO, HC, NOx and PM.

[32] Joint Research Center (2011), Protocol For The Evaluation Of Effects Of Metallic Fuel-Additives On The Emissions Performance Of Vehicles, Final Draft

- **Sources of data and methodology to be followed**

In this step the data need to be produced following the JRC protocol (for regulated emissions) or a comparable methodology (for unregulated emissions). A number of other methods are available for estimating or measuring the extent of emissions from the engine[33,34,35,36,37].

As a reminder, the applicant must select a base or reference fuel relevant to the market considered. It could namely use the Coordinating European Council (CEC) reference fuels (CEC P -017-97, Iss 10:2006 Reference Fuels Manual[38]) complying with the specifications laid down in the emission regulations (Directive 2009/30/EC). To test emissions, the applicant must ideally use the same batch of fuels for the entire program or at least minimise the variability in fuel composition and a representative vehicle fleet as well as the defined driving cycle.

- **Nature of data to be retrieved or produced**
  - Characterisation (quality and quantity) of emissions from vehicles per time or space[39]); including at least:
    - Particle-bound metals (e.g. Pt, Rh and Pd), which may remain in the exhaust or be formed during combustion[40]
    - Metallic oxides
    - Particle sizes[41] distribution in PM10, PM 2.5, TSP and ultrafine particles (<0.1 um)
    - Specific surface area of the >0.1 um particles
    - Fraction of the ultrafine particles

[33]For example a Dutch project with the aim to harmonise toxicity testing of engine emissions in which some emission aspects has been discussed and some harmonised conditions are under development Personal communication, Miriam Gerlofs-Nijland, RIVM, Netherlands, April 2012.
[34]ISO standards TC 70/SC 8 -regarding the Exhaust gas emission measurement. Available at: www.iso.org/iso/home/store/catalogue_tc/catalogue_tc_browse.htm?commid=49884
[35] Anders Westlund (2009), Measuring and Predicting Transient Diesel Engine Emissions. KTH. TRITA – MMK 2009:07ISSN 1400-1179 ISRN/KTH/MMK/R-09/07-SE. Academic thesis, which with the approval of Kungliga Tekniska Högskolan, Available at: www.cicero.kth.se/Outside/Archives/Lic%20theses/Measuring%20and%20Predicting%20Transient%20Diesel%20Engine%20Emissions,%20Anders%20Westlund%20Lic.pdf
[36]CIMAC (1999), Guide to Exhaust Emission Control Options. Rr32. Sept 99 MS3026. Series of paper for the CIMAC Committee. Available at: www.cimac.com/cimac_cms/uploads/explorer/Working%20groups/Guide_to_EEC_Options_Sep99.pdf
[37]George P. Reischl (2006), The characterisation of articulate motor vehicle emissions by electrostatic measurement techniques. Available at: www.dustmonitor.com/Publications/5601_Reischl_THE%20CHARACTERIZATION%20OF%20PARTICULATE%20MOTOR%20VEHICLE%20EMISSIONS.pdf
[38]www.iash.net/CECStandards.html
[39]Alternatively, energy metrics will make it possible to compare with emissions from other sources of emissions, for example wood smoke. Data per mass basis is not relevant for risk assessment.
[40] When characterising particle-bound metals, it is important to keep in mind that they might also originate from the exhaust catalyzer. Interpreting emission data as MFA-related only would create a bias, hence the interest of comparing exhaust of fuel with or without MFA.
[41]The size of the metallic particles emitted is important since it is decisive for the degree of penetration into the lungs and bloodstream. Yet, according to the present legislation, particles having a diameter lower than 23 nm are not included in the measurements for risk assessments, but such legislative are not primarily designed to measure impact on humans.

- HC, organic carbon CO, NOx, PN (where applicable) and CO_2
- Acidity of the exhausts (NH_3, SO_2)
- Elemental carbon (EC), aromatics (Nitro- and oxy PAH, total PAH), benzene, formaldehyde and acetaldehyde; and
- Volatile or semi volatile organic components, water soluble (transition) metals, C1-C5 and C6-C12 hydrocarbons, acrolein, polycyclic organic matter (POM), naphthalene, 1,3 butadiene.

- In case the applicant decides to modify the above-presented list, a justification will need to be provided.
- This step will permit to characterise the effects of using MFA on emissions quality and quantity: whether they are positive (e.g. reduced fuel consumption and thus related emissions) or negative (e.g. on pollution control systems)[42].

Presentation of the outcomes

The outcomes of this step need to be carefully interpreted before continuing the assessment. This step can be expected to produce multiple results on multiple vehicles with a certain level of variability and uncertainty. Annex 1.1 D highlights the possible sources of uncertainties. The applicants will have to professionally process and analyse the results in order to identify the statistically significant effects which can be attributed to the metallic additive, in particular whether relevant emission limits are significantly exceeded and/or emissions levels are significantly different when comparing the two sets of vehicles aged with and without the metallic additive (JRC Protocol). Data will have to be critically reviewed. However, as discussed earlier, there may be additional (unregulated) emissions which are not necessarily covered by the JRC protocol but which are relevant in the context of a health and environmental risk assessment. Unregulated pollutants as well as complex pollutant interactions altered through use of metallic additives could be considered in the assessment if relevant for the risk assessment. The applicant will propose a list of considered emissions and justify it. The advisory board will evaluate this choice and eventually ask the applicant to review its list.

4.4.5 Disposal

Objectives

The applicant is required to measure or estimate the types and extent of the emissions during the disposal step. The disposal stage includes the disposal or dumping of the unsold products

[42]The use of an MFA in fuel may have an impact on particle sizes, and other fuel combustion products, compared to combustion of the fuel without the additive. For example, there are studies that indicate lower vehicle emissions (e.g. benzene, aromatics) upon use of MFAs. US HEI conclude in a literature review (2001) that the use of cerium additives can change the PM mass emissions, proportions of elemental carbon (EC) and organic carbon (OC) from fuel combustion, whereas other literature reviews comment that data also exist where a very small (or no) measurable effect was reported on regulated emissions (CO, HC, and NOx).
Roos, Joseph W, Grande, Doni G. Hollrah Don P. and Cunningham, Larry J. (2002) Reformulating Gasoline for Lower Emissions Using the Fuel Additive MMT, Society of Automotive Engineers, 2002-01-2893)
Health Effects institute (2001) Evaluation of Human Health Risk from Cerium Added to Diesel Fuel Health Effects Institute Communication 9 August

themselves but could also include disposal of packaging or washing out of MFA as well as mixed/diluted product containers such as waste lubricating oil. Although MFAs are not added to the oil, the design of internal combustion engines (for both spark-ignited and compression-ignited engines) may indeed allow MFAs in the fuel to be mixed with the lubricating oil. It should be noted that the disposal of vehicles might also lead to contamination with fuel/fuel additives. Disposal stage is listed in the end of the life-cycle but it should be noted that it occurs after each step described earlier (e.g. manufacturing, use).

- **Nature of data to be retrieved or produced**
  - The applicant must carefully evaluate the specific conditions at the disposal site (e.g. recycling facilities, landfills or incineration) which could result in MFA emissions, considering the following aspects:
    - Conditions of MFA pure product disposal
    - Conditions of mixed/diluted product disposal
    - Are these products following a dedicated waste stream? If not, is their influence to the incineration exhaust nature significant?
    - How the washing of containers occurs (e.g. does cleaning and/or re-use of the tanks includes their inspection to ensure the complete discharge of the load?)[43].
- **Output**

Based on the consideration of the aspects mentioned above, the applicant is required to design a strategy to quantify the total loss of MFA from the disposal step per time unit (day/year), through measurements and/or modelling.

[43]The transportation or storage tankers are usually cleaned after use by cleaning contractors.

4.5 Hazard assessment

4.5.1 General aspects

Objective

The objective of the hazard assessment is to collect qualitative and quantitative information on possible hazards to humans and the environment of MFAs, emitted compounds and transformation products.

Figure 5 highlights the key steps to assess the emissions of MFA and related substances throughout the MFA life-cycle.

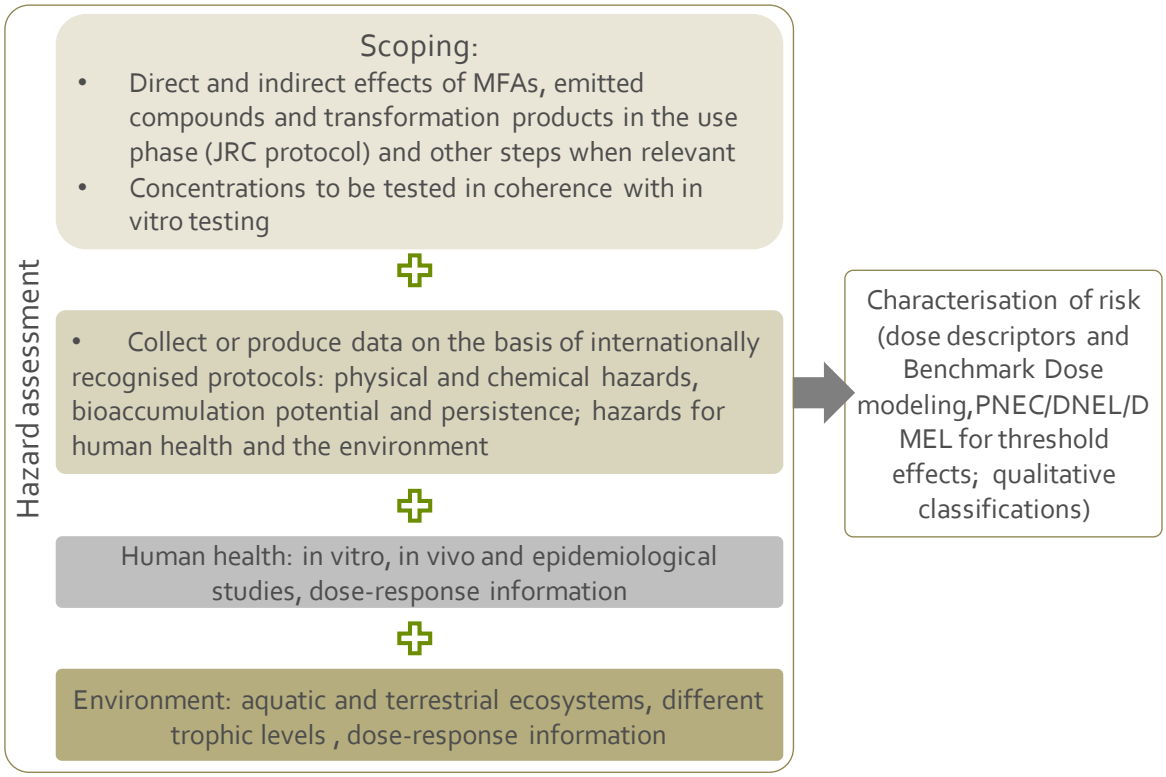


Figure 5: Key steps in assessing human health and environmental hazard throughout the substance life cycle

Scope

- The hazard assessment needs to include all the information on potential direct and indirect impacts across the product life cycle of a MFA for humans and the environment, including emitted compounds and transformation products, notably emissions in the use phase but also during other steps if considered relevant after emissions estimation.
- In particular for the use phase, a hazard screening using MFAs (i.e. concerning the emissions produced in the combustion of the fuel containing metallic additive in a vehicle as well as evaporative emissions) should always be compared to the hazard not using the metallic fuel additive (i.e. concerning the

emissions produced in the combustion of the fuel alone in a vehicle), following the JRC Protocol.

- **Nature of data to be retrieved or produced**

This section addresses general aspects that are common to the assessment of physical and chemical properties, to the assessment human health hazards and of environmental hazards. Detailed instructions on specific data to be presented are given in the next three sections.

For each MFAs and related substances, the applicant will need to evaluate the information provided for its quality, including its reliability, relevance and adequacy for the hazard assessment. Regarding the nature of chemicals to be considered in the hazard assessment for the use step, it should always be based on the output results for emissions monitoring as obtained in the JRC protocol (see also section 4.4). The metallic fuel additive itself and the combustion derived products have to be known and measureable.

- Data collected from different sources might be heterogeneous and not easily comparable. The test approach proposed by the applicant should be at least based on methods which have been previously validated by an independent organisation (e.g. OECD, ECVAM) (Cf. Section 4.2).
- The concentration range of substances that will be tested needs to be defined in accordance to realistic data on emissions and preliminary toxicity and ecotoxicity testing. It should be the same for all the toxicity/ecotoxicity tests for comparison. In vitro tests and other information may be used for selecting the appropriate dose levels to use in in-vivo studies[33].
- The emissions throughout the life cycle will be a mixture of diverse combusted particles and substances, in particular after the combustion step. In their testing strategy, the applicants will need to take into account the fact that some toxicity/ecotoxicity tests are not applicable to mixtures and may therefore not be appropriate to assess the toxicity of combustion products.

- **Perspective for further steps**

If the assessed hazards represent a relevant risk, it will depend on the results of the exposure assessment and on eventual risk management measures. Thus, if the exposure is above the threshold levels defined by the DNEL[44] or PNEC[45], the risk might be relevant and might require specific management measures.

4.5.2 Physical and chemical hazards, bioaccumulation potential and persistence

[44] level of exposure to the substance above which humans should not be exposed. The DNEL measures the potential of the substance to cause adverse health effects.

[45] concentration of a substance in any environment below which adverse effects will most likely not occur during long term or short term exposure.

Objective

The physicochemical properties of MFA, of related emitted compounds and transformation products may influence their behaviour in the environment or in the human body. These properties can also influence the contamination pathways and exposure scenarios. The applicant needs to collect, or in case of missing data produce, and present physical and chemical data on the MFAs and related substances which might be relevant for the assessment of health and environmental hazards.

Nature of data to be retrieved or produced

The most relevant physicochemical properties to collect or produce are:

- physical state;
- elemental speciation;
- particle size distribution (in case the substance assessed could be nanoparticles);
- melting point (°C);
- boiling point (°C);
- density (Kg/m^3);
- vapour pressure (Pa)[46];
- water solubility*;
- octanol-water partition coefficient: Log Kow*;
- organic carbon partition coefficient: Log Koc*; and
- data on environmental persistence and bioaccumulation (BCF).

*: not relevant for inorganic compounds, unless they are coated/functionalized with organic compounds

Sources

Data can be obtained from experimental sources, from cross comparison or from modelling. When experimental data on a specific substance is missing, properties of a similar compound can be reported since in a group of MFAs, the physicochemical properties of substances are often similar. This information should be collected from studies found in the peer-reviewed literature or in toxicological profiles contained in chemical databases or **produced** by the applicant.

In the case of modelling the applicant needs to specify the model used the results and predictions and specifically in the case of persistence the extrapolated half-life for each concerned compartment. The reliability of the used models needs to be discussed and in all cases priority should be given to experimental data[47].

[46]Vapour pressure is a key property to consider for fuel metallic additives since it is an indication of the evaporation of a substance in the air and subsequently an indication of the possible related exposure through inhalation. For instance, iron pentacarbonyl (Fe(CO)5), which has a vapour pressure of 21 mm Hg at 20 deg C, would be expected to exist as a vapour whenever in contact with air.

[47]US EPA (2008).Supporting Documents for Initial Risk-Based Prioritization of High Production Volume Chemicals Zinc Dialkyldithiophosphates (ZDDP).

Also, if the assessed metallic additive is already included in a category defined in an **internationally recognised classification** (e.g. from CLP, US EPA, industrial voluntary classification, etc.), this classification can be taken as an input for the hazard assessment and might provide sufficient information for this step. The determination of the appropriate classification and labelling of a substance on its own, in a preparation or in a product is a requirement under REACH. The CLP regulation lays out the criteria for the classification. As part of this classification, a metallic fuel additive might be classified as a PBT (persistent, bioaccumulative and toxic) and/or vPvB (very persistent, very bioaccumulative). These substances' categories are of particular concern given their potential to accumulate in the environment and may lead to unpredictable effects in the long-term.

- **Outputs**

The applicant must gather information on the physicochemical properties of each MFAs, relevant emitted compounds and transformation products. Ultimately, the applicant must be able to characterise the risk represented by these physicochemical properties in the context of different exposures scenarios.

4.5.3 Human health hazards

- **Objective**

The applicant needs to collect, or in case of missing data produce, and present information on hazards of the substance to humans.

- **Sources**

Published **sources of empirical data**, preferably peer-reviewed publications[48], should be used to collect the relevant information.

Similarly to physicochemical properties, if the assessed metallic additive is already included in a hazard category defined in an **internationally recognised classification**, this classification can be taken as an input for the hazard assessment and might provide sufficient information for this step.

If hazard data are not available an extrapolation from more extensive information on chemically similar substances to evaluate a particular MFA or its by-products has to be performed.

Reports on work-related accidents or adversely affected health conditions due to exposure to metallic additives reported in industry submissions.

The assessment of the toxicity for humans of a specific substance must be based on approved protocols such as OECD protocols (Cf. Section 4.2). For instance, regarding emission inhalation the OECD 412 test can be a reference point.

Some MFAs are or produce nano-sized particles. In these cases specific hazard test protocols need to be set. Quite a lot of work has been published on cerium nano and micro particles[49,50].

[48] Which does not exclude the use of other sources of information, as long as the information provided allow an independent review.

Nature of data to be retrieved or produced

While producing data related to the hazard of substances, it must be kept in mind that effects observed can be related either to the chemical nature of a substance (e.g. inhaled particle) or its physical presence (i.e. effect of particles in lungs). This is especially relevant to MFAs containing rare metals and/or having nano-sized fractions, since the effects observed can be due to stress or stimuli caused by the surface, size and/ or shape of the particles rather than by its chemical properties. However, it is not straightforward to distinguish these factors through in-vitro studies. As an example of cell based in vitro study of nano-sized MFA effects, please see:

Steiner S, Mueller L, Popovicheva O, Raemy D, Czerwinski J, Comte P, Mayer A, Gehr P, Rothen-Rutishausera B, Clift M. Cerium dioxide nanoparticles can interfere with the associated cellular mechanistic response to diesel exhaust exposure. Toxicology Letters 214 (2012) 218– 225.

- Data from a set of **cell-free and cell-based in vitro studies** including:
  - viability;
  - cytotoxicity (through effect on lysosomal enzyme release, protein synthesis, and cell morphology). The results of the toxicological test could also be used to collect some information regarding the mode of action of the metallic fuel additive;
  - oxidative potential;
  - inflammation[51]; and
  - mutagenicity and genotoxicity.

  The duration, the tested cell type and the doses need to be specified by the applicant.

  These studies will allow the applicant determining the appropriate range of dose levels for conducting in vivo animal experiments.
- Data from **in vivo animal experiments** on hazard originated by different routes of exposure has to be tested (oral, dermal, inhalation), including:
  - acute toxicity;
  - chronic and sub-chronic toxicity (sub-chronic studies are useful in identifying the organ(s) targeted by the substance. They can also be used to select dose levels for longer-term studies. The threshold levels obtained by repeated-dose toxicity studies are in general lower than the relatively high threshold obtained in acute toxicity studies);
  - developmental and reproductive studies;

[49]Cassee, F. R., Campbell, A., et al. (2012). The biological effects of sub-acute inhalation of diesel exhaust following addition of cerium oxide nanoparticles in atherosclerosis-prone mice. Environmental Research, 1-10.
[50]Cassee, F. R., van Balen, E. C., et al. (2011). Exposure, health and ecological effects review of engineered nanoscale cerium and cerium oxide associated with its use as a fuel additive. Critical reviews in toxicology, 41(3), 213-29.
[51] For instance, the release of inflammation mediators from lung cultured cells is important information on potential respiratory tract effects of studied compounds.

- local effects of sensitisation (e.g. skin irritation or respiratory effects):;
- systemic effects of acute or repeated exposure studies (chronic and sub-chronic);
- pathological alteration of specific organs (e.g. lung weight, alveolar epithelial hyperplasia, etc.);
- oxidative stress;
- urine analysis; and
- alteration of some enzymatic activities or blood composition.

The duration, the tested animal species, the age and sex of animals, the doses and the exposure routes need to be specified by the applicant.

- Results of **epidemiological studies** on general population or workers e.g. in metallic fuel additive production plant or gas stations (possible correlations between exposure and higher incidence of health effects), when available[52].Possible gender studies, childhood or other population susceptibility need to be mentioned. The test approach can be built on the basis of available epidemiological data.

In the case of threshold effects: determination of dose descriptors and DNEL

On the basis of previously collected or produced data, when substances are likely to present threshold effects, dose descriptors need to be defined. They allow identifying the relationship between a specific effect of a substance and the dose at which it takes place for a specific exposure pathway.

The dose descriptors to be defined are the following:

- The **LD50** (median lethal dose) or **LC50** which are respectively the dose and the concentration at which 50% of the sample population is eliminated[53]. The LD50 and the LC50 may vary depending on the experimental conditions. It is thus important to specify the cell type and the details of the testing protocol applied.
- The **NOAEL** (No Observed Adverse Effect Level), usually expressed in mg/kg/day, defines the dose of substance that produces no significant toxicological effects for a specific exposure pathway, or NOAEC (No Observed Adverse Effect Concentration).
- The **LOAEL** (Lowest Observed Adverse Effect Level), which is the lowest dose that produced an adverse effect.

[52] Only a few epidemiological studies on MFAs and relevant combustions products are available and due to high correlations with other substances the observed health effects are not strongly correlated with the substance of concern.

[53]For instance, cerium oxide had a LC50 of approximately 4 700 µM in Sprague-Dawley rat pulmonary alveolar macrophages (PAMs) as shown in *Palmer, RJ; Butenhoff, JL; Stevens, JB. (1987) Cytotoxicity of the rare earth metals cerium, lanthanum, and neodymium in vitro: comparisons with cadmium in a pulmonary macrophage primary culture system. Environ Res 43(1):142–156.*

- For each health effect and each relevant exposure pattern, a **DNEL** (Derived No-Effect Level) needs to be established. The DNELs are calculated by dividing the value of the health effect dose descriptor by an assessment factor (or safety factor) to allow for extrapolation to real human exposure situations. The applicant must justify the appropriateness of the assessment factor used.
- From all health effects, **the lowest DNEL for each exposure pathway** will be documented and will later be used for risk characterisation.

In Annex 1.2.A, Table 3 provides examples of NOAEL and LOAEL values for observed effects.

Outputs

Quantitative information has to be gathered or produced to define a dose-response relationship for a specific metallic additive substance, to identify the DNEL[54] threshold values for different exposure pathways (e.g. oral, dermal, inhalation) and environmental spheres. Appropriate methodologies include benchmark dose (BMD) modelling[55]. For cancer assessments, potency calculations as well as qualitative classifications of the weight of evidence regarding the hazard posed by a substance have to be developed.

The applicant at this step is expected to present the available data and provide a summary of the known effects on humans or animals models. Based on this the applicant will present his choice of each DNEL and explain the applied rationale for this choice. Any models and calculations used need also to be presented, with explanations of the underlying assumptions and the application of uncertainty factors. The smallest values of DNEL have to be selected to protect the most sensitive species/human populations and minimise the risk.

[54]The Predicted No Effect Concentration or PNEC is the concentration to which no effect is observed in the environment.
The Derived No-Effect Level or DNEL is the level of exposure to the substance above which humans should not be exposed.
[55]Cf. values from the U.S. EPA IRIS database:www.epa.gov/iris/

4.5.4 Environmental hazards

Objective

The applicant needs to collect, or in case of missing data produce and present information on hazards of the MFAs, emitted compounds and transformation products to the environment. Conclusions on the possible effects of the MFAs and related substances on living organisms representing different trophic levels in the relevant ecosystems should be provided.

Nature of data to be retrieved or produced

- ecosystems to be considered are:
  - aquatic ecosystems (surface and groundwater for freshwater ecosystems and where relevant marine ecosystems (e.g. fuels used for ships)); and
  - terrestrial ecosystems
- the applicant must study the effects on at least three trophic levels. For example:
  - for the aquatic environment:
    - fish;
    - invertebrates; and
    - algae/microorganisms;
  - for terrestrial ecosystems :
    - microorganisms;
    - invertebrates;
    - vertebrates (e.g. metal concentration in pigeon's liver)[56]; and
    - plants[57].

Annex 1.2.B provides a concrete example of the assessment of environmental hazards for different trophic levels.

[56] For example, according to Loranger& Zayed (1995), the concentration of Mn in pigeon's liver and feaces, as well as in several other tissues (kidney, lung, pancreas, intestine, brain, down feathers, whole blood, and blood serum) shows the potential exposure for both humans and ecosystems through air pathway. The urban pigeons (from Montreal) had 29% more Mn in their liver and 45% more in their feces than the rural ones (from Lachute).
Loranger& Zayed (1995), Environmental and occupational exposure to manganese: a multimedia assessment. International Archives of Occupational and Environmental Health, 1995, Volume 67, Number 2, Pages 101-110. Available at www.springerlink.com/content/w5148455406k07j5/

[57] A number of publications demonstrate Mn uptake in vegetation beside roadways. These namely include:

- Lytle C. et al. Manganese Accumulation Along Utah Roadways: a Possible Indication of Motor Vehicle Exhaust Pollution. Sci Tot Env. 162 (1995): 105-110.
- Lytle CM, McKinnon CZ, Smith BN. 1994. Manganese accumulation in roadside soil and plants. Naturwissenschaften 81:509-510.
- Brault N. et al. Bioaccumulation of Manganese by Plants: Influence of Methylcyclopentadienyl Manganese Tricarbonyl as a Gasoline Additive. Sci Tot Env. 153(1994): 77-84.

- endpoints to be analysed are:
  - viability of target species,
  - potential effects on growth (e.g. EC50 growth),
  - development, and
  - reproduction.

  For plants, relevant aspects that need to be considered include:
  - root growth, and
  - germination timing.

To assess the environmental hazards, the applicant can apply different biomonitoring methods (e.g. biota population and/or bacteria test, acute toxicity array, chronic toxicity array). The applicant will have to justify the choice of bioindicators used for the assessment.

Source

The applicant can use several OECD tests suitable to various species, as listed in Table 4 in Annex 1.2.C.

In the case of threshold effects: determination of dose descriptors and PNEC

From the experimental data collected or produced by the applicant, the Predicted No Effect Concentration, PNEC, the concentration below which no effect is expected in the environment, should be calculated. It needs to be determined for each environmental sphere: air, fresh (surface and groundwater) and marine water, soil, sediments. It is estimated by dividing the dose descriptor (i.e. the lowest observed, NOEC, EC50, or LC50-value) resulting from the most sensitive ecotoxicity test by the relevant assessment factor (or safety factor). Since dose descriptors are obtained from laboratory tests involving a limited number of species, the assessment factor is required to account for the uncertainties involved in the extrapolation to the real ecosystems. The applicant must justify the assessment factor used. Where several dose descriptors are available for a specific environmental sphere, all possible PNECs will be derived but only the lowest PNEC for each compartment will be reported to be later used for risk characterisation. Alternatively, the most sensitive test endpoint should be used. PNEC values should be based on conservative assumptions. The assumptions underlying the derivation of PNEC must be transparent and justified.

Outputs

In the case of threshold effects, PNEC validity needs to be discussed. Several criteria have to be taken into account such as the pathway and time of exposure, the species considered, etc. in order to select the most relevant value. The smallest values of PNEC have to be selected to protect the most sensitive species/human populations and minimise the risk.

In the case of non-threshold effects or where testing is not technically possible, values must be determined with other appropriate methodologies.

4.6 Exposure assessment

Objectives

The **exposure assessment** is the process of measuring or estimating the dose or concentration of the substance to which humans and the environment are or may be exposed, depending on the uses of the substance[58].

This chapter provides guidance on how to perform an exposure assessment, in **two steps**: how to (a) develop exposure scenarios (Figure 6); and (b) exposure estimation for both humans and the environment. The concentrations of MFAs, emitted compounds and transformation products using fuel with and without MFA in use (accordingly to the JRC protocol), distribution and storage step in the environment and the situations in which humans and biota are exposed to these levels must be described (a) and evaluated (b). Please refer to Annex 1.3.A which provides further consideration on the reasons why the exposure assessment is made a mandatory steps, not conditioned by the result of the hazard assessment.

Definitions

Exposure refers to contact between a contaminant and a receptor (e.g. human and non-human biota). Exposure typically occurs via one or more environmental pathways or media, i.e., air, water, sediment, and soil. Routes of exposure refer to the manner in which a substance enters the organism, e.g. for humans inhalation, ingestion, and dermal absorption (other routes such as injection and ocular absorption are possible but less common). The term "dose" is defined and used in various ways in the risk assessment field. In accordance with the U.S. Environmental Protection Agency (EPA) Integrated Risk Information System (IRIS) program (www.epa.gov/iris), the dose can be defined as "the amount of a substance available for interactions with metabolic processes or biologically significant receptors after crossing the outer boundary of an organism."[59]. Exposure and dose are part of a series of events potentially leading to biological and toxicological effects in an organism. Such effects depend not only on the delivered dose, but also on several other factors, including spatiotemporal dimensions of the exposure (e.g. frequency, duration, location), as well as characteristics of an organism such as age, reproductive status, size, metabolic function, and even exposure to other contaminants or agents.

[58] ECHA (2009), Guidance in a Nutshell - Chemical Safety Assessment

[59] The IRIS program also distinguishes:
POTENTIAL DOSE as the amount ingested, inhaled, or applied to the skin;
APPLIED DOSE as the amount presented to an absorption barrier and available for absorption (although not necessarily having yet crossed the outer boundary of the organism);
ABSORBED DOSE as the amount crossing a specific absorption barrier (e.g. the exchange boundaries of the skin, lung, and digestive tract) through uptake processes;
INTERNAL DOSE as a more general term denoting the amount absorbed without respect to specific absorption barriers or exchange boundaries; and
DELIVERED or BIOLOGICALLY EFFECTIVE DOSE for a particular organ or cell as the amount of a chemical available for interaction in that organ or cell.

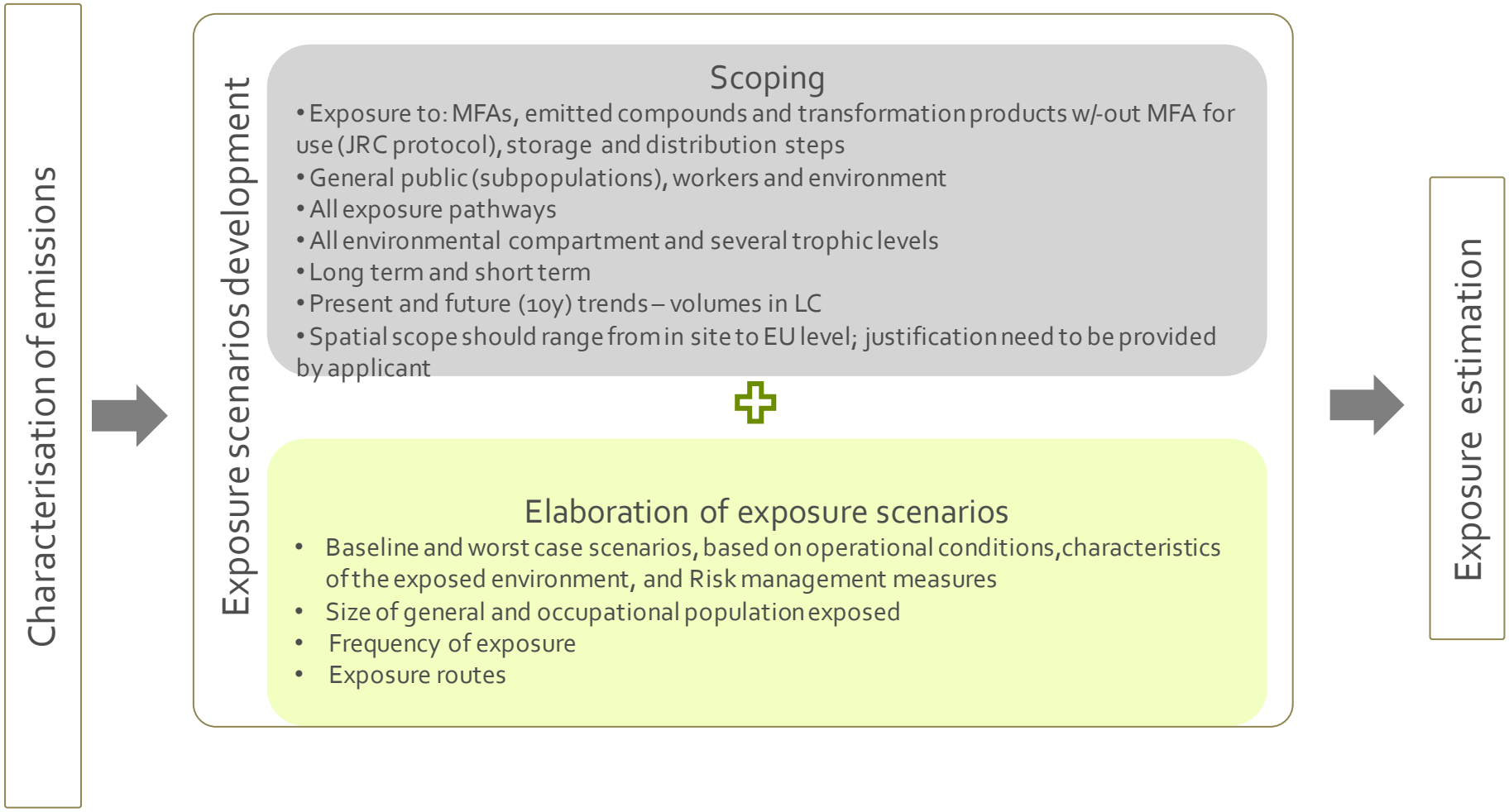


Figure 6: Key steps for the development of exposure scenarios

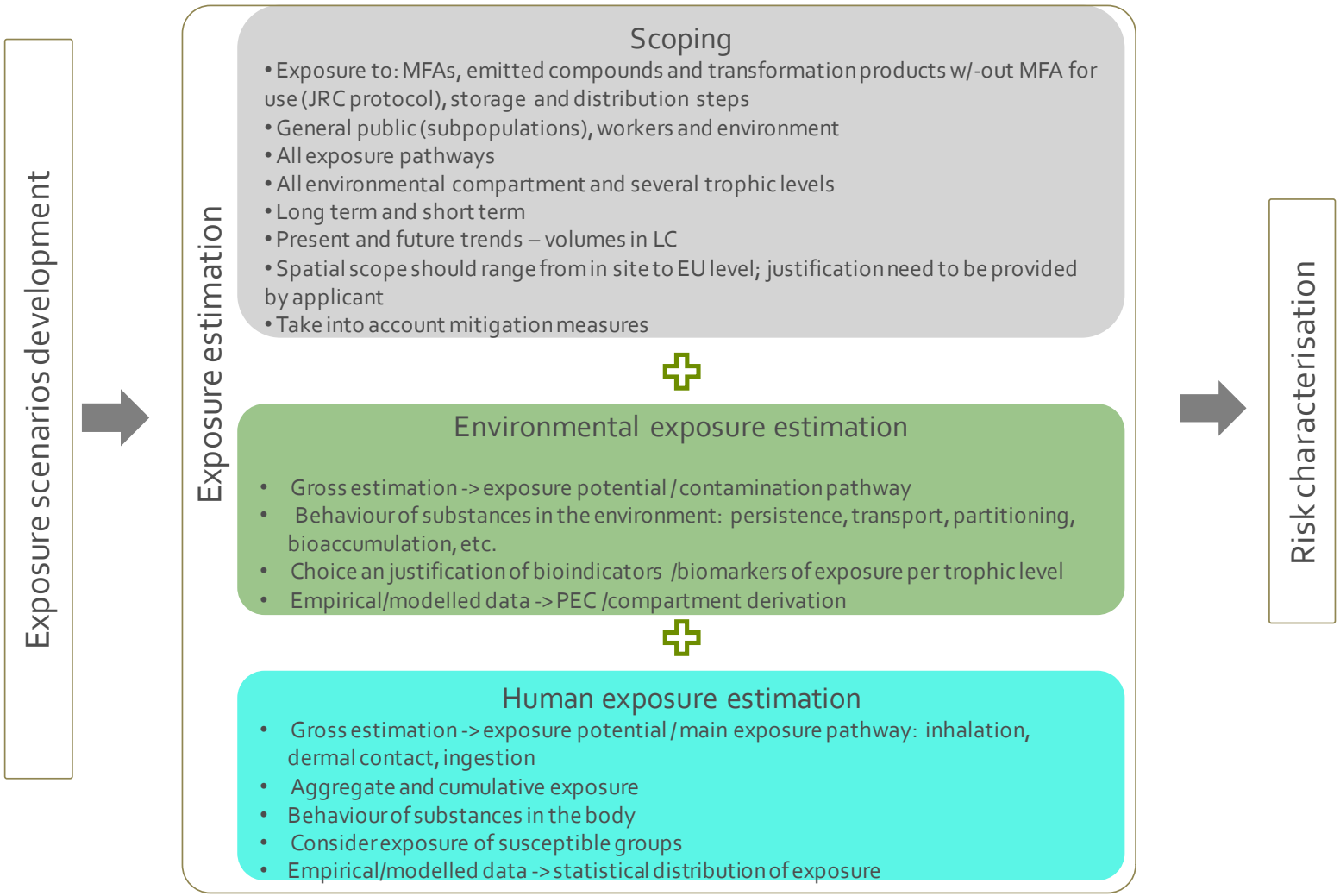


Figure 7: Key steps for exposure assessment

- **Scope**
  - This step should describe possible exposure pathways to MFAs products, emitted compounds and transformation products in the distribution, storage and use phase (from combustion in vehicle engine) as defined in the JRC protocol and the emissions characterisation step of this document. The natural occurrence of the metal additive particles in the environment, and the use of the metal (or other substances contained in the MFA product or derived by its combustion) in other industrial applications needs to be considered (as background concentrations) when assessing exposure and related risks, in order to obtain a picture of the total exposure and the importance of additional exposure through MFA.
  - The spatial scale range from onsite to EU level, depending on the specific MFA, its behaviour in the environment, and the considered exposure situations per life cycle step. Geographic scale and specific location needs to be considered since the concentration of pollutants changes with distance from pollution source[60] and since different categories of populations can be concerned[61]. In particular, both indoor and outdoor environments must be considered.
  - The time scale chosen for this step needs to be justified depending on the ability of the specific MFA and its associated substances (see first point of the scope) to have a relatively long or short half-life in the environment. In this respect, the applicant must consider information such as the persistence, degradation and biodegradation characteristics of a given MFA and associated substances. Both **long and short-term exposure** should be assessed.
  - The applicant will be required to consider both the **potential exposure for aquatic (freshwater and groundwater) and terrestrial environmental sphere** (and at least 3 trophic levels within these compartments) **and for relevant human groups** (general public, occupational exposure groups, sensitive groups).
  - Should the applicant consider that a particular compound presents no hazard, one's must provide evidence for waiving consideration when performing the exposure assessment of that particular compound. Otherwise, the default position is that an exposure analysis is needed for any potentially hazardous emission associated with a MFA.

[60] For example: an exposure zone within a range of 500 m from a major road is the area most highly affected by traffic emissions; air borne pollutant concentrations vary with height over ground; soil concentrations decrease both with depth and distance from roadways. This would explain why the highest concentrations in air as well as in soil are generally found in urban locations and especially in road canyons, the highest concentrations are typically found in the inner city.

[61] Specific demographic groups of the population may be more or less exposed, e.g. minorities and the poor, due to localisation patterns. Similarly occupational exposure may be high on site, compared to a more diffuse distribution of the compounds in the environment.

4.6.1 Exposure scenario development

Objectives

This section aims to provide instructions on how develop exposure scenarios[62] which describe qualitatively the potential exposure for both humans and the environment all along the life cycle of MFAs and related products. In particular, secondary by-products, associated to the different steps of the life cycle (processing, manufacturing, distribution and storage, use, disposal) must not be neglected[63]. One or more selected exposure scenarios will serve as a starting point to set a strategy for the quantitative estimation of exposure[64].

Sources of information

Exposure scenarios can be developed based on the conclusions drawn from the emission data collected in the emissions characterisation step, physicochemical data contributing to a better knowledge of the substances behaviour in the environment, and literature sources, as well as information collected on operational conditions and existing risk management measures in all life cycle stages of the substance.

Nature of data to be retrieved or produced

- The scenarios should include a baseline scenario and a worst case/conservative scenario.
- This step needs to consider present and future (10 years) trends of emissions at each step of the life cycle, accordingly with market projection data.
- The exposure scenarios have to cover human exposure (of general public and occupational[65]) and environmental exposure throughout all life cycle steps and the relevant environmental spheres. In particular, the waste stage must be considered, although it is often omitted from a life cycle view of fuel additives, because fuels and additives are usually considered "consumed" in the use phase. As experienced with the organic FA methyl tertiary butyl ether (MTBE) has shown, the storage and distribution phases of the product life cycle can also be critically important and possibly even overshadow concerns about emissions and

[62] In this context, guidance related to REACH is available on ECHA website: echa.europa.eu/web/guest/guidance-documents/guidance-on-reach [Accessed online 04/05/2012]

[63] For example, biosolids such as sewage sludge could potentially be spread in fields as a fertilizer and MFA substances could in this way reach food products, although levels of contaminants in sewage sludge used in this way are normally closely monitored.

[64] Specific guidance is available in the following document: ECHA (2009) Guidance in a Nutshell Chemical Safety Assessment. Available online at: echa.europa.eu/documents/10162/13632/nutshell_guidance_csa_en.pdf [Accessed online 04/05/2012]

[65] In the marketing/distribution and transport steps, employees facing elevated exposure to airborne MFA include individuals who work in or near urban canyons, and toll booth attendants.
In the use step, the people residing or undertaking activities close to the distribution points are more likely to be exposed. Most parts of the population could potentially be exposed in one way or the other to emissions from the use step, at least in urban environments, including e.g. sensitive groups in the general population, e.g. infants, pregnant women, asthmatics, and elderly people. Exposed population especially includes car owners, individuals who live or work in e.g. offices near urban highways, taxi drivers, and garage mechanics, toll booth attendants, etc.
Murgueytio, A. M.; Evans, R. G.; Sterling, D. A.; Clardy, S. A.; Shadel, B. N.; Clements, B. W. (1998) Relationship between lead mining and blood lead levels in children. Arch. Environ. Health 53: 414-423.

exposure during usage (Davis& Farland, 2001)[66]. Although releases from underground storage tanks (USTs) in Europe have not been as prevalent as in the U.S[67], monitoring in groundwater in the UK and Germany have shown significant concentrations of MTBE[68].

Some exposure scenarios might be partially controlled through existing regulatory frameworks (e.g. legislation on occupational exposure). Their efficiency need to be discussed by the applicant.

- The applicant will be required to qualitatively consider at this step the **different potential exposure pathways** (detailed in the following sections). Annex 1.2.B discusses the predominant routes of exposure.
- When estimating exposure, the applicant will need to take into account the **operational conditions**, such as duration and frequency of use, amount of substance employed, concentration of substance in a product, and process temperature. It could also consider specific **characteristics of the considered exposed environment** (e.g. seasonal and weather variability, precipitation trends, wind direction; presence of other sources of metal particles in the exposed environment[69]) and set up relevant boundaries. The applicant will have to provide a justification for the **boundaries** defined. This will permit to define the **nature** (e.g. mechanics, truck drivers, employees at the manufacturing site) **and size of the exposed population / ecosystems**, the **time and frequency (single, continuous) of exposure** (e.g. presence of workers in site, time spent by the users in gas station) and potential exposure in **microenvironments**, e.g. in a "closed" space (e.g. between high buildings), or more open spaces the expected working/ exposure conditions (e.g. whether outdoors, ventilated, or indoors).
- Based on their physicochemical characteristics (i.e. Long-range transport properties) and their behaviour in the environment, can these substances enter soil, water, or other environmental spheres?
- What are the existing risk management measures (e.g. local ventilation, air filtering systems, wastewater treatments, personal protection equipment)? In many cases the staff working at R&D as well as manufacturing sites is limited in number, educated about the potential health effects of the MFAs, and possessing the means to use adequate protective equipment. The applicant is required to consider a worst case scenario along with the baseline scenario and to justify the underlying assumptions.
- The applicant is required to discuss the possible factors influencing uncertainty which will be estimated in the following step. For instance, in estimations of

[66] Davis, J. M.; Farland, W. H. (2001) The paradoxes of MTBE.Toxicological Sciences, 61: 211-217,
[67] 2001 A.D. Little Report to the EC
[68] Schirmer et al., Groundwater Quality: Natural and Enhanced Restoration of Groundwater Pollution [Proceedings of the Groundwater Quality 2001 Conference held at Sheffield, UK. June 2001]. IAHS Publ. no. 275, 2002)
[69] For example, metals in indoor air can be related to house dust or to contaminated soil, as has been observed in the case of lead. *US Environmental Protection Agency, National Center for Environmental Assessment-RTP Division, Office of Research and Development, (2006) Air Quality Criteria for Lead Volume I , October, EPA/600/R-05/144aF)*

concentrations of MFA or related products in the air, meteorological conditions are of importance. This will unavoidably introduce a level of uncertainty regarding to what extent the experimental results will represent the real life situation in different conditions (and the exposure scenario).

- **Output**

A set of initial exposure scenarios which need to be prioritised by the applicant in order to set up a strategy to quantitatively describe the exposure in the next section, notably the expected range in which measures will need to be taken. Some exposure scenarios may be specific to particular MFAs, whereas other scenarios may be common to a variety of MFAs. For example, exposure scenarios related to usage could be similar across different MFAs, but exposure related to production could vary for different MFAs. The applicant is required to clearly identify the relevant exposure scenario(s) and justify its choice.

4.6.2 Environmental fate and ecological receptor exposure estimation

- **Objectives**

The environmental exposure needs here to be estimated for each selected exposure scenario to characterise the risk for ecosystems.

- **Sources of data**

The applicant is expected to produce or collect both empirical data from dedicated monitoring or results from modelling, with a preference for the former.

- **Type of data to be retrieved or produced**
  - The applicant must describe **the fate and behaviour** of the considered substance in each environmental sphere, (based on information collected in the hazard assessment section 4.5.2). This includes information on the substance's:
    - partitioning and reactivity in the ecosystem (adsorption/desorption, immobilisation/mineralisation, dissolution/precipitation, oxidation/reduction);
    - bioaccumulation ability: since metallic substances are not degraded in the environment or living organisms, they can accumulate to higher levels in the long-term. Accumulation is especially common in soil, sediments, and certain types of living tissue.
    - persistence (biodegradation/metabolism); and
    - long-range transport potential

Annex 1.3.D presents a rough description of the possible fate and behaviour of MFA in water and soils.

- Based on these results, the emissions characterisation, and the exposure scenarios, the applicant can estimate the gross exposure potential for terrestrial

and aquatic (ground water and freshwater) ecosystems. Based on this gross exposure potential, the applicant may define relevant protocols of monitoring or modelling.

- The gross exposure potential will permit applicants to choose relevant biomarkers of exposure for each trophic level to be monitored in the ecosystems/compartment of interest. For example, fish biomarkers used to assess exposure to or effects of environmental metal pollution on aquatic ecosystems include metallothioneins (MTs), haematological parameters, immunological parameters, reproductive and endocrine parameters, histological and morphological parameters (Van der Oost, 2003)[70]. Biomarkers may also include oxidative stress, cytotoxicological responses such as genotoxicity, lysosomal alterations, immunocompetence and cholinesterase activities, etc.[71] Annex1.3.E provides further details on biomarkers and biomonitoring for aquatic metal pollution.
- The results of monitoring will need to be presented highlighting the uncertainties, and discussing to which extent there is a causal relationship between the marker and the level of exposure specifically due to MFA and related substances. Other sources (natural and anthropogenic) could indeed confound the relationship. For example plants can serve as markers of exposure related to metallic particles, assuming that naturally occurring levels or levels due to different human activities, if any, can be distinguished from other sources of the MFA-related substances themselves. Moreover, many factors may affect the bioavailability of metals to plants, such as ambient metal concentrations, pH of soil or water, concentration of ligands, competition with other metals for binding sites, and mode of exposure. For example, water acidification affected aquatic plant concentrations of some metals and was especially important in submerged pondweed (Sparling & Lowe, 1998)[72]. The results of monitoring of biomarkers must therefore be considered with care by the applicant.

Output

Calculation of predicted environmental concentration (PEC, in mg/L) for each relevant receiving environmental sphere. PEC values should be based on conservative assumptions. Conservative assumptions include limited atmospheric dispersion, limited soil attenuation or other losses. Similarly, the effects of dilution, mixing and sedimentation which are likely to occur in receiving waters and may decrease the risk posed by the substance may not be taken into account. The assumptions underlying the derivation of PEC must be transparent and justified.

[70]R. van der Oost, J. Beyer, N.P.E. Vermeulen, Environ. Toxicol.Pharm. 13 (2003) 57.
[71]Qunfang Zhou, Jianbin Zhang, Jianjie Fu, Jianbo Shi, Guibin Jiang (2007);Biomonitoring: An appealing tool for assessment of metal pollution in the aquatic ecosystem; State Key Laboratory of Environmental Chemistry and Ecotoxicology, Research Center for Eco-Environmental Sciences, Chinese Academy of Sciences, Beijing 100085, China; analytica chimica acta 6 0 6 (2 0 0 8) 135–150
[72]Sparling, D.W. Lowe, T.P.(1998) Metal concentrations in aquatic macrophytesas influenced by soil and acidification.Water, Air, Soil Pollut.108:203-221.

The PEC could then be compared to the PNEC obtained in the hazard assessment to derive the risk characterisation.

4.6.3 Human exposure estimation

- **Objectives**

The human exposure needs here to be estimated for each selected exposure scenario to characterise the risk for all human populations liable to exposure.

- **Sources of data**

The applicant is expected to produce or collect both empirical data from dedicated monitoring or results from modelling[73], with a preference for the former. Exposure data are often collected for worker populations before general population studies are conducted, and thus occupational studies may provide information that can be used in estimating exposure and effects in the general population.

- **Type of data to be retrieved**

  - In the case of MFAs for which limited information exists, basic data such as production volumes or other gross indicators of usage previously collected can be used in estimating gross exposure potential. This could be used in prioritising various MFAs or exposure pathways for more detailed investigation or assessment efforts. The gross exposure potential can be influenced at least by the following factors which must be taken into account by the applicant:
    - meteorology (e.g. wind speed, precipitation, mixing layer height);
    - topography/geography of the considered site (e.g. street canyons, terrain, elevation);
    - various metrics related to vehicle characteristics (e.g. the proportions of vehicle/engine types, emission rates, traffic density, average speed and distance travelled) when considering the use life cycle step;
    - fuel characteristics (e.g. co-constituents, variations in allowable vs. actual MFA concentrations);
    - ambient background levels of the metal in a given MFA (e.g. from both crustal and anthropogenic sources).
  - Although studies often focus on the inhalation route of exposure, the potential for oral, dermal, and ocular exposure should also be considered in a

[73] For instance applying probabilistic sampling techniques as in E. D. Pellizzari, C. A. Clayton, C. E. Rodes et al., "Particulate matter and manganese exposures in Toronto, Canada," Atmospheric Environment, vol. 33, no. 5, pp. 721–734, 1999.;

comprehensive assessment if considered relevant based on the gross estimation[74]. A comprehensive assessment should include:

- inhalation of MFA product vapours during handling, pre-combustion and pre-use (mostly occupational exposure but also including other high exposure scenarios such as hobby mechanics);
- inhalation of several emitted substances upon combustion of the additive-containing fuel in a vehicle's engine. This should be considered an important scenario, and both occupational groups and the general public can be expected to be exposed;
- dermal/ocular contact, directly (through spills) or indirectly (contact with soil), with the un-combusted MFAs. Based on the section 4.4 and as a general assumption for MFAs, these releases are expected to be relatively small except in the case of major accidents. Yet, past experience has shown that accidental releases are almost certain to occur and such events need to be acknowledged and included at least qualitatively; and
- ingestion via contaminated food/feed, water or soil[75].

- The applicant must describe the fate and behaviour of the considered substances in the body[76], based on information collected in the hazard assessment (section 4.5.3), experimental data (in vivo) and/or existing pharmacokinetic models[77] across the exposure routes as obtained by the exposure scenario development. This step will permit to identify:
  - tissues concentrations;
  - factors influencing uptake and elimination rates;
  - delivery to key organs; and
  - relationship between environmental concentration and organ/tissue concentrations[78].

Annex 1.3.F highlights the different mechanisms at stake.

[74]For example, releases of an MFA during distribution or storage could contaminate water supplies used for drinking, cooking, and bathing. If so, ingestion and dermal exposure would need to be included as part of a comprehensive exposure assessment of the MFA, along with inhalation exposure to evaporative and combustion emissions.
[75]For example, contaminated soil can be directly ingested through hand-to-mouth behaviour common in children. *Lanphear, B. P.; Hornung, R.; Ho, M.; Howard, C. R.; Eberly, S.; Knauf, K. (2002) Environmental lead exposure during early childhood. J. Pediatr. 140: 40-47.*
[76]Knowledge of the MFAs and relevant combustion products' fate once in the body is a key factor to understand their likely effects.
[77]As done for instance in Dorman D. et al. (2012). David C. Dorman, Melvin E. Andersen, Jerry M. Roper, and Michael D. Taylor(2012), Update on a Pharmacokinetic-Centric Alternative Tier II Program for MMT—Part I: Program Implementation and Lessons Learned. Journal of Toxicology, Article ID 946742, 10 pages.
[78] For instance the applicant could measure the blood metal concentration in exposed sub-populations comparison before and after the introduction of the MFA in the assed area.

- The applicant shall describe the relationship between the dose at which a specific human sub-population is or might be exposed, the frequency and the duration of exposure and the kinetic in the body which might be influenced by homoeostatic control systems.
- If available, the applicant could provide statistical distributions of epidemiological data[79].

  The applicant at this step should also consider specific vulnerable subpopulations such as the young and the elderly.
- Both aggregate exposure[80]from multiple sources of a given contaminant and cumulative exposure to multiple contaminants from a single source must be considered.
- Comprehensive exposure assessment should characterise not only typical or "average" personal exposure scenarios and conditions but should also include "high-end" exposures[81], or in other words "the highest level of exposures that could be expected to occur within a given population".

Output

The output will be an exposure concentration calculated for each relevant exposure pathway. The estimated exposure should then be compared to the results of the hazard assessment (e.g.

[79]Few studies capable of providing such empirical data in connection with MFAs have been conducted because of the complexity and expense of such studies. Other than large-scale epidemiological studies or surveillance programs to measure blood lead (PbB) levels in populations exposed to Pb from tetra-ethyl Pb in petrol and other sources (e.g. Pirkle JLet al., 1994), the only probabilistic personal exposure studies relative to an MFA have been focused on manganese (Mn) in relation to the use of MMT® in gasoline in North America (e.g. Pellizarri et al., 1999). Given the long history of MMT® usage and both the regulatory and scientific activities surrounding its use (EPA, 1994; Davis, 1998), it arguably provides the best available illustration of the types of probabilistic personal human exposure data that could be used in a quantitative inhalation exposure assessment of an MFA. Even so, extrapolating from data obtained under conditions in North America to European conditions (which in themselves are varied) would involve further effort, such as developing predictive models. Furthermore, as the 1994 EPA assessment illustrates, modelling of personal exposure levels can involve numerous inferences and assumptions even when personal exposure data (collected for other purposes and/or other locations) are available.

Davis, J. M. (1998) Methylcyclopentadienyl manganese tricarbonyl (MMT): health risk uncertainties and research directions. Environmental Health Perspectives 106 (Supplement 1): 191-201

Davis, J. M., Jarabek, A. M., Mage, D. T., & Graham, J. A. (1998).The EPA Health Risk Assessment of Methylcyclopentadienyl Manganese Tricarbonyl (MMT). Risk Analysis, 18(1), 57-70. doi:10.1111/j.1539-6924.1998.tb00916.x

Pellizzari, E.D., Clayton, C.A., Rodes, C.E., Mason, R.E., Piper, L.L., et al. (1999).Particulate matter and manganese exposures in Toronto, Canada. Atmospheric Environment, 33 (5):721-734.

Pirkle JL, Brody DJ, Gunter EW, Kramer RA, Paschal DC, Flegal KM, Matte TD. (1994) The decline in blood lead levels in the United States. The National Health and Nutrition Examination Surveys (NHANES). JAMA. Jul 27;272(4):284-91

U.S. Environmental Protection Agency (1994) Reevaluation of Inhalation Health Risks Associated with Methylcyclopentadienyl Manganese Tricarbonyl (MMT) in Gasoline. Office of Research and Development, U.S. Environmental Protection Agency, Research Triangle Park, NC, EPA report no. 600/R-94/062

[80]For some MFAs, in addition to the use of the MFA in vehicles sources of emission can include smelters and incinerators for example as well as dietary sources (e.g. for Fe and Mn).

[81]High-end exposures refer to the upper end or tail of a distribution, which often is arbitrarily described as the 90th, 95th, or even the 98th or 99th percentile of a distribution. It is important to keep in mind that even though such high-end exposures are relatively uncommon, the absolute numbers of individuals in question could be quite large. To illustrate, for a population of 500 million people (roughly that of the European Union), the 98th percentile would comprise around 1 million persons.

DNEL) to derive the risk characterisation for threshold effects. Conclusions need to be drafted as well for exposure leading to non-threshold effects.

The precision and accuracy of such estimates based on the conjunction of empirical measurements of emissions or environmental levels with exposure models can vary greatly depending on the quality of the input data and the uncertainties and assumptions associated with the models employed. Whether or not estimates of this type can support quantitative risk assessment is a question that the applicant would have to answer on a case by case basis.

Results can be presented in the form of reporting templates (e.g. Annex 1.3.F).

4.7 Risk characterisation

Objective

This chapter provides guidance on how to perform a risk characterisation (Figure 8). Risk characterisation has to be performed by comparing the expected levels of exposure to the predicted no effect levels from the hazard assessment for both humans and the environment (DNEL/DMEL or PNEC). The ratio between exposure and no effect levels will provide a rough measure of the risk and an indication of (a) whether a more refined risk assessment is needed and/or (b) whether or not steps to reduce or manage risks are appropriate.

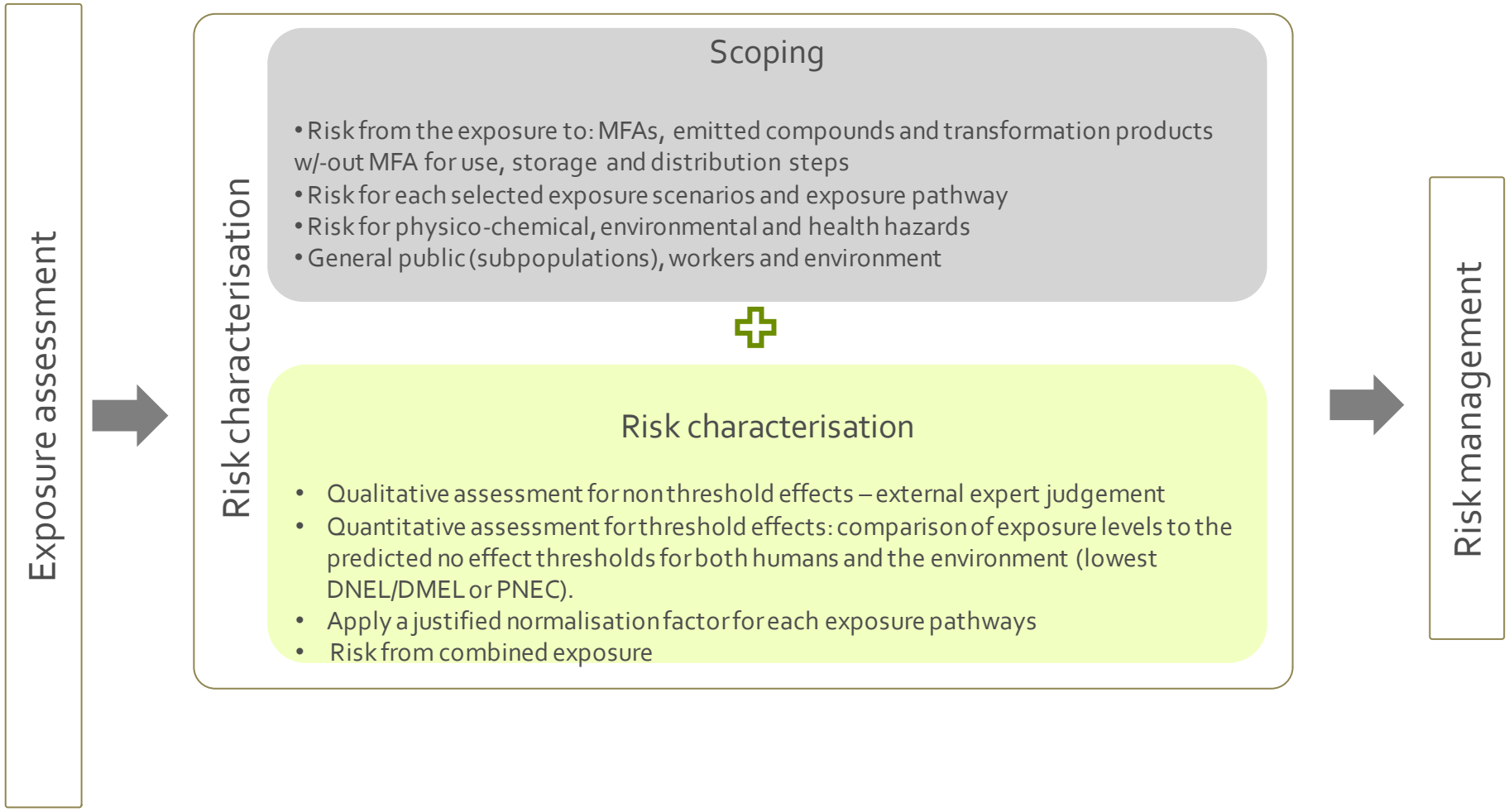


Figure 8: Key steps for risk characterisation

- **Scope**
  - It is important to compare the risk due to the presence of MFAs, emitted compounds and transformation products using fuel with and without MFA in use (accordingly to the JRC protocol), distribution and storage step.
  - Risk characterisation needs to be carried out for each relevant exposure scenario, taking into account the operational conditions and possible risk management measures. In the case of fuel metallic additives the most relevant exposure scenarios might be those related to the emissions in the use phase of the life cycle (see section 4.6.1).The relevant exposure scenarios need to be chosen by the applicant on a case-by-case basis. This selection need to be justified.
  - The risk characterisation should be done for the physicochemical hazards, human health and the environment.
  - The risk characterisation should be done for the general public, including vulnerable sub-populations, workers and the environment.
- **Nature of data to be retrieved or produced:**
  - **Risk characterisation for physicochemical hazards**
    - The identification of the physicochemical hazards will permit the evaluation of the probability that the substance is at the origin of a dangerous event (risk of explosion, fire, etc.). MFAs have to be assessed for the associated risk of explosion, flammability and oxidising potential, notably if during the hazard assessment (section 4.5) the applicant has underlined conditions for accidental events[82].
    - Following the evaluation of physicochemical risks, the applicant will provide conclusions on whether the life cycle of the MFA is at an origin of a significant risk or not and if further risk reduction measures are required.
  - **Risk characterisation for human health**
    - Compare the estimated exposure level for all the relevant exposure scenarios and associated exposure patterns with the lowest DNEL/DMEL available – for the threshold and non-threshold effects.

[82] An example is the iso-octane (2,2,4 trimethylpentane or TMP) used in gasoline, which is not an MFA per se but relates to HF acid. This acid is highly caustic and has been involved in the past with accidental releases having serious ecological consequences. It has been noted that increasing TMP in order to compensate the decrease in MTBE additive (or other sources of octane) could result in more accidental releases of HF, transported by tank trucks or rail cars in the U.S. (Mike Davis, personal communication).

- This step will permit to determine the Margins of Exposure (MoE) for the threshold effects[83], which represent uncertainties and allow ensuring general public safety.
- The applicant need to evaluate if the obtained MoE are considered adequate to account for uncertainties in the data set, the reliability of exposure scenarios and the possible interspecies normalisation factors, considering as well the possible conservative approach taken to calculate the exposure and critical effect levels. Moreover, the MoE values for general population can be different from specific classes of public, e.g. children who could ingest MFA contaminated soil which may present an additional exposure route. All this aspects need to be discussed and justified by the applicant.
- In cases in which a quantitative estimation of risk cannot be performed (e.g. for non-threshold health effects like mutagenicity), a DMEL or a qualitative assessment has to be performed. In these cases, it is not possible to compare if the non-threshold health effect is less or more critical than other effects for which a DNEL can be derived. Thus two separate risk assessment need to be performed: one quantitative or semi-quantitative and one qualitative. When deciding if the risk poses low, medium or high concern an expert judgement is required. The two assessments will have to demonstrate control of risks.

Risk characterisation for the environment

- The quantitative characterisation of the environmental risk is performed comparing the Predicted Exposure Concentration (PEC) for all the relevant exposure scenarios, or the observed concentrations, with the Predicted No Effect Concentration (PNEC) which is the environmental exposure threshold (Cf. Section 4.6). This is done separately for each environmental sphere at the chosen scale according to the relevant exposure scenario[84].
- In cases where a quantitative estimation of environmental risk cannot be performed (e.g. for persistent additives) an alternative is to carry out a qualitative assessment. In these cases it is not possible to

[83] For instance, Margins of exposure allow assessing the risk posed by dermal exposure to zinc BDBP in the use phase when added to motor oil. The comparison of the lowest observed effect level ((LOEL)= 884 mg/kg-bw/day (rabbits)) and the estimated maximum exposure through the environment (which is of the order of magnitude of 10^{-3} µg/kg-bw/day)shows a difference (Margin of exposure) of an order of magnitude of 10^{8}. The comparison with dermal exposure levels for the consumer (which is 0.858 mg/kg-bw, according to an exposure scenario consisting of adding the product to motor oil) instead of maximum exposure through the environment shows a difference of the order of 10^{30}. One can consider that such differences cover the possible uncertainties related to individual differences and are thus considered sufficient to ensure general public safety (U.S. EPA IRIS database: www.epa.gov/iris/).

[84] For instance, if according to the presented scenario a predicted environmental concentration (PEC) for aquatic pelagic organisms of 0.0153 mg/L and a long-term (chronic) predicted no-effect concentration (PNEC) of 0.017 mg/L are derived, the resulting risk quotient (PEC/PNEC) is = 0.9. Given the conservatism in the derivation of both the PEC and PNEC, this result indicates that harm to pelagic aquatic organisms is unlikely (U.S. EPA IRIS database: www.epa.gov/iris/).

determine if the adverse effect considered is less or more critical than the other ones for which a PNEC can be derived. Thus two separate risk assessment need to be performed: one quantitative or semi-quantitative and one qualitative[85]. When deciding if the risk poses low, medium or high concern an expert judgement is required. The two assessments will have to demonstrate control of risks.

- **Conclusions and discussion**

  - Following the evaluation of the physicochemical, human health and environmental risks, the applicant will provide conclusions on whether the use of the MFA poses risks and, if so, what risk reduction measures would be effective in addressing such risks. In this case the exposure of both environment and humans need to be re-evaluated considering the application of the new risk management measures. The exposure scenario that ensures that risks are under control is called the **final exposure scenario.** Another option would be to improve the hazard assessment by obtaining more data to reduce the uncertainties added by safety factors and see if the risk is still significant.
  - The applicant needs to present and discuss all the uncertainty factors influencing the final conclusions of the risk assessment, being general or specific to MFAs. Some of these aspects can be presented in the previous step of the assessment, but a summary is needed in this final step. The uncertainty factors to be discussed will include at least:
    - intra- and inter-species variability, in terms of anatomy and physiology between animal models and humans which impact the toxicological significance of the absorption pathway;
    - normalisation factors used to derive the exposure of specific subpopulations;
    - micro-environments of exposure (e.g. high-traffic urban areas)
    - potentially limited data availability concerning combustion products (characterisation, exposure and effects);
    - extrapolate to other combustion by-products[86];
    - general uncertainty related to potential differences in toxico-kinetics and potential toxicity of different combustion products;
    - risks from combined exposures via different routes or via different sources; and

[85] As an example of qualitative estimation, the US EPA identifies a medium potential that aquatic organisms might be exposed to the environmental releases of zinc-based fuel additives, which are highly persistent and present low potential for bioaccumulation. These characteristics in combination with the low acute toxicity to aquatic invertebrates and aquatic plants for these chemicals indicate a low concern for potential risk from environmental releases (US EPA. (2008). Supporting Documents for Initial Risk-Based Prioritization of High Production Volume Chemicals, 1-42).

[86] By-products can be extremely different compounds presenting for instance difference in solubility which might affect their availability to humans and living organisms.

- differences in local use patterns for metallic additives.

Table 1 provides a schematic summary of the risk assessment steps and the possible outputs.

Table 1: Risk assessment step summary and possible outputs

Risk assessment step	Sub-steps	Qualitative assessment	(Semi) quantitative assessment	Risk under control?	Additional risk management measures required
Physicochemical risk	Explosion potential; Oxidising potential; Flammability; Bioaccumulation; Persistence	Low/Medium/High considering the control measures in place	-	Yes* / No	Yes (the exposure has to be re-evaluated including the new risk management measures) / No
Human health	Non threshold effects or other not quantifiable effects	Low/Medium/High considering the control measures in place	DMEL when possible	Yes* / No	Yes (the exposure has to be re-evaluated considering the new risk management measures) / No
	Threshold effects	-	> lowest DNEL < lowest DNEL	Yes / No	Yes (the exposure has to be re-evaluated considering the new risk management measures) / No
Environment	Non Quantifiable effects	Low/Medium/High considering the control measures in place	-	Yes* / No	Yes (the exposure has to be re-evaluated considering the new risk management measures) / No
	Quantifiable effects	-	PEC/PNEC>1 PEC/PNEC<1	Yes / No	Yes (the exposure has to be re-evaluated considering the new risk management measures) / No
*= for medium and high categories					

4.8 Risk management

Objective

Risk assessment characterizes the potential for adverse impacts on human health and ecological receptors; risk management uses risk assessments as input in deciding what actions, if any, to take in addressing such potential impacts. In the case of MFAs, risk management is typically a process of finding a balance between the benefits and risks of these substances. Given that the present assessment methodology calls for comparative evaluation of fuels formulated with and without a given MFA, the information afforded risk managers should enable them to better judge the risk-benefit trade-offs of a MFA in relative terms since risk management is inherently a matter of making choices among different options[87].

Aspects to be considered in the process

Clear and complete information on the potential comparative benefits and risks of MFAs facilitates the task of risk management, but in practice the amount and quality of information available for both the risk assessment and risk management processes often fall short of the ideal[88]. The greater the uncertainties in characterising the risks and benefits of a MFA, the more likely that the risk management process will involve policy considerations or other value judgments more so than weighing trade-offs in a strictly technical sense. Both technical and value judgments are part of risk management decisions, but the relative dominance of one or the other can vary depending on the quality of the risk assessment, the societal significance of the issue under consideration, the requirements of legislative mandates, and other factors.

Thus, it is important for the risk management process that risk assessments of MFAs be as comprehensive, transparent, and rigorous as possible.

Management actions

Demonstrated benefit-risk relationship:

Various courses of action could conceivably be invoked in the risk management of MFAs. To illustrate with a simplified case, if the putative benefits to society of a MFA are "low" (e.g., marginal improvement in particulate emission reductions or in engine performance) and potential risks are relatively "high" (e.g., likely

[87] As an analysis of these and other illustrations has shown (Late Lessons from Early Warnings: The Precautionary Principle 1896-2000, European Environment Agency, Luxembourg (2002), http://www.eea.europa.eu/publications/environmental_issue_report_2001_22), the joint efforts of risk assessment and risk management might not provide a guarantee of averting unintended consequences, but if lessons can be learned from past experience and applied to future issues, it may at least be possible to "increase the chances of anticipating costly impacts, of achieving a better balance between the pros and cons of technological innovations, and of minimising the costs of unpleasant surprises."

[88] By having a comprehensive risk assessment available to the risk manager, the risk management process can be facilitated and thereby used to reduce the potential for unintended consequences, a problem that has occurred not only with metallic fuel additives (e.g., tetra-ethyl lead) but with other fuel additives (e.g., MTBE) and technological innovations (e.g., asbestos). (e.g., Rosner D, Markowitz G. A 'gift of God'?: The public health controversy over leaded gasoline during the 1920s. Am J Public Health. 1985 Apr;75(4):344–352) and oxygenates (e.g., Goldstsein B, Erdal S. Methyl tert-butyl ether as a gasoline oxygenate: lessons for environmental public policy. Ann Rev Energy Environ, 2000 25: 756-802).

impacts on morbidity in humans or reduced viability of certain indicator species of ecological health), then presumably the risk management decision would lean toward not allowing the use of such an additive or, if allowed, to the adoption of mitigation actions such as those listed below.

- **Uncertainties in the risk-benefit relationship:**

  When the trade-offs between benefits and risks are less clear-cut, the risk manager might consider a wide range of possible actions, including but not limited to requiring that more or better information be generated through research or testing to assist in a reiteration of the risk assessment process.

- **Mitigation actions**

  The number of strategies available to a risk manager to mitigate risks will depend on societal, legal, and technical constraints. Assuming a risk manager has a legislative or legal mandate to act, more than one technological option might be available to help reduce certain risks. For example:

  - The trade-offs between risks and benefits could be optimized by requiring a lower maximum concentration of an MFA than initially proposed or used.
  - Undesirable emissions could be reduced through the addition or improvement of suitable control technologies such as particle traps or other vehicular components.

  Specific choices among possible options available to risk managers would necessarily be based on detailed consideration of the technology itself and the key risk issues to be addressed.

4.9 Summary of the key steps

- **Step 1: Emissions during life cycle**
  - **Scoping**
    - Substances: MFAs, emitted compounds and transformation products with and without MFA during use (JRC protocol), storage and distribution.
    - Spatial scale: from in site to EU level (justification need to be provided by applicant)
    - Time scale (representative of the life-cycle)
  - **Handling conditions and contamination pathways**
    - Description of handling conditions at each step of the life cycle
    - Identification of safety procedures or mitigation measures taken accordingly to EU / legislation at each step of the life cycle
    - Description of contamination pathways
  - **Estimation of emissions and reporting**
    - Experimental estimation of the quantity and quality of emissions
    - Modelled estimation can be applied, presenting assumptions and expected uncertainty.
- **Step 2: Hazard assessment**
  - **Scoping**
    - Substances: MFAs, emitted compounds and transformation products with and without MFA during use (JRC protocol), storage and distribution if relevant emissions are detected.
    - Concentration ranges to be tested in coherence with the results of the emission phase.
    - Collection or production of data obtained on the basis of internationally recognised protocols
  - **Physical and chemical hazards, bioaccumulation potential and persistence**
    - Physical state; elemental speciation; melting point (°C);boiling point (°C);density (Kg/m3);vapour pressure (Pa) ;water solubility; octanol-water partition coefficient: Log Kow; organic carbon partition coefficient: Log Koc; data (experimental or QSAR) on environmental persistence and bioaccumulation (BCF).
  - **Human health hazards**
    - In vitro testing of: viability; cytotoxicity ; oxidative potential; inflammation ; mutagenicity and genotoxicity.
    - In vivo testing (oral, dermal, inhalation): acute toxicity; chronic and sub-chronic toxicity; developmental and reproductive studies; local effects of

sensitisation; systemic effects of acute or repeated exposure studies (chronic and sub-chronic); pathological alteration of specific organs, oxidative stress; urine analysis; alteration of some enzymatic activities or blood composition.

- Epidemiological studies when available
- Determination of dose descriptors (e.g. DNEL in the case of threshold effects or DMEL when no DNEL can be derived), for different exposure pathways
- In case of non-threshold values qualitative classifications of the weight of evidence regarding hazard.

Environmental hazards

- Data on aquatic and terrestrial ecosystems
- Data on at least three trophic levels: viability of target species, potential effects on growth (e.g. EC50 growth), development, and reproduction. For plants, root growth, and germination timing.
- Determination of dose descriptors (e.g. PNEC) in the case of threshold effects, for each compartment
- In case of non-threshold values qualitative classifications of the weight of evidence regarding hazard.

Step 3: Exposure assessment

Scoping

- Substances: MFAs, emitted compounds and transformation products with and without MFA during use (JRC protocol), storage and distribution if relevant emissions are detected: exposure scenarios can be selected.
- Spatial scale: from in site to EU level (justification need to be provided by applicant)
- Compartments and populations considered in hazard assessment
- All possible exposure and contamination pathways
- Time scale: long term and short term exposure

Exposure scenario development

- Identification of present and future (10y) trends in volumes over the life-cycle
- Determination of operational conditions, characteristics of the exposed environment and micro-environments, and risk management measures
- Determination of the nature and size of general and occupational population exposed and the environmental spheres
- Estimation of the frequency of exposure (e.g. single, continuous)
- Identification of exposure routes (e.g. dermal, inhalation, oral)
- Development of baseline and worst case scenarios based on current and

future trends of emissions at each step of the life-cycle, the efficiency of regulatory frameworks and the exposure pathways.

- Prioritisation of the scenarios for further assessment

- **Environmental fate and ecological receptor exposure estimation**
  - Gross estimation of the exposure potential for terrestrial and aquatic ecosystems per main contamination pathway
  - Choice and justification of biomarkers of exposure per trophic level
  - Calculation (based on empirical or modelled data) of PEC for each relevant compartment
- **Human exposure estimation**
  - Gross estimation of the exposure potential per main exposure pathway: inhalation, dermal contact, ingestion
  - Characterisation of the fate and behaviour of substances in the body.
  - Description of the interactions between doses, frequency/duration of exposure and kinetics in the body, including aggregate and cumulative exposure
  - Determination of the statistical distribution of exposure, based on empirical and/or modelled data.

- **<u>Step 4: Risk characterisation</u>**
  - **Scoping**
    - Consideration of the risk for each selected exposure scenarios and exposure pathway
    - Consideration of general public (subpopulations), workers and environmental chosen compartments
    - Consideration of the risk linked to physicochemical, environmental and health hazards
  - **Characterisation**
    - Comparison of exposure levels to the predicted no effect thresholds for both humans and the environment (lowest DNEL or DMEL for non-threshold or PNEC), along with the presentation of the degree of uncertainty.
    - Application of a justified normalisation factor for each exposure pathways
    - Determination of the risk from combined exposure
    - Qualitative assessment for non-threshold effects, based on external expert judgement
    - Conclusions on whether the use of MFA is problematic or not and if further risk reduction measures are required.

Step 5: Risk Management

- Identification of possible actions
- Performing mitigation actions
- Re-consider exposure assessment and risk characterisation

An advisory board has to be set up for each risk assessment procedure. The advisory board will validate decisions on the assessment scope, conduct, and conclusions as well as provide technical guidance, review, and feedback on all aspects of the assessment. The advisory board should be consulted on especially complex or contentious technical issues. All written feedback and comments from the board should be recorded and included as part of an annex to the assessment dossier.

Annex 1 – Discussion on the guidance requirements

Annex 1.1 – Emissions during the life cycle

Relative to Section 4.4.

A. Discussion on the categorization of MFAs

The type and extent of emissions expected (and the exposure, as described in the following sections) may vary depending on category or type of fuel additive. It might be relevant to further specify risk assessment requirements for the additives depending on their function (e.g. combustion improvement, octane enhancement, reduced valve wear). However, a single additive may claim multiple or multipurpose benefits. Therefore in this guidance, we suggest specifying the point at which the MFA is added to the fuel rather than specifying additive structure or function.

The functional, performance or after-market nature of the products considered will have to be specified. For the first two categories the risk of unintended leaking or other types of emissions will be similar to the fuel in question. Fuels are handled in Europe as hazardous for the environment and health. They are normally handled by professionals in assigned locations. As for the third category, which is added to fuel by consumers, the products are handled by the general public and will thus be stored and handled in a different way to mixed/diluted fuel, not necessarily including professional protection, leakage prevention, etc.

B. Example for reporting of emissions

The applicant must report the volumes of losses of MFA during its life cycle in a specific table (Table 2) or a mass flow tool, along with the underlying assumptions for these estimations. Other reporting tools can be required to describe the emissions at different steps, such as e.g. a dedicated reporting tool on MFA combustion products.

Table 2: Example table on estimated losses of MFA product during its life cycle

MFA type of loss/emissions	Proportion (%)	Life cycle steps
Wastewater	1.9%	Production, Disposal
Air emissions	0%	Use
Chemical transformation	…	…
Loss to paved/unpaved surfaces		

MFA type of loss/emissions	Proportion (%)	Life cycle steps
Disposal to landfill		
Disposal by incineration		

C. Information on distribution and trade

Description of distribution and trade

From the factory or the storage facility, the MFA product will be transported to the sales or use points. The means of transport and handling will vary depending on product type, but pipes or containers (e.g. steel barrels) are often used for bulk products. The bulk product is normally distributed by oil companies to service stations in tankers. On the site, the contents of the road tanker are discharged either by gravity or by pump into storage tanks.

For the trade step, additives will be sold with fuel (mixed/diluted or bulk product) at e.g. gas stations, or distributed to local tap stations. The fuels which the MFAs are mixed with are in themselves potentially hazardous products and therefore handled according to certain licenses/requirements. Content of storage tanks are discharged into customer vehicle tanks or refuelling containers.

Many countries do not produce the fuel additives (or fuel products including additives) domestically, but are dependent on imports.

Discussion on contamination pathways

Spillage of petrol during transfer from the tanker trucks to underground storage at consumer petrol outlets or from bowers to consumer vehicles can result in small releases. However, these losses are not expected to be substantial, previous experience in the assessment of fuel additives indicates that losses are not expected to amount to more than 0.5% of petrol volume

It has been reported that spill incidents involving (diluted) metallic additives may occur from road tankers during transportation to customers and retail service stations and during transfer activities.

Unintentional releases during distribution normally appear at managed facilities which are in principle operating under specific protective legislation. If spills appear during transport because of leaking tanks, however, the risk might be substantial that these will end up in non-managed sites and potentially cause a larger environmental exposure. In petrol stations, mixes of additive and fuel can be loaded into underground tanks (on-site), which reduce the risk for human exposure. Subsequently, upon sale, the bulk fuel will be pumped into a vehicle fuel tank for use. Evaporation losses of MFA in this procedure are not expected to be significant for the general public. However, the MFAs may have an effect on the overall evaporation of fuel vapour components to the air, which could influence workers exposure.

D. Discussion on uncertainties of estimating emissions from the use stage

Given the wide variety of compounds emitted (influenced by fuel composition and blending components, vehicle ages, models[89], driving cycles, etc.), the applicants will have to interpret the results of eventual measurements or estimations of emissions with care.

Vehicle emissions derived by fuel combustion contain a vast range of regulated and unregulated pollutants. The composition depends on fuel type and varies with factors including refinery processes employed, and use of blending components such as ethanol. Vehicle and motor state may also lead to emission of a wide range of metals in addition to the MFA combustion products, e.g. metallic particles from wear of vehicle parts such as engine, and brake-pads. The number of compounds emitted from motor vehicles could then extend to more than 1000[90]. However, levels of engine exhaust pollutants are in general influenced not only by fuel composition but also by several other factors such as differences in vehicle ages, models[89], driving cycles, etc. Thus the results of eventual measurements or estimations need to be interpreted with care.

The effects of using MFA on emissions quality (compounds emitted, toxicity) and quantity can be positive (e.g. reduced fuel consumption and thus related emissions) or negative (e.g. on pollution control systems).

For example, Platinum group elements catalyst (PGEs) are developed as a means of reducing exhaust emissions of e.g. carbon monoxide (CO), nitrogen oxides (NOx) and hydrocarbons (HCs).

The type of emissions to be characterised will be decided by a number of factors including the category to which the MFA belongs in terms of the possible use classes of the metallic fuel additive (octane enhancer), the physicochemical properties of the metallic fuel additive (i.e. the nature of the metal), etc.

Annex 1.2 – Hazard

Relative to Section 4.5.

[89] ACEA & EUROPIA (1997) European Programmes on Emissions, Fuels and Engine Technologies, EPEFE Report
[90] Afton chemical corporation (2011) Mobile Source Air Toxics (MSATs): Identifying and Controlling MSATs that Present the Greatest Risks to Human Health and the Environment A White Paper Describing the U.S. Environmental Protection Agency's Action to Reduce MSAT Emissions from Mobile Sources in the United States

A. Example of NOAEL and LOAEL (Cf. Section 4.5.3)

Table 3: Example of NOAEL and LOAEL values for observed effects[91]

Toxicological effects	Sex	NOAEL (mg/m^3)	LOAEL (mg/m^3)
Organ weight changes			
Absolute lung weight	M, F	5	50.5
Relative lung weight	M, F	5	50.5
Absolute spleen weight	M, F	507.5	–
Relative spleen weight	M	50.5	

B. Examples of approaches to assess environmental hazards at different trophic levels

Three test methodologies are commonly used for the determination of the toxicity in the aquatic environment: flow-through, static, and static renewal tests. The environmental hazard has to be studied in several trophic levels.

For example the toxicity of CeO2 nanoparticles has been examined by Van Hoecke et al. (2009)[92] in four test aquatic organisms covering three different trophic levels. CeO2 nanoparticles acute toxicity was not observed in two crustaceans and *D. rerio* embryos while an effect was detected in *Daphnia magna* and the green algae *P. Subcapitata*. The effects of CeO2 nanoparticles were examined in four edible plants: corn, alfalfa, tomato and cucumber where they produced decreased germination as well as reducing root growth[93].

[91] US EPA.(2009). Toxicological review Cerium Oxide and Cerium Compounds.
[92] Van Hoecke K , Q uik JTK , et al. (2009). Fate and Effects of CeO2 Nanoparticles in Aquatic Ecotoxicity Tests.Environ Sci Technol, 43, 4537±4546.
[93] Lopez-Moreno ML, De La Rosa G ,et al.(2010). X-ray absorption spectroscopy of CeO2 nanoparticles and assessment of their differential toxicity in four edible plants. Jour. Agric. Food Chem. 58, 3689 ± 3693.

C. OECD Guideline tests

Table 4: OECD Guideline tests

No.	Title	Species
201	Growth inhibition test	Alga
202	Acute immobilization test	Daphnia sp.
	Reproduction test	
203	Acute toxicity test	Fish
204	Prolonged toxicity test: 14-day study	
210	Early-life stage toxicity test	
215	Juvenile growth test	
229	Short term reproduction assay	
207	Acute toxicity tests	Earthworm
222	Reproduction test	
208	Growth test	Terrestrial plants
213	Acute oral toxicity test	Honeybees

Annex 1.3 – Exposure

Relative to Section 4.6.

A. Consideration on the importance to make the exposure assessment a mandatory step of the risk assessment

In the REACH framework, if the chemical has already been judged not to be dangerous, an exposure assessment would not be required. However, this would refer to the Active Ingredient, and not the MFA product (which may contain several ingredients), nor the mixture of MFA and fuel, and also not the toxicity of the combusted product (or by-products). The decision about hazard is not designed to take into consideration the dose, exposure duration and (amount of) humans and biota at risk, and may therefore not sufficiently consider e.g. sensitive sub-groups or other special exposure factors. Also, if the judgment about hazard involves extrapolating from short-term effects to long-term effects, can we be sure that the uncertainties in extrapolating have been considered? One has to consider the possibility that even a low toxicity chemical could have significant impacts under certain exposure conditions, such as very high exposure levels (e.g. accidents), widespread population exposures (which would include sensitive sub-groups),

and chronic exposures. We would therefore support making the exposure assessment a mandatory step and that the decision tree for doing an exposure assessment does not truncate if the FA is not classified as hazardous.

B. Discussion about predominant routes of exposure (Cf. Section 4.6.1)

The **R&D, manufacturing and storage** steps could release MFAs in a diffuse manner that might result in contamination of any or all of the environmental spheres. Thus the general public might be exposed to MFAs through one or more environmental pathways and routes (e.g., inhalation, oral, dermal). Leaking fuel storage facilities have been a notable source of contamination of water resources and point to the potential for exposure from public water supplies as well as private wells. Occupational exposure could also occur during the formulation of fuels and handling of MFAs at the production and storage sites.

In the **marketing/distribution and transport,** accidents or major spills from transport and handling have been estimated to be a minor route of exposure for public exposure. However, the applicant will need to assess its relevance on a case-by-case basis. The exposure for the general public occurring from this life cycle step will be covered by the exposure situations in the scenario outlined for the R&D, manufacturing and storage step.

In the **use** step, exposure to chemicals produced can take place through air but also through soil and surface water (possibly also groundwater) following deposition from air. The predominant occupational exposure path is expected to be through inhalation (e.g. persons engaged in formulating fuels and in disposing of engines, oils, and other materials as wastes), when exposed to vehicle exhausts, i.e. possible inhalation of un-combusted or combusted product. Based on the experience from lead use in fuel, there may also be a risk for "take-home exposure": children with a parent in e.g. an automobile body or maintenance occupation showed increased blood Pb levels[94]. Most parts of the population could potentially be exposed in one way or the other to emissions from the use step, in both urban and rural environments[95], including potentially sensitive groups in the general population, e.g. infants, pregnant women, asthmatics, and elderly people, although this might depend on the MFA under study. Studies indicate that populations living, working or going to school near major roads may be subjected to an increased risk for a number of adverse health effects including respiratory, cardiovascular, premature mortality, birth and developmental effects, and cancer (e.g. Pearson et al., 2000[96]; Wilhelm and Ritz, 2003[97];

[94] The Silver Valley lead study: the relationship between childhood blood lead levels and environmental exposure. AJ Yankel, IH von Lindern, SD Walter - Journal of the Air Pollution , 1977 -

[95] In remote regions of the southern and northern hemispheres in the late 1980s, blood lead levels were reported to be 0.78 µg/dl and 3.20 µg/dl, respectively (Flegal & Smith, 1992),compared to the pre-industrial blood lead level in people estimated to have been about 0.016 µg/dl.
Flegal AR, Smith DR (1992). Lead levels in preindustrial humans. New England Journal of Medicine, 326(19):1293–1294.

[96] Pearson, R.L., Wachtel, H., Ebi, L., 2000. Distance-weighted traffic density in proximity to a home is a risk factor for leukemia and other childhood cancers. Journal of the Air & Waste Management Association 50, 175-180

[97] Wilhelm, M., Ritz, B., 2003.Residential proximity to traffic and adverse birth outcomes in Los Angeles County, California, 1994-1996. Environmental Health Perspectives 111, 207-216.

Finkelstein et al., 2004[98]; Gauderman et al., 2005[99]; Samet, 2007[100]; Samal et al., 2008[101]). Exposure includes dermal and eye contact when refuelling vehicles, while using fuel products as a solvent or cleaner, or through substance abuse (petrol sniffing). Skin and eyes may thus be directly exposed to the additive. In particular, dermal exposure from a do-it-yourself motor oil change can be considered a "high-end" exposure due to the contamination of motor oils by MFAs and/or the remaining of MFAs in recycled motor oils as well as the high likelihood of hand exposure during the change.

Populations may also be exposed during the end-of-life management of engines , oils and other contaminated materials.

C. Discussion about fate and behaviour of substances in water and soils (Cf. Section 4.6.2)

In soil, substances can undergo various biological, physical, and chemical processes, including biodegradation/metabolism, adsorption/desorption, immobilisation/mineralisation, oxidation/reduction, and complexation, as well as dissolution/precipitation between different phases as solids (minerals and organic components of the soil), liquids (interstitial water) and gases (porosity without water in it). The ability of particle-bound metals to adsorb to the soil and have a low mobility in this compartment will mostly depend on the soil particle size and the ability of the overall substance considered leaching in air and/or water. Some substances readily volatilise and transfer to the atmosphere, whereas other substances may tend to move downward and infiltrate groundwater, depending on soil characteristics and the depth to ground water. Taking gasoline as an example, porous soil allows gasoline to be transported quickly; dense soil slows down the transport. Once gasoline reaches the water table, it tends to accumulate on top of it, because it is less dense than water and not readily soluble in it.

Water includes both marine and fresh water, with the latter typically divided into surface and subsurface (e.g. ground water) aspects. Sediments can also be considered here but are sometimes viewed as distinct from water and soils. If released to water, particle-bound metals can be absorbed by suspended solids and sediment, depending in part on their octanol: water coefficient (K_{ow}). Volatilisation from water surfaces can also occur as a function of Henry's Law constant. MFAs can be directly degraded by hydrolysis and other processes (Environment Canada Health Canada, 2010). Yet, this does not mean that exposure to the metallic compound is diminished in the short and long-run.

[98]Finkelstein, M.M., Jerrett, M., Sears, M.R., 2004. Traffic air pollution and mortality rate advancement periods. American Journal of Epidemiology 160, 173-177.
[99]Gauderman, W.J., Avol, E., Lurmann, F., Kuenzli, N., Gilliland, F., Peters, J., McConnell, R., 2005. Childhood asthma and exposure to traffic and nitrogen dioxide. Epidemiology 16(6), 737-743.
[100]Samet, J.M., 2007. Traffic, Air Pollution, and Health. Inhalation Toxicology, 19:1021–1027
[101]Samal, M.T., Islam, T., Gilliland, F.D., 2008. Recent evidence for adverse effects of residential proximity to traffic sources on asthma. Current Opinion in Pulmonary Medicine 14(1), 3-8.

D. Discussion about fate of substances in the body (Cf. Section 4.6.3)

Knowledge of the MFAs and relevant combustion products' fate and in particular of particle bound metals, once in the body is a key factor to understand their likely effects. Main steps to be considered include: Administration, Adsorption, Distribution; Complexation; Metabolism (limited to oxidation state transitions and alkylation/dealkylation reactions); Elimination. The target organs where the metallic compounds will deposit depend on the administration's route and the speciation pattern of the metallic substance considered. Chemical speciation has an impact on solubility, bioavailability, and persistence of metals and metal compounds in the environment (e.g., inorganic arsenic versus organic compounds, inorganic and organic mercury compounds). Metals and their complexes are often ionized, with tissue uptake (membrane transport) having greater potential to be diffusion-limited or use specialized transport processes. Often sequestered once absorbed, metal compounds are bound to specific plasma or tissue proteins (intrinsically capacity-limited) or bone[102].

For instance, studies have shown that after inhalation, cerium uptake in several organs (including lungs, brain, heart, etc.)[103]. Indeed, exposure to a high dose could occur accidentally in very rare cases for example workers in a fuel additives plant or ingestion of fuel additive by children[104], thus hazard related to this kind of exposure would also be important to know.

E. Discussion on biomonitoring (Cf. Section 4.6.2)

For aquatic metal pollution, commonly used bioindicator organisms include plankton, insects, molluscs, fish, and plants. Their use varies depending on the metal considered. Each type of bioindicator has specific advantages for the biomonitoring of metal pollution in aquatic ecosystems[105]. For example, aquatic algae are important primary producers in marine and fresh water, and therefore the type and number of algae species can not only affect water quality but serve as an indicator of existing conditions. Fish have also attracted attention in the biomonitoring of water pollution due to their relatively large body size, long life, and ease of production. Water pollution type and level may be reflected in measures of species numbers and types, amounts, physiological and biological responses, and residue contents (metal exposure can cause the disturbance of normal metabolism and biological function, inhibition of photosynthesis, reduction of cytochrome, cellular mutation, putrescence, and death of algae). In particular, fish, which are near the top of the aquatic food chain and may directly affect the

[102]Robert Goyer (2004), Issue paper on the human health effects of metals. Contributors: Mari Golub, Harlal Choudhury, Michael Hughes, Elaina Kenyon, Marc Stifelman. Submitted to: U.S. Environmental Protection Agency Risk Assessment Forum. August 19, 2004. Available at: www.epa.gov/raf/publications/pdfs/HUMANHEALTHEFFECTS81904.PDF

[103] Geraets L, et al. (2012). Tissue Distribution of Inhaled Micro- and Nano-sized Cerium Oxide Particles in Rats: Results from a 28-day Exposure Study.

[104]NICNAS. (2003b). Tricarbonyl (MMT) Priority Existing Chemical Assessment Report No. 24

[105]*Qunfang Zhou, Jianbin Zhang, Jianjie Fu, Jianbo Shi, Guibin Jiang (2007);Biomonitoring: An appealing tool for assessment of metal pollution in the aquatic ecosystem; State Key Laboratory of Environmental Chemistry and Ecotoxicology, Research Center for Eco-Environmental Sciences, Chinese Academy of Sciences, Beijing 100085, China; analytica chimica acta 6 0 6 (2 0 0 8) 135–150*

health of humans, have great utility for biomonitoring. A suite of endpoints such as metallothioneins (MTs), hematological parameters, immunological parameters, reproductive and endocrine parameters, histological and morphological parameters can be used to assess exposure to environmental metal pollution on aquatic ecosystems[106]. Likewise, plants can serve as markers of exposure related to MFA. Several studies have documented that plants can actively take up certain metals (e.g. Mn) and other substances from soil as well as serve as passive surfaces for atmospheric deposition of vehicular emissions as a function of their proximity to traffic[107,108].

F. Example of reporting template

For reporting, a possible table for tracking exposure of the general public is exemplified by Health Canada[109]in the Table 5. Occupational exposure warrants special attention, as workers may encounter higher levels of exposure to contaminants than would the general population.

Table 5: Example of table used for tracking exposure

Route of exposure	Estimated intake (µg/kg-bw per day) of metal by various age groups					
	Breast milk/feed to infants	0.5 to 4 years	5–11 years5	12–19 years6	20–59 years7	60+ years8
Air						
Drinking water						
Food						
Soil intake						
Dermal exposure						

[106]Oost, R. van der Beyer, J. Vermeulen, N.P.E. (2003) Environ. Toxicol.Pharm. 13 (2003) 57. Review article Fish bioaccumulation and biomarkers in environmental risk assessment: a review

[107] Zayed J. (2001), Use of MMT in Canadian gasoline: Health and environment issues. American Journal of Industrial Medicine Volume 39, Issue 4, pages 426–433, April 2001

[108]Baldauf, R.W., E. Thoma, V. Isakov, T. Long, J. Weinstein, I. Gilmour, S. Cho, A. Khlystov, F. Chen, J. Kinsey, M. Hays, R. Seila, R. Snow, R. Shores, D. Olson, B. Gullett, S. Kimbrough, N. Watkins, P. Rowley, J. Bang. (2008). "Traffic and Meteorological Impacts on Near Road Air Quality: Summary of Methods and Trends from the Raleigh Near Road Study." J. Air & Waste Manage Association, 58:865–878

[109]Environment Canada and Health Canada (2010) Screening Assessment for the Challenge Zinc, bis[O,O-bis(1,3-dimethylbutyl) phosphorodithioato-S,S']-, (T-4)- Chemical Abstracts Service Registry Number 2215-35-2 , July

Annex 2 – Fuel additives factsheets

In this Annex we present for illustrative purposes only the factsheets prepared on the MFAs or relevant metals listed in Figure 7. This list is not limited to the substances targeted by the Fuel Quality Directive. Physicochemical properties and potential effects of relevant metals such as aluminium, palladium, platinum and rhodium are presented in factsheets because existing literature indicated the possible use of these metals in MFAs, even if they are not yet or anymore components of MFAs currently placed on the market. The factsheets do not represent assessment documents on the risk posed by individual substances following the methodology presented in the report. They aim to illustrate how information could be presented and some factsheets' sections are not necessarily relevant for all the MFAs. They are based on the collection of available information but are not intended to be comprehensive and do not necessarily reflect the latest developments in the field of MFAs. They are grouped on the basis of the nature of metallic compound and are presented in alphabetical order. In the factsheets some properties and findings for the non-nano-scale material are provided, however please note that this information need to be used carefully since nano-scale additives may not behave the same as larger scale additives and large uncertainties exist regarding their risk assessment for health and the environment. When the information is specifically relevant to nanoparticles this has been indicated by explicit wording.

Table 6: List of the metallic fuel additives or relevant metals in different groupings

Additive	Metal	CAS number	Fuel type	Existing hazard classifications	Function in the fuel[13,14]	Physical and chemical structure based grouping
Aluminium powder (only at the R&D stage for space and naval vessels, not yet in use)	Al	7429-90-5	Diesel	**CLP classification:** H 228: Flammable solid H250: Catches fire spontaneously if exposed to air. H261: In contact with water releases flammable gases	Lubricity improver; Combustion catalyst	Nanoparticles
Cerium (di) oxide (CeO2)	Ce	1306-38-3	Diesel	Substance not listed in Annex VI (table 3.1) of Regulation (EC) N° 1272/2008 (CLP), including its first ATP (Regulation (EC) N° 790/2009).	Fuel-borne catalysts Antioxidants	Nanoparticles, Rare Earth metal oxides
Chrome salts of mono- and dialkylsalicylic acid or dodecyl sulfosuccinic acid (for naval vessels).	Cr	7440-47-3 (Chrome element)	Gasoline	For Chromium Hex-Cem ©: Xn – Harmful R38 - Irritating to skin. R65 - Harmful: may cause lung damage if swallowed. R66 - Repeated exposure may cause skin dryness or cracking.	Antistatic	Transition metal
Copper compounds	Cu	7440-50-8 (copper element)	Diesel[110]	67/548/EEC self industrial classification H400 : very toxic to aquatic life	Fuel-borne catalysts	Transition metal

[110] J.P.A. Neeft, ;S.J. Jelles, , M. Makkee, J.A. Moulijn(1998), Copper catalysis for particulate removal from diesel exhaust gas. Copper fuel additives in combination with copper coatings , in: N. Kruse, A.Frennet, J-M. Bastin (1998), Catalysis and Automotive Pollution Control IV. Studies in Surface Science and Catalysis, Vol.116. Elsevier Science.

Additive	Metal	CAS number	Fuel type	Existing hazard classifications	Function in the fuel[13,14]	Physical and chemical structure based grouping
				H302 : harmful if swallowed H332 : harmful if inhaled		
Cr-perovskite (only on R&D not used in fuel)	Cr	12049-50-2 ($CaTiO_3$)	Diesel	**Accordingly to the Safety Data Sheet:** Inhalation: May be harmful if inhaled. May cause respiratory tract irritation. Ingestion: May be harmful if swallowed. Skin: May be harmful if absorbed through skin. May cause skin irritation. Eyes: May cause eye irritation.	Catalyst	Perovskite compounds
Dicyclopentadienyl iron (ferrocene)	Fe	55404-68-7 102-54-5	Diesel	**CLP classification:** Flammable solids (category 1) Acute toxicity, Oral (category 4) H228 Flammable solid H302 Harmful if swallowed	Fuel-borne catalysts Metal deactivators	Iron based additives
Diethyldimethyl lead[111]	Pb	1762-27-2	Gasoline	**Lead element:** **EU Classification** Symbol: T+ = very toxic, N= dangerous for the environment R 61 May cause harm to the	Lubricant Antiknock or octane improver Anti-valve seat	Alkyl leads

[111] Not used or produced since the early 1990's according to ATC

Additive	Metal	CAS number	Fuel type	Existing hazard classifications	Function in the fuel[13,14]	Physical and chemical structure based grouping
				unborn child R 26 /27/28 Very toxic by inhalation, in contact with skin and if swallowed R33 danger of cumulative effects R 62 possible risk of impaired fertility R50/53 very toxic to aquatic organism , may cause long-term adverse effects in the aquatic environment **United Nations Classification** UN Hazard Class: 6.1 UN Pack Group:I	recession additives	
Ethyltrimethyl lead[112]	Pb	1762-26-1	Gasoline	**Lead element:** **EU Classification** Symbol: T+ = very toxic, N= dangerous for the environment R 61 May cause harm to the unborn child R 26 /27/28 Very toxic by inhalation, in contact with skin and if swallowed R33 danger of cumulative effects	Antiknock or octane improver Lubricant Anti-valve seat recession additives Oxygenates	Alkyl leads

[112] Not used or produced since the early 1990's according to ATC

Additive	Metal	CAS number	Fuel type	Existing hazard classifications	Function in the fuel[13,14]	Physical and chemical structure based grouping
				R 62 possible risk of impaired fertility R50/53 very toxic to aquatic organism , may cause long-term adverse effects in the aquatic environment **United Nations Classification** UN Hazard Class: 6.1 UN Pack Group:I		
Ferox	Fe	97467-73-7 12562-64-0 18829-42-0 299-29-6 68476-34-6	Diesel	**Accordingly to the Safety Data Sheet:** May be harmful if ingested, inhaled or absorbed through the skin. Vapour or mist may be irritating to the eyes, mucous membranes, and upper respiratory tract. Exposure can cause gastro-intestinal disturbances, nausea, headache, or vomiting. Chronic dermal exposure to an ingredient in the product has been shown to increased incidence of skin tumours in laboratory animals.	Fuel-borne catalysts Demulsifiers	Iron based additives

Additive	Metal	CAS number	Fuel type	Existing hazard classifications	Function in the fuel[13,14]	Physical and chemical structure based grouping
				inhalation of an ingredient in this product has been shown to cause cardiovascular changes similar to atherosclerosis in laboratory animals.		
Ferrous picrate	Fe	14866-25-2	Diesel	Accordingly to safety data sheet : R10 Flammable R20 Harmful by inhalation R37 Irritating to respiratory system	Fuel-borne catalysts Dyes	Iron based additives
Fine Nickel-Coated Aluminium Powder (only on R&D not use)	Ni, Al	7429-90-5 (Aluminium element)	Diesel	**CLP classification for Aluminium element** H 228: Flammable solid H250: Catches fire spontaneously if exposed to air. H261: In contact with water releases flammable gases	Combustion catalysts?[113] Corrosion inhibitors	Metal carbonyl
Iron pentacarbonyl	Fe	13463-40-6 37220-42-1	Diesel	Iron pentacarbonyl Acute Tox. 2 H300 Fatal if swallowed H310 Fatal in contact with skin	Fuel-borne catalysts Corrosion inhibitors	Iron based additives

[113]Karmakar et al. (2011).International Journal of Energetic Materials and Chemical Propulsion, Issue 1.

Additive	Metal	CAS number	Fuel type	Existing hazard classifications	Function in the fuel[13,14]	Physical and chemical structure based grouping
				H330 Fatal if inhaled		
La-Perovskite ($CaTiO_3$) (R&D stage)	Ti	12049-50-2 ($CaTiO_3$)	Diesel	**Accordingly to the Safety Data Sheet:** Inhalation: May be harmful if inhaled. May cause respiratory tract irritation. Ingestion: May be harmful if swallowed. Skin: May be harmful if absorbed through skin. May cause skin irritation. Eyes: May cause eye irritation.	Catalyst Colour stabilizers	Perovskite compounds, Rare metals group, Nanoparticles
Li-perovskite (R&D stage)	Li	12049-50-2 ($CaTiO_3$)	Diesel	**Accordingly to the Safety Data Sheet:** Inhalation: May be harmful if inhaled. May cause respiratory tract irritation. Ingestion: May be harmful if swallowed. Skin: May be harmful if absorbed through skin. May cause skin irritation. Eyes : May cause eye irritation.	Catalyst	Perovskite compounds or rare metals group
Methylcyclopentadienyl Manganese Tricarbonyl (MMT®)	Mn	12108-13-3	Gasoline/diesel	Hazard symbols T+ R 24/25 Toxic in contact with skin and if swallowed R26 very toxic by inhalation	Antiknock or octane improver Lubricant Anti-valve seat recession	Metal carbonyl

Additive	Metal	CAS number	Fuel type	Existing hazard classifications	Function in the fuel[13,14]	Physical and chemical structure based grouping
				Accordingly to the safety data sheet Very toxic by inhalation, in contact with skin and if swallowed. May cause eye irritation May cause skin irritation. Toxic in contact with skin. May cause irritation of the digestive tract. Poison by ingestion. May be fatal if inhaled. May cause respiratory tract irritation.	additives Anti-static	
Methyltriethyl lead[114]	Pb	1762-28-3	Gasoline/ diesel	**Lead element:** **EU Classification** Symbol: T+ = very toxic, N= dangerous for the environment R 61 May cause harm to the unborn child R 26 /27/28 Very toxic by inhalation, in contact with skin and if swallowed R33 danger of cumulative effects	Antiknock or octane improver Lubricant Anti-valve seat recession additives	Alkyl leads

[114] Not used or produced since the early 1990's according to ATC

Additive	Metal	CAS number	Fuel type	Existing hazard classifications	Function in the fuel[13,14]	Physical and chemical structure based grouping
				R 62 possible risk of impaired fertility R50/53 very toxic to aquatic organism , may cause long-term adverse effects in the aquatic environment **United Nations Classification** UN Hazard Class: 6.1 UN Pack Group:I		
Palladium (DFP/FAP)	Pd	7440-05-3	Diesel	Accordingly to the Safety Data Sheet: Slightly hazardous in case of skin contact (irritant), of eye contact (irritant), of ingestion, of inhalation.	Catalyst Antifoams	Platinum group metal
Platinum (either as FBC or DPF/FAP)	Pt	7440-06-4	Diesel	Accordingly to the Safety Data Sheet Hazardous in case of skin contact (irritant), of eye contact (irritant), of ingestion, of inhalation.	Catalyst Demulsifiers	Platinum group metal
Potassium acetate	K	127-08-2	Gasoline	**CLP classification for potassium element** Water-react 1 H260: In contact with water releases flammable gases which may ignite spontaneously.	Anti-valve seat recession additives Diesel fuel stabilisers	Alkaline metal salt

Additive	Metal	CAS number	Fuel type	Existing hazard classifications	Function in the fuel[13,14]	Physical and chemical structure based grouping
				Skin Corr. 1B H314: Causes severe skin burns and eye damage. Skin irrit. 2 H315: Causes skin irritation Eye irrit. 2 H319: Causes serious eye irritation		
Potassium (1,2-bis(2-ethylhexyloxycarbonyl)ethanesulphonate potassium salt)	K	7491-09-0	Gasoline	Accordingly to the safety data sheet : Very hazardous in case of skin contact (irritant), of ingestion, of inhalation. Hazardous in case of skin contact (corrosive), of eye contact (corrosive). R14/15 reacts violently with water, liberating extremely flammable gases. R34 Causes burns. Others classification : OSHA : Hazardous by definition of Hazard Communicaion Standard (29 CFR 1910. 1200) WHMIS (Canada): Class B-6 : Reactive and very flammable material. Class E : Corrosive solid.	Anti-valve seat recession additives Diesel fuel stabilisers	Alkaline metal salt

Additive	Metal	CAS number	Fuel type	Existing hazard classifications	Function in the fuel[13,14]	Physical and chemical structure based grouping
Resin acid (abietic acid) with MnO_2 or MgO	Mg	1309-48-4	Gasoline	Accordingly to the safety data sheet : May cause eye irritation. May cause respiratory tract irritation. Inhalation of fumes may cause metal fume fever.	Anti-valve seat recession additives Multifunctional diesel additive packages	
Rhodium	Rh	7440-16-6	Diesel	CLP classification : H413 May cause long lasting harmful effects to aquatic life H228 Flammable solid H302 Harmful if swallowed H318 Causes serious eye damage H334 May cause allergy or asthma symptoms or breathing difficulties if inhaled H250 Catches fire spontaneously if exposed to air H315 Causes skin irritation H319 Causes serious eye irritation H335 May cause respiratory irritation	Catalysts	Platinum group metal
SB86 boron nanoparticles (only on R&D not use)	B	19287-88-2 (Boron	Not applicable	R11 : Highly flammable	Air breathing propulsion	Metalloid Nanoparticles

Additive	Metal	CAS number	Fuel type	Existing hazard classifications	Function in the fuel[13,14]	Physical and chemical structure based grouping
		element)		R22 Harmful if swallowed Slightly hazardous in case of skin contact (irritant, permeator), of eye contact (irritant), of ingestion, of inhalation.	systems -really in use? [115] Cetane improvers	
SB99 boron nanoparticles (only on R&D not use)	B	19287-88-2 (Boron element)	Not applicable	R11 : Highly flammable R22 Harmful if swallowed Slightly hazardous in case of skin contact (irritant, permeator), of eye contact (irritant), of ingestion, of inhalation.	Air breathing propulsion systems Detergents	Metalloid Nanoparticles
Tetraethyl lead	Pb	78-00-2	Gasoline	**Lead element:** **EU Classification** Symbol: T+ = very toxic, N= dangerous for the environment R 61 May cause harm to the unborn child R 26 /27/28 Very toxic by inhalation, in contact with skin and if swallowed	Antiknock or octane improver Lubricant Anti-valve seat recession additives Anti-valve seat recession additives	Alkyl leads

[115]Karmakar et al. (2011).International Journal of Energetic Materials and Chemical Propulsion, Issue 1.

Additive	Metal	CAS number	Fuel type	Existing hazard classifications	Function in the fuel[13,14]	Physical and chemical structure based grouping
				R33 danger of cumulative effects R 62 possible risk of impaired fertility R50/53 very toxic to aquatic organism , may cause long-term adverse effects in the aquatic environment **United Nations Classification** UN Hazard Class: 6.1 UN Pack Group:		
Tetramethyl lead[116]	Pb	75–74–1	Gasoline	**Lead element:** **EU Classification** Symbol: T+ = very toxic, N= dangerous for the environment R 61 May cause harm to the unborn child R 26 /27/28 Very toxic by inhalation, in contact with skin and if swallowed R33 danger of cumulative effects R 62 possible risk of impaired fertility R50/53 very toxic to aquatic organism , may cause long-	Antiknock or octane improver Lubricant Anti-valve seat recession additives Deposit control additives	Alkyl leads

[116] Not used or produced since the early 1990's according to ATC

Additive	Metal	CAS number	Fuel type	Existing hazard classifications	Function in the fuel[13,14]	Physical and chemical structure based grouping
				term adverse effects in the aquatic environment **United Nations Classification** UN Hazard Class: 6.1 UN Pack Group:		
Zirconium salt	Zr	22464-99-9	Diesel	R20 Harmful when inhaled R36/37/38 : Irritating to eyes, respiratory system and skin- R51/53 Toxic to aquatic organisms, may cause long-term adverse effects. R65 Harmful, may cause lung damage if swallowed R67 Inhalation may cause sleepiness and dizziness	Lubricity improvers	Nanoparticles

Acronyms	Details
BCF	Bioconcentration factor
CEC	Coordinating European Council
CLP	Classification Labelling and Packaging
DNEL	Derived No-Effect Level (DNELs are calculated by dividing the value of the health effect dose descriptor by an assessment factor (or safety factor) to allow for extrapolation to real human exposure situations)
DMEL	Derived Minimal Effect Level
EC50	half maximal effective concentration
GHS	Globally Harmonized System of Classification and Labelling of Chemicals
IPPC	Integrated Pollution Prevention and Control
Kow	Octanol – water coefficient
LC50	median lethal concentration (concentration at which 50% of the sample population is eliminated)
LD50	median lethal dose (dose at which 50% of the sample population is eliminated)
LOAEL	Lowest Observed Adverse Effect Level (lowest dose that produced an adverse effect)
MFA	metallic fuel additives
MMT	methylcyclopentadienyl manganese tricarbonyl
NOAEL	No Observed Adverse Effect Level (usually expressed in mg/kg/day, it defines the dose of substance that produces no significant toxicological effects for a specific exposure pathway)

A. Aluminium powder and nanoparticles

For illustrative purposes only. This factsheet does not represent the assessment documents on the risk posed by individual substances following the methodology presented in the report. They aim to illustrate how information could be presented and some factsheet's sections are not necessarily relevantfor all the MFAs. They are based on the collection of available information but are not intended to be comprehensive and do not necessarily reflect the latest developments in the field of MFAs.

In the stated form (CAS 7429-90-5), aluminium is insoluble to fuel, but it is presented for informative purposes because existing literature indicated the possible use of this metal in MFAs. Alumina, or aluminum oxide, is among the most abundantly produced nanosized particles, estimated to account for approximately 20% of the 2005 world market of nanoparticles (Rittner, 2002). Thus relevant information highlighting the effects of aluminium as an element have been added in this factsheet.

Product name	**Aluminium**
Chemical names	Aluminium

Product name	**Aluminium**
Family compounds	Metal
CAS	7429-90-5
EINECS	2310723
Chemical Formula	Al
Classification / Labelling	**Annex VI to Regulation (EC) No 1272/2008 on Classification, Labelling and Packaging of Dangerous Substances** H 228: Flammable solid H250: Catches fire spontaneously if exposed to air. H261: In contact with water releases flammable gases **Indication of danger** F - highly flammable **Risk phrases** R11 - highly flammable R15 - contact with water liberates extremely flammable gases R17-spontaneously flammable in air **Safety phrases** S2 - keep out of the reach of children S7/8 - keep container tightly closed and dry S43 - in case of fire, use... (indicate in the space the precise type of fire-fighting equipment. if water increases risk, add 'never use water')
Chemical/Physical properties	■ Aluminium is a silver-white, solid and odourless compound. It is highly resistant to oxidation and is often used in oxidized form. Aluminium is also found in water in soluble form and is usually found in combination with other ions, such as Aluminium chlorine. Aluminium in its water-soluble form can cause harmful effects due to its high reactivity ■ Aluminium is soluble in alkalis, sulphuric acid, hydrochloric acid but is insoluble in concentrated nitric acid or hot acetic acid (Lenntech database; sciencelad database).
Major constituents	Pure element
Information on possible hazards	**HEALTH** **Toxicity values:** ■ Workers

Acronyms	Details
BCF	Bioconcentration factor
CEC	Coordinating European Council
CLP	Classification Labelling and Packaging
DNEL	Derived No-Effect Level (DNELs are calculated by dividing the value of the health effect dose descriptor by an assessment factor (or safety factor) to allow for extrapolation to real human exposure situations)
DMEL	Derived Minimal Effect Level
EC50	half maximal effective concentration
GHS	Globally Harmonized System of Classification and Labelling of Chemicals
IPPC	Integrated Pollution Prevention and Control
Kow	Octanol – water coefficient
LC50	median lethal concentration (concentration at which 50% of the sample population is eliminated)
LD50	median lethal dose (dose at which 50% of the sample population is eliminated)
LOAEL	Lowest Observed Adverse Effect Level (lowest dose that produced an adverse effect)
MFA	metallic fuel additives
MMT	methylcyclopentadienyl manganese tricarbonyl
NOAEL	No Observed Adverse Effect Level (usually expressed in mg/kg/day, it defines the dose of substance that produces no significant toxicological effects for a specific exposure pathway)

Product name	**Aluminium**
	▫ Long-term exposure - local effects ▫ Inhalation DN(M)EL 3.72 mg/m³ ■ General population ▫ Long-term exposure - systemic effects ▫ Oral DN(M)EL 3.95 mg/kg bodyweight/day **Behaviour in the body:** ■ A recent study, conducted according to the principles of Good Laboratory Practice, tested the effects that numerous aluminium compounds had on human health (OECD guideline 417). The novel aluminium compounds tested included: aluminium nitrate, aluminium chloride, commercial aluminium hydroxide, alumina, powdered pot electrolyte, aluminium metal, SALP, Kasal, sodium aluminium silicate, and FD&C red 40 aluminium lake. The bioavailability of aluminium metal particles is lower than the bioavailability of soluble aluminium compounds (ECHA database). ■ According to literature reviews, aluminium and its compounds are

Product name	**Aluminium**
	shown to be poorly absorbed in humans and the mechanism of gastrointestinal absorption remains unclear. If absorbed, the highest levels of aluminium can be found in the lungs as inhaled insoluble particles. The urine is the most important route of aluminium excretion (Flarend et al., 2001; WHO, 1997). **Health effects:** ■ Nano: Alumina nanoparticles induce expression of endothelial cell adhesion molecules (Oesterling, et al.2008). ■ Nano: Manufactured aluminum oxide nanoparticles decrease expression of tight junction proteins in brain vasculature (Chen, et al.2008). ■ Nano: Nanosized aluminum altered immune function (Braidich-Stolle et al.2010). ■ An acute oral toxicity study in accordance with the OECD 423 and the Principles of GLP was performed with aluminium hydroxide in female rats. Aluminium hydroxide was administered by a single oral gavage to animals after an overnight food withdrawal at a concentration of 2000 mg/mL in PEG 400 considering 10 mL/kg body weight. The following endpoints have been observed during the study: mortality, clinical signs, and weight gain. During the 14 day observation period, there were no mortalities or clinical signs of intoxication related to aluminium hydroxide. At the end of the observation period, a macroscopic examination of the rats did not reveal any aluminium-related changes between the treatment group and control group. Under the conditions of this study, the acute oral median lethal dose (LD_{50}) of aluminium hydroxide is 2000 mg/kg in female CRL rats (ECHA database). ■ A study has been conducted in male Fischer 344 rats (10-12 weeks old) to investigate and compare the acute inhalation toxicity of aluminium and brass flake dusts. No mortalities, changes in lung function, or toxic signs were observed even at the highest aluminium flake concentration of 1000 mg/m³. At concentrations > 10 mg/m³, an inflammatory response to Aluminium flakes has been observed and indicates that the presence of insoluble aluminium flakes retained in the lungs will produce a chronic irritant response. Additionally, the acute inflammatory response to aluminium flakes was less dramatic than that of more soluble brass dust. The results of lung function measurements were not provided in the publication and the highest dose was not intended to allow estimation of the LC_{50} (Thomson et al., 1986). ■ In short-term studies using rats, mice or dogs as experimental subjects with various aluminium compounds in the diet or

Acronyms	Details
BCF	Bioconcentration factor
CEC	Coordinating European Council
CLP	Classification Labelling and Packaging
DNEL	Derived No-Effect Level (DNELs are calculated by dividing the value of the health effect dose descriptor by an assessment factor (or safety factor) to allow for extrapolation to real human exposure situations)
DMEL	Derived Minimal Effect Level
EC50	half maximal effective concentration
GHS	Globally Harmonized System of Classification and Labelling of Chemicals
IPPC	Integrated Pollution Prevention and Control
Kow	Octanol – water coefficient
LC50	median lethal concentration (concentration at which 50% of the sample population is eliminated)
LD50	median lethal dose (dose at which 50% of the sample population is eliminated)
LOAEL	Lowest Observed Adverse Effect Level (lowest dose that produced an adverse effect)
MFA	metallic fuel additives
MMT	methylcyclopentadienyl manganese tricarbonyl
NOAEL	No Observed Adverse Effect Level (usually expressed in mg/kg/day, it defines the dose of substance that produces no significant toxicological effects for a specific exposure pathway)

Product name	Aluminium
	drinking-water, no mortality or clinical signs of intoxication were observed at the highest administered doses. However, following the intra-tracheal administration of aluminium oxide, particle-associated fibrosis was observed. No overt toxicity to foetus was noted in this study, nor were general reproductive parameters noted after gavage treatment of rats (Browning, 1969; Clayton et al., 1982; Thomson et al., 1986). ■ After repeated occupational exposure to aluminium fumes, workers in a limited study experienced severe neurological syndromes including impairment of cognitive function, motor dysfunction and peripheral neuropathy. (Gosselin et al., 1984; Venugopal et al., 1978). In another occupational exposure study, workers' inhalation of finely divided aluminium and aluminium oxide created severe lung damage. One example of lung problems caused by the inhalation of aluminium particulates is Shaver's Disease, or bauxite fibrosis, which is complicated by the presence silica and iron oxide particulates (ECHA database). ■ Aluminium dust can cause eye irritation (ECHA database).

Product name	**Aluminium**

ENVIRONMENT

Ecotoxicity values

PNEC aqua (freshwater): No data, aquatic toxicity unlikely
PNEC aqua (marine water): No data, aquatic toxicity unlikely
PNEC aqua (intermittent releases): No data, aquatic toxicity unlikely
PNEC STP: 20 mg/L
PNEC sediment (freshwater):No or insufficient data available at present
PNEC sediment (marine water): No or insufficient data available at present
PNEC soil: No or insufficient data available at present
PNEC oral: No or insufficient data available at present

Behaviour in the environment:

- The behaviour of the aluminium in the environment depends on the pH of the considered compartment. Environmental acidification is known to mobilize aluminium from land to aquatic environments. The bioconcentration of aluminium is observed in aquatic plants and plants grown in soil with a low pH (Gallon et al., 2004; IPCS, 1997).
- Aerial deposition of aluminium dust also appears to contribute to plant surface levels of aluminium (IPCS, 1997).

Environmental effects:

- In fish, the short-term toxicity of aluminium was tested but did not follow OECD test guidelines. These experiments are listed in the ECHA database:
  - The 96-hr LC_{50} for the fish species *P.promelas* exposed to $AlCl_3$ in unfiltered water was greater than the highest measured concentration tested, 218644.1 µg/L total Al. The NOEC and LOEC in the unfiltered water was 37196.9 and 72890.0 µg/L, respectively. There was no relationship between the amount of dissolved Al and fish mortality and no effects on fish survival after 96 hours in the filtered toxicity test at the highest measured concentration tested of 1949.4 µg/L (ECHA database).
  - For Atlantic salmon alevins (Salmo salar) exposed to aluminium concentrations up to 4,700 µg/L and four fluoride concentrations at pH 6.5, the range for the 96-hr LC50 was 599- 1134 µg/L (Hamilton et al., 1995).
  - The 96-hr LC50 estimates for Fathead minnows (Pimephales promelas) exposed to Al at two pHs could not be determined as there were no mortalities at the highest exposure concentration tested of 50 mg/L.
  - No mortalities were observed for Channel catfish

Acronyms	Details
BCF	Bioconcentration factor
CEC	Coordinating European Council
CLP	Classification Labelling and Packaging
DNEL	Derived No-Effect Level (DNELs are calculated by dividing the value of the health effect dose descriptor by an assessment factor (or safety factor) to allow for extrapolation to real human exposure situations)
DMEL	Derived Minimal Effect Level
EC50	half maximal effective concentration
GHS	Globally Harmonized System of Classification and Labelling of Chemicals
IPPC	Integrated Pollution Prevention and Control
Kow	Octanol – water coefficient
LC50	median lethal concentration (concentration at which 50% of the sample population is eliminated)
LD50	median lethal dose (dose at which 50% of the sample population is eliminated)
LOAEL	Lowest Observed Adverse Effect Level (lowest dose that produced an adverse effect)
MFA	metallic fuel additives
MMT	methylcyclopentadienyl manganese tricarbonyl
NOAEL	No Observed Adverse Effect Level (usually expressed in mg/kg/day, it defines the dose of substance that produces no significant toxicological effects for a specific exposure pathway)

Product name	**Aluminium**
	(Ictalurus punctatus) that were exposed to Al concentrations of up to 50 mg/L at a measured pH of 7.54 for 96 hours. ■ The concentration of Aluminium is higher in acidified water and thus the effects of aluminium on aquatic species are more important. Furthermore, the biomagnification of aluminium was found to occur across trophic levels. For example, a bird that has eaten a fish with a high concentration of aluminium may produce offspring with low birth-weights (Scheuhammer et al., 2003)
Timing of action categorisation: **- distribution system additives** **- vehicle fuel system additives** **- additives sold in filling station**	No data found
Function (category)	Combustion catalyst

Product name	**Aluminium**
Concentration in gasoline (average)	No data found
Emissions in the environment during life cycle	No data found
Vehicle emissions impacts	No data found
Environmental exposure	Aluminium is released to the environment by both natural processes and anthropogenic sources. It is highly concentrated in soil-derived dusts from activities such as mining and agriculture, and in particulate matter from coal combustion. Aluminium occurs ubiquitously in the environment in the form of silicates, oxides and hydroxides, combined with other elements such as sodium and fluorine and as complexes with organic matter. It is not found as a free metal because of its high reactivity (WHO, 1997). Aluminium dissolves and mobilizes in acidified soil and lake sediments, becoming available for uptake into plants and animals. The solubility of aluminium depends on the pH characteristics of the soil (Walton, 2011).
Human exposure	While the general population can be exposed to aluminium via medication (aluminium-containing antacids or buffered aspirin), food and potable water remain the major intake sources of aluminium. In the workplace, humans are mainly exposed to aluminium through dust inhalation (Clayton et al., 1982).
References	ECHA database: apps.echa.europa.eu/registered/data/dossiers/DISS-9eb0e19f-e4e7-5137-e044-00144f67d031/DISS-9eb0e19f-e4e7-5137-e044-00144f67d031_DISS-9eb0e19f-e4e7-5137-e044-00144f67d031.html Lenntech database: www.lenntech.com/periodic/elements/al.htm Sciencelad database: www.sciencelab.com/msds.php?msdsId=9922844 Braydich-Stolle, L.K.,Speshock, J., Castle, A., Smith, M.,Murdock, R. and Hussain, S.M. Nanosized Aluminum Altered Immune Function, ACS Nano, 2010, 4 (7), pp 3661–3670. Browning, E. (1969). Toxicity of Industrial Metals. 2nd ed. New York: Appleton-Century-Crofts, p. 8. Chen, L., Yokel, L.A., Hennig B. and Toborek M.Manufactured Aluminum Oxide Nanoparticles Decrease Expression of Tight Junction Proteins in Brain Vasculature. Journal of Neuroimmune Pharmacology Volume 3, Number 4 (2008), 286-295. Clayton, G. D. and F. E. Clayton (eds.). (1981-1982). Patty's Industrial Hygiene and Toxicology: Volume 2A, 2B, 2C: Toxicology. 3rd ed. New York: John Wiley Sons,., p. 1499. Gosselin, R.E., R.P. Smith, H.C. (1984). Hodge. Clinical Toxicology of Commercial

Acronyms	Details
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Product name	**Aluminium**
	Products. 5th ed. Baltimore: Williams and Wilkins, p. II-128. Hamilton, S.J. and T.A. Haines (1995). Influence of fluoride on aluminium toxicity to Atlantic salmon (Salmo salar), Canadian Journal of Fisheries and Aquatic Sciences. 52:2432-2444. IPCS (International Programme on Chemical Safety). (1997). *Aluminium*. Environmental Health Criteria 194. Geneva: World Health Organization. Oesterling, E., Chopra, N., Gavalas, V. Arzuaga, X., Jin Lim, E. Sultana, R., Butterfield, D.A., Bachas, L., Hennig, B. Alumina nanoparticles induce expression of endothelial cell adhesion molecules. Toxicology Letters. Volume 178, Issue 3, 30 May 2008, Pages 160–166 Rittner, M.N..Market analysis of nanostructured materials, Am. Ceram. Soc. Bull., 81 (2002), pp. 33–36 Scheuhammer, A.M. (1987). The chronic toxicity of aluminium, cadmium, mercury, and lead in birds: A review ;Canadian Wildlife Service, Environment Canada, Ottawa, Ontario, Canada K1A 0E7. Strigul N., Vaccari L., Galdun C., Wazne M., Liu X., Christodoulatos C., Jasinkiewicz J. (2009). Acute toxicity of boron, titanium dioxide, and aluminum nanoparticles to Daphnia magna and Vibrio fischeri, Stevens Institute of Technology, Center for

Product name	**Aluminium**
	Environmental Systems. Desalination 248 (2009) 771–782. Thomson, S.M., Burnett, D.C., Bergmann, J.D., and Hixson, C.J. (1986). Comparative inhalation hazards of aluminium and brass powders using bronchopulmonary lavage as an indicator of lung damage. *J. Appl.Toxicol.* 6:197-209. Venugopal, B. and T.D. Luckey (1978). Metal Toxicity in Mammals, 2. New York: Plenum Press, p. 111. Walton, J.R. (2011). Bioavailable Aluminium: Its Metabolism and Effects on the Environment; Australian Institute for Biomedical Research, Sydney, NSW, Australia. WHO, World Health Organization (1997). International Programme on Chemical Safety. Environmental Health Criteria 194. Aluminium. pp. 1-13.

B. Boron nanoparticles

For illustrative purposes only. This factsheet does not represent the assessment documents on the risk posed by individual substances following the methodology presented in the report. They aim to illustrate how information could be presented and some factsheet's sections are not necessarily relevantfor all the MFAs. They are based on the collection of available information but are not intended to be comprehensive and do not necessarily reflect the latest developments in the field of MFAs.

Little information is available about boron nanoparticles used as metallic fuel additives. Most probably these compounds are not on the market but only developed in R&D tests. Thus relevant information highlighting the effects of boron as an element has been added in this factsheet. In the factsheet some properties and findings for the non nano-scale material are provided; however please note that this information needs to be used carefully since nano-scale additives may not behave the same as larger scale additives.

Product name	**SB99 Boron nanoparticles**
Chemical names	Boroethane, boron hydride, diboron hexahydride, diborane
Family compounds	Metalloid
CAS	Boroethane 19287-88-8
EINECS	Boroethane 242-940-6
Chemical Formula	B2
Classification / Labelling	Not available
Chemical/Physical properties	Boron has high energetic potential, a high heating value on both gravimetric and volumetric bases, and a high vaporization temperature. It is difficult for Boron to

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Product name	**SB99 Boron nanoparticles**
	completely go through combustion due to an oxide layer on the particle's outermost surface which inhibits the diffusion process of oxygen.
Major constituents	Boron
Information on possible hazards	**HEALTH** **Toxicity values:** Acute oral toxicity in mice (LD50): 560 mg/kg (MSDS boron) **Behaviour in the body:** ■ Boron compounds are rapidly absorbed into the bloodstream and body tissues of several mammalian species following ingestion (95 % in humans and rats). Once in the body, the distribution of boron occurs by passive diffusion throughout bodily fluids. In contrast to soft tissues and blood, bone shows selective uptake of boron (4 times higher than serum) and significantly longer retention times. Boron does not breakdown, most of it leaves the body in the urine within a few days. (INCHEM, 1998). **Health effects:** ■ Although little data is available on the effects of boron on human

Product name	SB99 Boron nanoparticles

health, some studies illustrate that exposure to boron via inhalation is associated with short-term irritant effects on the upper respiratory tract, naso-pharynx and eyes. The aforementioned effects are reversible and no long term effects were identified (Sittig, 1985).

- Animal studies on developmental and reproductive toxicity show that a lower fetal body weight in rats is the critical effect[117]. As the dose level increases, the effects seen include: continued rib effects, testicular atrophy, sterility, and pathology in rats, decreased foetal body weight and increased foetal cardiovascular malformations in rabbits, and reduced foetal body weight in mice (Sittig, 1985; WHO, 1998).

ENVIRONMENT
Ecotoxicity values:

- Nano: A study by Strigul et al. (2009), shows that boron nanoparticles can be classified as "harmful" to aquatic microorganisms. The EC50 ranges from 56- 66 mg/L depending on the age of the solution used for the experiments.

Behaviour in the environment:

- Adsorption-desorption reactions are expected to be the only significant mechanism influencing the fate of boron in water. The extent of boron adsorption depends on the pH of the water and the concentration of boron in solution (INCHEM, 1998).
- In the soil compartment boron is adsorbed onto soil particles, with the degree of adsorption depending on the type of soil, pH, salinity, organic matter content, iron and aluminium oxide content, iron- and aluminium-hydroxy content and clay content. Boron adsorption can vary from being fully reversible to irreversible, depending on the soil type and condition (INCHEM, 1998).
- The short-term degradation products of boron in the environment are not likely to be hazardous whereas the effects of long-term degradation products are unknown (MSDS boron).

Environmental effects:

- Suloway et al. (1983) studied the bioaccumulation potential of the components of coal fly ash extract in Fathead minnows (*Pimephales promelas*) and Green sunfish (*Lepomis cyanellus*). Five fish of each species were exposed for 30 days to fly ash extracts containing boron at concentrations ranging from 1.23 to 91.7

[117] Critical effect is defined as an adverse effect that impedes the cellular function of a critical organ, resulting from the relationship between the dose threshold and effects in an individual (Encyclopaedia of Occupational Health and Safety).

Acronyms	Details
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LOAEL	Lowest Observed Adverse Effect Level (lowest dose that produced an adverse effect)
MFA	metallic fuel additives
MMT	methylcyclopentadienyl manganese tricarbonyl
NOAEL	No Observed Adverse Effect Level (usually expressed in mg/kg/day, it defines the dose of substance that produces no significant toxicological effects for a specific exposure pathway)

Product name	**SB99 Boron nanoparticles**
	mg/litre. Whole-body concentrations of boron ranged from 1.16 to 4.15 µg/g in the exposed fathead minnows and from 1.08 to 4.62 µg/g in the exposed green sunfish. The bioconcentration factor was 0.3 for both species. These results indicate that boron does not bioaccumulate significantly in fish.
Timing of action categorisation: **- distribution system additives** **- vehicle fuel system additives** **- additives sold in filling station**	No data found
Function (category)	■ Air breathing propulsion systems (Gan et al., 2011). ■ Addition of energetic boron particles to fuel increases the total energy release (Gan et al., 2011).

Product name	**SB99 Boron nanoparticles**
Concentration in gasoline (average)	No data found
Emissions in the environment during life cycle	No data found
Vehicle emissions impacts	No data found
Environmental exposure	■ Boron is the 51st most common element found in the earth's crust and is found in an average concentration of 8 mg/kg (approximately 0.0008%) (Cotton et al. 1999; Jansen 2003). ■ Boron is widely distributed in surface water and groundwater. An average surface water boron concentration in the United States is about 0.1 mg/L (Butterwick et al. 1989; EPA 1986b), but concentrations vary greatly, depending on boron content of local geologic formations and anthropogenic sources of boron (Butterwick et al. 1989).
Human exposure	■ Boron compounds can be released to air from natural and industrial sources. Natural sources include oceans, volcanoes, and geothermal steam (Graedel 1978). Boron compounds are released from anthropogenic sources such as coal-fired and geothermal steam power plants, chemical plants, and rockets as well as manufacturing facilities producing fiberglass and other products (EPA 1987; Graedel 1978; Hollis et al. 1988; Lang et al. 1986; Rope et al. 1988; Stokinger 1981).
References	Barres M (1967). Contribution à l'étude de l'isopoly-condensation des borates alkalines par électrométrie et partages. Rev Chem Minér,4: 803-838. Butterwick L, de Oude N, Raymond K. (1989). Safety assessment of boron in aquatic and terrestrial environments. Ecotoxicol Environ Safety 17:339-371. EPA. (1986a). Broad scan analysis of the FY82 national human adipose tissue survey specimens: Vol. I. Executive summary. Washington, DC: U.S. Environmental Protection Agency, Office of Toxic Substances. EPA560586035. EPA. (1987). Toxic air pollutant/source crosswalk: A screening tool for locating possible sources emitting toxic air pollutants. Research Triangle Park, NC: U.S. Environmental Protection Agency, Office of Air Quality Planning and Standards. EPA450487023a. PB88161146. Gan Y., Lim S., Qiao L. (2011). Combustion of nanofluid fuels with the addition of boron and iron particles at dilute and dense concentrations; Combustion and Flame 159 1732–1740.

Acronyms	Details
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GHS	Globally Harmonized System of Classification and Labelling of Chemicals
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LD50	median lethal dose (dose at which 50% of the sample population is eliminated)
LOAEL	Lowest Observed Adverse Effect Level (lowest dose that produced an adverse effect)
MFA	metallic fuel additives
MMT	methylcyclopentadienyl manganese tricarbonyl
NOAEL	No Observed Adverse Effect Level (usually expressed in mg/kg/day, it defines the dose of substance that produces no significant toxicological effects for a specific exposure pathway)

Product name	**SB99 Boron nanoparticles**

Graedel TE. (1978). Inorganic elements, hydrides, oxides and carbonates. In: Chemical compounds in the atmosphere. New York, NY: Academic Press, 35-49.

Hollis JF, Keren R, Gal M. (1988). Boron release and sorption by fly ash as affected by pH and particle size. J Environ Qual 17:181-184.

INCHEM (1998). International Programme on Chemical Safety. Environmental Health Criteria 204, Boron.

Lang FJ, Bingham FT, Hendrix FF, et al. (1986). Boron deposition on soil and native vegetation from geothermal emissions. J Environ Qual 15(3):260-265.

Lovatt CJ & Dugger WM (1984). Boron. In: Frieden E ed. Biochemistry of the essential ultratrace elements. New York, London, Plenum Press, pp 389-421.

MSDS (Materiel Safety Data Sheet)boron
www.sciencelab.com/msds.php?msdsId=9923126

Nordberg M., Duffus J. H., Templeton D. M., *Pure Appl. Chem.*, **76**, 1033-1082 (2004).

Rope SK, Arthur WJ, Craig TH, et al. (1988). Nutrient and trace elements in soil and desert vegetation of southern Idaho. Environ Monit Assess 10:1-24.

Sittig, M. (1985). Handbook of Toxic and Hazardous Chemicals and Carcinogens, 1985. 2nd ed. Park Ridge, NJ: Noyes Data Corporation, p. 138.

Product name	SB99 Boron nanoparticles
	Stokinger HE. (1981). Boron. In: Clayton GD, Clayton FE, eds. Patty's industrial hygiene and toxicology. Vol. 2B. Toxicology. 3rd ed. New York, NY: John Wiley and Sons, 2978-3005. Strigul N., Vaccari L., Galdun C., Wazne M., Liu X., Christodoulatos C., Jasinkiewicz J. (2009). Acute toxicity of boron, titanium dioxide, and aluminum nanoparticles to Daphnia magna and Vibrio fischeri, Stevens Institute of Technology, Center for Environmental Systems. Desalination 248 (2009) 771–782. Suloway JJ, Roy WR, Skelly TM, Dickerson DR, Schuller RM, & Griffin RA (1983). Chemical and toxicological properties of coal fly ash. Champaign, Illinois, Illinois State Geological Survey (Publication NTIS PB84-116110) U.S. Department of Health and Human Services (2010). Toxicological Profile for Boron. Public Health Service, Agency for Toxic Substances and Disease Registry (ATSDR). World Health Organization. (1998). International Programme on Chemical Safety. Environmental Health Criteria 204. Boron pp. 1-10 (1998)

C. Cerium Oxide

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Nanoscale Cerium (di) oxide is used as fuel additive. In the factsheet some properties and findings for the non-nano-scale material are provided; however please note that this information needs to be used carefully since nano-scale additives may not behave the same as larger scale additives.

Cerium oxide is typically used as a fuel borne catalyst or as an aftermarket/captive fleet additive. Although these applications are outside the scope of the Fuel Quality Directive, cerium potentially could find application in retail or wholesale diesel fuel as a diesel combustion improver.

Product name	Nanoscale Cerium (di) oxide
Chemical names	■ cerium oxide ■ cerium dioxide, ■ ceric oxide,

Acronyms	Details
BCF	Bioconcentration factor
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LD50	median lethal dose (dose at which 50% of the sample population is eliminated)
LOAEL	Lowest Observed Adverse Effect Level (lowest dose that produced an adverse effect)
MFA	metallic fuel additives
MMT	methylcyclopentadienyl manganese tricarbonyl
NOAEL	No Observed Adverse Effect Level (usually expressed in mg/kg/day, it defines the dose of substance that produces no significant toxicological effects for a specific exposure pathway)

Product name	**Nanoscale Cerium (di) oxide**
	■ cerium (IV) oxide, ■ ceria
Commercial names	■ Envirox; ■ Eoly DPX-9 (Rhodia)
CAS	1306-38-3
EINECS	215-150-4
Chemical Formula	CeO_2
Classification / Labelling	Not available yet
Chemical/Physical properties	Cerium oxide is a white to pale yellow powder, soluble in sulfuric acid and insoluble in dilute acid and water. Ambient air cerium is associated with the fine and ultrafine particles (<2 µm). The particle sizes of cerium oxide polishing powders are in the low-micrometer range (e.g. 0.45 to 6 µm).
Major constituents	Cerium

Product name	**Nanoscale Cerium (di) oxide**
Information on possible hazards	**HEALTH** **Toxicity values:** ■ Workers □ Long-term exposure - systemic effects: □ Dermal DN(M)EL 8.33 mg/kg bw/day □ Inhalation DN(M)EL 3 mg/m³ ■ General population □ Dermal DN(M)EL 4.17 mg/kg bw/day □ Inhalation DN(M)EL 1.5 mg/m³ □ Oral DN(M)EL 4.17 mg/kg bw/day (ECHA database) **Bioaccumulation:** ■ After airborne exposure, poorly-soluble nanoscaleCeO_2 particlescan deposit within the respiratory tract based on aerodynamic properties such as size, distribution, and agglomeration\ aggregation state (Oberdörster et al. 2005). ■ CeO_2 NPs, in combination with diesel exhaust, can significantly interfere with the cell machinery, indicating a specific, potentially adverse role of CeO_2 NPs in regards to the biological response of diesel exhaust exposure (Steiner et al. 2012)[118]. Other studies have detected nanoscale cerium within: ■ Liver and skeleton (Lundgren 1992); ■ Lymph nodes (Liedscher and Schonfeld 1996); ■ Lung tissue and alveolar macrophages of subjects with chronic exposure to cerium fumes or dust(Vocaturo et al, 1983; Sabbioni et al. 1982). **Health effects:** ■ ■ Adverse lung effects, such aspneumoconiosis, were observed but it is unclear whether there is a direct causative link between the effects and cerium exposure or of a multiple exposures to other

[118] It has to be noted here that these results are based on CeO_2 NPs that were not mixed with the diesel fuel, but instead applied after diesel exhaust exposure (Communication from Energenics)

Acronyms	Details
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NOAEL	No Observed Adverse Effect Level (usually expressed in mg/kg/day, it defines the dose of substance that produces no significant toxicological effects for a specific exposure pathway)

Product name	Nanoscale Cerium (di) oxide
	chemicals in the workplace (Gomez Aracena et al. 2006) ■ Myocardial infarction was suggested by Gomez Aracena et al. (2006) as well as links to endomyocardial fybrosis (Kutty et al. 1996; Eapen 1997) ■ Studies of cerium systemically injected into the bloodstream indicate that cerium can cause liver toxicity with a NOAEL of 1 mg/kg after a single intravenous injection and a LOAEL of 2 mg/kg for effects on liver detoxifying enzymes. Effects on other organs where cerium can accumulate (such as spleen, bones, and kidney) have not been studied (HEI 2001) ■ No studies on chronic exposure were identified. However, Cassee et al. (2011) states that there exists a high degree of uncertainty regarding the health implications of chronic exposure to emissions generated with this fuel additive and further testing is required to ensure that such an approach is not associated with a chronic inflammatory response which may eventually cause long-term health effects. ■ According to Cassee et al. (2011), the full range of health implications are not known for using CeO_2 as a diesel fuel

Product name	Nanoscale Cerium (di) oxide

additive, an additive that also changes the chemical composition of its diesel emissions. However, the addition of CeO_2 nanoparticles to fuel may decrease the number of particles in exhaust and hence reduce atherosclerotic burden associated with exposure to standard diesel fuel.

- Most studies focus on the effects of cerium and not on the effects of CeO_2, which is suggested by HEI (2001) to be the most important cerium compound in diesel emissions.
- The most concerning effect observed in a study by Cassee et al. (2012), after subacute inhalation of diesel exhaust following addition of cerium oxide nanoparticules in astherosclerosis-prone mice was a slightly raised level of cytokines in a region of the central nervous system.
- No dose reponse relationship has been found in the study (Cassee et al., 2012).
- Finally, studies differ in terms of particle size, concentration, duration and endpoint studied. The review realised by Cassee et al (2011) reveals that few studies on the effects of nanoscale cerium oxide are quoted.

ENVIRONMENT
Ecotoxicity values:
No or insufficient data available at present
Behaviour in the environment:

- According to Cassee et al. (2011) CeO_2 nanoparticles may persist in the environment and biological systems, and if used on a large scale for a long period of time, the nanoparticlesmay increase in concentration and\or accumulation thereby posing seriouspublic health risks.
- CeO_2 nanoparticles are believed to accumulate in soil and sediments (HEI, 2001), notably due to an ion-exchange between the particles and carbonates, organic matter, and iron and manganese oxides/hydroxides (preference for the latter two forms at pH >7) (Pang et al., 2002)
- Natural organic matter appears to reduce the aggregation of CeO_2 nanoparticles thus producing a suspension of CeO_2 nanoparticles that is stable for several days (Keller et al. 2010; Quik et al. 2010)
- In the exit stream of a model wastewater treatment plant, the particle mass of CeO_2 nanoparticles was found to be around 6% of the total mass (Kimbach et al. 2008)
- CeO_2 nanoparticles are suggested to have the ability to be taken up by alfalfa, corn, tomato and cucumber thusposing a serious

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MFA	metallic fuel additives
MMT	methylcyclopentadienyl manganese tricarbonyl
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Product name	**Nanoscale Cerium (di) oxide**
	threat to the food chain (Lopez-Moreno et al. 2010) **Environmental effects:** ■ The full range of environmental and ecological effects of using nanoscale CeO_2 as a diesel fuel additive in current and new fuel formulations and engine redesigns and thenew composition of its diesel emissions, are not known (Cassee et al. 2011) ■ CeO2 nanoparticle-induced ecotoxicity was observed in the water flea species Daphnia magna and the green algae P. subcapitata at concentrations <10 mg/L (Van Hoecke et al. 2009) ■ CeO2 nanoparticle-induced acute toxicity was not observed in two crustaceans and *D. rerio* embryos at concentrations >200 mg/L (Van Hoecke et al. 2009)
Timing of action categorisation: **- distribution system additives** **- vehicle fuel system additives**	■ Diesel additive ■ Vehicle fuel system additive

Product name	**Nanoscale Cerium (di) oxide**
- additives sold in filling station	
Function (category)	■ To serve as fuel-borne catalysts ■ Intended to increase mileage (performing as a combustion catalyst) by increasing fuel combustion efficiency and decreasing diesel soot emission (enhancement of the combustion of the soot) (HEI 2001, Park et al. 2007; Park et al. 2008a; EPA 2009). ■ Cassee et al., in 2012 show that addition of CeO2 nanoparticles to fuel can can induce a reduction of the number of particles in exhaust and decrease astherosclerotic burden associated with exposure to standard diesel fuel. The authors suggest that the net effect of using CeO2 is the formation of more condensed particle agglomerates in the exhaust.
Concentration in diesel (average)	■ 5ppm (Park et al. 2007)
Emissions in the environment during life cycle	■ According to engine tests employing nanoscale cerium in the particulate phase, a small amount of cerium emitted with the diesel exhaust was found to be nanoscale (or ultrafine) particle (<100 nm) (HEI, 2001; Jung et al. 2005).;. ■ Diesel emissions may contain several types of cerium coumpounds: CeO2 (major), Ce sulfate and Ce phosphate (Park et al. 2008a). ■ Park et al. (2008a) measured the impact of using Envirox on existing ambient PM levels in London and Newcastle. Following the introduction of Envirox at Newcastle, the concentration of cerium increased fourfold and soluble Ce formed.
Vehicle emissions impacts	■ Cerium diesel fuel additive can decrease the total numbers of particles but an increase in NOx and CO levels has been observed but these alterations were small and non-significant (Cassee et al., 2012). ■ Cerium diesel fuel additive can increase ultrafine particules (<100nm in size), CO, hydrocarbon content and volatile organic compounds , as suggested by HEI (2001), Farfaletti et al. (2005), Jung et al. (2005).
Environmental exposure	■ The increase in ambient air concentrations of nanoscale CeO2 could contribute to the presence of these particles in other environmental media, including water and soil, as well as uptake into the food chain (Cassee et al. 2011) ■ The addition of nanoscale cerium to diesel fuel in Newcastle is

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Product name	**Nanoscale Cerium (di) oxide**
	associated witha fourfold increase in cerium concentration in ambient air (Park et al 2008a). ■ There is uncertainty about the amount of cerium that will be released in the environment as a result of its use as a fuel additive. Because cerium is already present in soil and is used in some vehicle manufacturing and other industrial processes, a baseline level exists in both ambient air and soil
Human exposure	■ Inhalation has been identified as the main route of exposure by HEI (2001) ■ Dermal contact may also occur (HEI 2001)
References	Cassee FR, van Balen EC, Singh C, Green D, Muijser H, Weinstein J and Dreher K (2011) Exposure, health and ecological effects review of engineered nanoscale cerium and cerium oxide associated with its use as a fuel additive. Critical reviews in toxicology41: 213-29. Cassee,F.R.,et al.,The biological effects of subacute inhalation of diesel exhaust following addition of cerium oxide nanoparticles in atherosclerosis prone mice.Environ.Res.(2012),dx.doi.org/10.1016/j.envres.2012.03.004

Product name	Nanoscale Cerium (di) oxide
	ECHA database: apps.echa.europa.eu/registered/data/dossiers/DISS-a217355e-db00-127d-e044-00144f67d031/AGGR-47b9b69d-8c88-48c4-88c1-e2173c64da34_DISS-a217355e-db00-127d-e044-00144f67d031.html#AGGR-47b9b69d-8c88-48c4-88c1-e2173c64da34 Eapen JT (1997) Cerium Levels are Elevated in the Serum of Patients with Endomyocardial Fibrosis (EMF) Biological Trace Element Research, 59: 41-44. EPA, US (2007) Nanotechnology White Paper. EPA 100/B -07/February 2007. www.epa.gov/osa/pdfs/nanotech/epa-nanotechnology-whitepaper-0207.pdf EPA, US (Sept. 2009). Toxicological Review of Cerium Oxide and Cerium Compounds. EPA/635/R-08/002F. www.epa.gov/iris/toxreviews/1018tr.pdf Farfaletti F, et al. (2005). Effect of Water\Fuel Emulsions and Cerium Based Combustion Improver Additive on HD and LD Diesel E xhaust Emissions. Environ. Sci. Technol. 39: 6792-6799 Gomez-Aracena J, R iemersma R A, G uti`rrez-B edmar M, B oden P, K ark JD, Garcia-Rodriguez A, Gorgojo L, Veer PV, Fernandez-Crehuet J, Kok FJ and Martin-Moreno JM (2006). Toenail Cerium Levels and Risk of first Acute Myocardial Infarction: The Euramic and Heavy Metals Study.Chemosphere 64: 112-120. HEI - Health Effects Institute, Research Report, 2001. Evaluation of Human Health Risk from Cerium added to Diesel Fuel. HEI Research Communication 9. North Andover Ma: Flagship Press. pubs.healtheffects.org/view.php}id = 172. Jung J, Kittelson DB, Zachariah MR (2005). The Influence of a Cerium Additive on Ultrafine Emissions and Kinetics of Oxidation. Combustion and Flame 142: 276 - 288. Keller, AA, W ang H, Zhou D, Lenihan HS, Cherr G , Cardinale B J, Miller R , Ji Z (2010). Stability and aggregation of metal oxide nanoparticles in natural aqueous matrices. Environ. Sci. Technol. 44: 1962-1967. Kutty VR , Abraham S and Kartha CC (1996). G eographical Distribution of Endomyocardial Fibrosis in South Kerala. International J Epidemiology 25: 1202-1207. Limbach LK , Bereiter R , Muller E, Krebs R , Galli R and Stark W J (2008). Removal of Oxide Nanoparticles in a Model Wastewater Treatment Plant: Influence of Agglomeration and Surfactants on Clearing Efficiency. Environ Sci Technol 42: 5828-5833 Lopez-Moreno ML, De La Rosa G, Hernandez JA, Peralta-Videa JR, Gardea-Torresdey JL (2010). X-ray absorption spectroscopy of CeO2 nanoparticles and assessment of their differential toxicity in four edible plants. Jour. Agric. Food Chem. 58: 3689-3693 Oberdorster G, Oberdorster E, Oberdorster J (2005). Nanotoxicology: an Emerging Discipline Evolving from Studies of Ultrafine Particles. Environ. Health Perspect. 113: 823-839 Pang X, Li D, and Peng A (2002). Application of rare-earth elements in the

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	agriculture of China and its environmental behavior in soil. Environ Sci Pollut Res Int 9: 143-148 Park B, Donaldson K, Duffin R, Tran L, Kelly F, Mudway I, Morin JP, Guest R, Jenkinson P, Samaras Z , Giannouli M, Kouridis H and Martin P (2008a) Hazard and Risk Assessment of a Nanoparticulate Cerium Oxide-Based Diesel Fuel Additive - A Case Study. Inhal Toxicol 20: 547-566. Park B, Martin P, Harris C, Guest R , Whittingham A, Jenkinson P and Handley J (2007) Initial in Vitro Screening Approach to Investigate the Potential Health and Environmental Hazards of Enviroxtrade Mark – A Nanoparticulate Cerium Oxide Diesel Fuel Additive. Part Fibre Toxicol 4: 12. Park EJ, Choi J, Park ZK and Park K (2008b). Oxidative Stress Induced by Cerium Oxide Nanoparticles in Cultured B eas-2b Cells. Toxicology 245: 90-100. Quik JTK, Lynch I, Van Hoecke K, Miermans CJH, De Schamphelaere KAC, Janssen CR, Dawson KA, Stuart MAC, De Meent DV (2010). Effect of natural organic matter on cerium dioxide nanoparticles settling in model fresh water. Chemosphere, doi:10.1016/j.chemosphere.2010.07.062. Sabbioni E, Pietra R, Gaglione P, Vocaturo G , Colombo F, Zanoni M, Rodi F (1982). Long-term occupational risk of rare-earth pneumoconiosis. A case report as

Product name	**Nanoscale Cerium (di) oxide**
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D. Iron fuel additives

For illustrative purposes only. This factsheet does not represent the assessment documents on the risk posed by individual substances following the methodology presented in the report. They aim to illustrate how information could be presented and some factsheet's sections are not necessarily relevantfor all the MFAs. They are based on the collection of available information but are not intended to be comprehensive and do not necessarily reflect the latest developments in the field of MFAs.

Iron fuel additives compounds contain four mains fuel additives which are the dicyclopentadienyl iron much known as the ferrocene , the pentacarbonyl iron, the ferox and the ferrous picrate. In this factsheet information about each compound have been collected or otherwise less specific information about the effects of iron element are provided.

Products names	**Dicyclopentadienyl iron (ferrocene)** **Pentacarbonyl iron** **Ferox** **Ferrous picrate**
Chemical names	■ **Dicyclopentadienyl iron**: Biscyclopentadienyliron;dicyclopentadienyliron;di-2,4-cyclopentadien-1-yliron;di-pi-cyclopentadienyl iron;iron bis(cyclopentadiene);ferrotsen;iron bis(cyclopentadienide);iron,bis(eta(5)-2,4-cyclopentadien-1-yl)-iron dicyclopentadienyl;ai3-23119;ccris ■ **Pentacarbonyl iron**: Iron carbonyl ; Iron carbonyl Fe(CO)5 ; Iron, pentacarbonyl-Pentacarbonyliron

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Products names	**Dicyclopentadienyl iron (ferrocene)** **Pentacarbonyl iron** **Ferox** **Ferrous picrate**
	■ **Ferox**:Ferroglyconicum; Ferronicum; Ferrose;ferrous gluconate;gluco-ferrum ;glucomax;gluconic acid iron salt;gluconic acid, iron(2+) salt (2:1), d-;gluferate;iromon;iron gluconate;iron-ii gluconate;irox;nionate ;ray-gluciron; ■ **Ferrous picrate**: iron dipicrate
Commercial names	■ Dicyclopentadienyl iron: ferrocene ■ **Ferox:** ferrin 55, biofergate
CAS	**Dicyclopentadienyl iron (ferrocene):** 55404-68-7/102-54-5 **Pentacarbonyl iron:** 13463-40-6/37220-42-1 **Ferox:** 97467-73-7/12562-64-0/18829-42-0/299-29-6/68476-34-6 **Ferrous picrate:** 14866-25-2
EINECS	**Dicyclopentadienyl iron (ferrocene)**:203-039-3

Products names	**Dicyclopentadienyl iron (ferrocene)** **Pentacarbonyl iron** **Ferox** **Ferrous picrate**
	Pentacarbonyl iron: 236-670-8 **Ferox:** 206-076-3 **Ferrous picrate:** 238-934-8
Chemical Formula	**Dicyclopentadienyl iron** (ferrocene):C10H10Fe **Pentacarbonyl iron:** C_5FeO_5 **Ferox:** $C_{12}H_{24}FeO_{14}$ **Ferrous picrate:** $C_6H_2FeN_3O_7^+$
Classification / Labelling	**Labelling according Regulation (EC) No 1272/2008 (CLP) for the dicyclopentadienyl iron (ferrocene)** Flammable solids (category 1) Acute toxicity, Oral (category 4) H228 Flammable solid H302 Harmful if swallowed ▪ CERCLA Reportable Quantities: Iron pentacarbonyl is an Extremely Hazardous Substance (EHS) subject to reporting requirements when stored in amounts in excess of its Threshold Planning Quantity (TPQ) of 45,36 kg according to the CERCLA[119](40 CFR 355, 2004).
Major metallic constituents and concentration	**Ferrocene** Iron content: 29.4-30.6% (Lewis, 1997)
Chemical /physical properties	**Ferrocene** ▪ Slightly soluble in petroleum ether (Hawley,1977) ▪ Dissolves in dilute nitric and concentrated sulfuric acids; soluble in alcohol, ether; practically insoluble in 10% sodium hydroxide, and concentrated boiling hydrochloric acid (O'Neil, 2001) ▪ Solubility at 25 deg C: 19 g/100 g benzene; 10 g/100 g catalytically cracked gasoline; 9 g/100 g straight run gasoline; 6 g/100 g jet fuel (jp-4); and 5 g/100 g diesel fuel. ▪ 20 mg/mL in 2-methoxyethanol; 7 mg/ml in ethanol

[119]CERCLA: The Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA), commonly known as Superfund, was enacted by US Congress on December 11, 1980. This law created a tax on the chemical and petroleum industries and provided broad Federal authority to respond directly to releases or threatened releases of hazardous substances that may endanger public health or the environment

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Products names	**Dicyclopentadienyl iron (ferrocene)** **Pentacarbonyl iron** **Ferox** **Ferrous picrate**
	■ <0.1 mg/mL in water (Green FJ, 1990) **Iron pentacarbonyl** ■ Practically insoluble in water, liquid ammonia. Readily soluble in most organic solvents including ether, petroleum ether, carbon tetrachloride, carbon disulfide; slightly soluble in alcohol. (O'Neil, 2001) ■ Soluble in nickle tetracarbonylsoluble with decomposition in acids and alkalies (Lewis, 1997) ■ Completely miscible with petroleum ether, hexane, benzene, pentanol, and higher alcohols, ethyl ether, acetone, acetic acid, and ethyl acetate. It is partially miscible with paraffin oil and lower alcohols up to butanol. (Gerhartz, 1989) ■ Water solubility data for iron pentacarbonyl are contradictory; a value of 50-100 mg/L can be assumed the solubility of water in iron

Products names	**Dicyclopentadienyl iron (ferrocene)** **Pentacarbonyl iron** **Ferox** **Ferrous picrate**
	pentacarbonyl is 200-400 mg/kg. (Gerhartz, 1989)
Information on possible hazards	**HEALTH** **Toxicity values:** **Ferrocene:** ■ Acute toxicity: LD50 120Oral 600 to 1320 mg/kg (species: rat and mouse) (Bingham et al, 2001) **Pentacarbonyl iron:** ■ Oral: LD50 12 to 200 mg/kg (species: mouse, rat rabbit cat and guinea pig) ■ Inhalation: 0,08 to 2,19 mg/L (species: mouse and rat) ■ Dermal: LD50 56 to 240 mg/kg (species: rabbit) (Lewis, 1996; O'Neil, 2001) **Ferox:** ■ Oral: LD50 464 to 3700 mg/kg (Lewis et al., 1996; Lysionek et al., 2003; O'Neil 2001) **Behaviour in the body:** **Iron element:** The half-life for clearance of radiolabeled iron was shown to be 200 days for the bronchopulmonary region and 70 days for the nasopharyngeal region in studies by Bingham et al. (2001) **Ferrocene:** ■ The metabolism of ferrocene was studied in rats following a 17 min inhalation exposure and suggest that ferrocene deposition was significant in the nasopharynx and lungs. Within 24 hours after exposure, 75% of the radiolabeled hydrogen was cleared from the respiratory tract. For the retained radiolabeled iron, 90% was in the bronchopulmonary and nasopharyngeal regions of the lungs, 10% was in the liver, and 1% was in the spleen.(Investigation of Otto Engine Exhaust Resulting from the Combustion of Fuel with Added Ferrocene, july 1996). ■ Animals were exposed to ferrocene for 18 hours/day, 5 days/week for 12 months (for chronic toxicity), or for 24 months + 6 months recovery (for carcinogenicity). Pulmonary end points included particle retention, lung clearance, biochemical and cytological

[120] LD50(Lethal Dose)is the amount of a substancerequired to kill 50% of a given test population.

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Products names	**Dicyclopentadienyl iron (ferrocene)** **Pentacarbonyl iron** **Ferox** **Ferrous picrate**
	measurements in bronchial lavage fluid, and mechanical lung function. Histopathology, clinical chemistry, and urine analysis were also conducted. Animals exposed to exhaust from ferrocene-containing fuel did not respond differently than those exposed to fuels not containing ferrocene. No toxic effects were observed in the animals after 24-30 months(Investigation of Otto Engine Exhaust Resulting from the Combustion of Fuel with Added Ferrocene, july 1996). **Health effects:** ■ If inhaled, iron compounds have been suggested to act as a local irritant to the lungs and gastrointestinal tract (Encyclopaedia of occupational health and safety, 1998). ■ According to studies conducted by O'Neil (2001), symptoms of overexposure to iron include irritation of eyes, mucous membranes, respiratory system, headache, dizziness, nausea, vomiting, fever,

Products names	**Dicyclopentadienyl iron (ferrocene)** **Pentacarbonyl iron** **Ferox** **Ferrous picrate**

cyanosis, cough, dyspnea, liver, kidney, lung injury, degenerative CNS changes

Iron pentacarbonyl

Iron pentacarbonyl, as reported by Sittig (1985), is one of the most hazardous metal carbonyls in existence due to its volatility and toxicity. Sittig suggests that death from overexposure to the chemical may occur within 4 -11 days after contact due to ensuing pneumonia, liver damage, vascular injury, and central nervous system degeneration.

Ferrocene

- Ferrocene, an iron compound whose derivatives are often used in fuel additives, can create harmful health effects from short and long-term exposure. In one study of chronic ferrocene exposure, mice that were fed a diet containing 0.04-0.2% w/w ferrocene for 115 days displayed severe lung inflammation (hepatic siderosis of hepatocytes) accompanied by a 15-fold induction of nonheme iron content compared to control mice. Furthermore, the ferrocene treatment for mice led to a significant increase in the death rate of liver cells (hepatocellular necrosis). Histological assessment of hepatic fibrosis revealed mild increases in collagen deposition localized with accumulations of hemosiderin primarily in centrilobular hepatocytes. Hepatic fibrosis was confirmed by measurement of hepatic hydroxyproline content that was increased 4-fold in ferrocene-fed animals compared to control animals not ingesting ferrocene. Hepatic siderosis was accompanied by significant increases in hepatic malondialdehyde content suggesting the ferrocene-induced iron burden initiated lipid peroxidation in vivo. Expression of the heavy-chain isoform of ferritin mRNA and protein measured in liver after ferrocene feeding was increased approximately 8- and 2-fold, respectively, compared to the appropriate controls.(Valerio et al., 2000)
- A study by Dresow et al. (1995) show that the feeding of a diet enriched with 0.5% TMH-ferrocene up to 31 weeks resulted in a large increase in liver iron concentration to about 25 mg/g wet weight (w wt) in rat. Plasma as well as hepatic alpha-tocopherol decreased with progressive iron loading. In addition, a significant depletion in hepatic

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Products names	**Dicyclopentadienyl iron (ferrocene)** **Pentacarbonyl iron** **Ferox** **Ferrous picrate**
	ubiquinol 9 and 10 was noted (Dresow et al., 1995) ■ The Octel company[121] has provided exhaust emission toxicological data on vehicles using gasoline containing ferrocene. In none of the studies conducted, could differences be detected in the toxic effects of the exhausts, deriving from fuel without and with 30 ppm ferrocene (Octel recommended maximum dosage),. Particularly in the inhalation studies, using the highest exhaust concentrations technically possible, no toxic effects from the exhaust from engines equipped with 3-way catalysts, could be detected. **ENVIRONMENT** **Ecotoxicity Values** **Pentacarbonyl iron** ■ LC50 Leuciscus idus (Ide) 990 mg/L/96 hr; static /purity >99.5%/ (

[121] The Octel Company is acompany that produced fuel additives in the past.

Products names	**Dicyclopentadienyl iron (ferrocene)** **Pentacarbonyl iron** **Ferox** **Ferrous picrate**
	IUCLID dataset) ■ EC50 122Scenedesmus subspicatus (Green algae; cell multiplication inhibition) 150 mg/L/72 hr. Conditions of bioassay not specified in source examined(IUCLID dataset) **Ferrocene** ■ The degradation of the dicyclopentadienyl iron has been tested with several OECD guideline tests including the following results: □ Predicted Ultimate degradation half-life: 15 days □ The MITI test: probability of biodegradation: 0.0997 days □ EPI Predicted Ozone reaction half-life 0.01674 days □ EPI Predicted Atmospheric Oxidation half-life 0.02806 days □ This substance is classified as persistent in light of these results by the OECD.(OECD webnet) **Behaviour in the environment:** **Iron pentacarbonyl** ■ Iron pentacarbonyl (Fe(CO)5), which has a vapor pressure of 21 mm Hg at 20 deg C, exists in vapor form when in contact with air. When exposed to light, iron pentacarbonyl slowly converts to diiron nonacarbonyl (Fe2(CO)9), a compound highly sensitive to air. Further decomposition products were not identified. (Stolzenberg, 1995) **Environmental effects:** **Ferrocene** ■ According to Australia's Environmental Protection Authority exist classification database of environmental hazards, the effects of ferrocene on species are: ■ Classification 9.1B: Ecotoxic in the aquatic environment to fish, crustaceans, and algae ■ Classification 9.3B: Ecotoxic to terrestrial vertebrates
Timing of action categorisation:	**Ferrocene** ■ distribution system additives

[122]EC50: the half maximal effective concentrationrefers to the concentration of a drug, antibody or toxicant which induces a response halfway between the baseline and maximum after a specified exposure time.

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EC50	half maximal effective concentration
GHS	Globally Harmonized System of Classification and Labelling of Chemicals
IPPC	Integrated Pollution Prevention and Control
Kow	Octanol – water coefficient
LC50	median lethal concentration (concentration at which 50% of the sample population is eliminated)
LD50	median lethal dose (dose at which 50% of the sample population is eliminated)
LOAEL	Lowest Observed Adverse Effect Level (lowest dose that produced an adverse effect)
MFA	metallic fuel additives
MMT	methylcyclopentadienyl manganese tricarbonyl
NOAEL	No Observed Adverse Effect Level (usually expressed in mg/kg/day, it defines the dose of substance that produces no significant toxicological effects for a specific exposure pathway)

Products names	**Dicyclopentadienyl iron (ferrocene)** **Pentacarbonyl iron** **Ferox** **Ferrous picrate**
- distribution system additives **- vehicle fuel system additives** **- additives sold in filling station**	■ vehicle fuel system additives **Iron pentacarbonyl** ■ distribution system additives ■ vehicle fuel system additives **Ferox** ■ vehicle fuel system additives **Ferrous picrate** ■ vehicle fuel system additives ■ additives sold in filling station
Functions	■ Antiknock additive for gasoline; catalyst

Products names	**Dicyclopentadienyl iron (ferrocene)** **Pentacarbonyl iron** **Ferox** **Ferrous picrate**
	■ The iron fuel additives have been suggested to: □ Eliminate carbon deposits from the combustion surfaces of the engine and deposit a layer of iron that effectively to prevents further buildup of carbon deposits (WHO, EHC 192, 1997). □ Result in more complete combustion and lower emissions of Carbon monoxide (CO , Sulfur oxides (SOx) , Nitrogen oxides (NOx), High hydrocarbons (HC's) and 10 micrometers or less particules (PM10) (WHO, EHC 192, 1997). □ increase the fuel consumption, improve vehicle performance, and decrease the need for vehicle maintenance. Improving the octane number rating of the fuel composition in order to improve antiknock properties (WHO, EHC 192, 1997). ■ Ferrocene, according to the World Health Organization (WHO), effectively suppresses vehicle smoke by oxidizing soot in the gas phase as well as by pronounced charring of the substrate in the condensed phase (WHO, EHC 192, 1997). ■ High levels of ferrocene in diesel fuel can create "effective knock" in the diesel engine. Such effects have been noted with dicyclopentadienyl iron concentrations as low as 20+ppm. ■ Disadvantages noted include causing wear in the engine parts (wear of the piston rings) because of the abrasive properties of the pentacarbonyl iron so this properties have thus far prevented its use commercially in motor vehicles (WHO, EHC 192, 1997).
Concentration in gasoline (average)	■ A diesel engine operates with fuel containing a concentration of ~20-30 ppm of dicyclopentacarbonyl iron, an amount that is reduced by half after the first reaction. (US Patent 4389220). ■ The amount of iron needed in diesel fuel to improve the composition's octane number is ~0.01- 0.22 g/ 4L of gasoline. (US patent 4,336,033). ■ This additives are available in liquid form or solid form like the ferox tablets. ■ A Ferox Fuel Tab, an engine performance enhancer, treats up to 57Lof gasoline or diesel fuel with a Ferox tablet that removes and prevents carbon deposits. The tablet is placed into the fuel mixes

Acronyms	Details
BCF	Bioconcentration factor
CEC	Coordinating European Council
CLP	Classification Labelling and Packaging
DNEL	Derived No-Effect Level (DNELs are calculated by dividing the value of the health effect dose descriptor by an assessment factor (or safety factor) to allow for extrapolation to real human exposure situations)
DMEL	Derived Minimal Effect Level
EC50	half maximal effective concentration
GHS	Globally Harmonized System of Classification and Labelling of Chemicals
IPPC	Integrated Pollution Prevention and Control
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LD50	median lethal dose (dose at which 50% of the sample population is eliminated)
LOAEL	Lowest Observed Adverse Effect Level (lowest dose that produced an adverse effect)
MFA	metallic fuel additives
MMT	methylcyclopentadienyl manganese tricarbonyl
NOAEL	No Observed Adverse Effect Level (usually expressed in mg/kg/day, it defines the dose of substance that produces no significant toxicological effects for a specific exposure pathway)

Products names	**Dicyclopentadienyl iron (ferrocene)** **Pentacarbonyl iron** **Ferox** **Ferrous picrate**
	with the fuel and dissolves completely within minutes (www.feroxfueltabs.com)
Emissions in the environment during life cycle	■ Iron is abundant in nature and is a basic constituent of motor vehicles. Ferrocene emissions from vehicle exhaust tailpipes include iron oxide whether or not the fuel is treated with additives. The presence of iron oxide in ferrocene emissions, according to Duncan Seddon Associates (2000), indicates that ferrocene use at recommended levels may not significantly add to the total levels of ferrocene emissions. However, this further investigation is needed.
Vehicle emissions impacts	■ WHO suggest that the use of Iron fuel additives could lower emissions of CO,Sox,Nox,HC's and PM10 (WHO, EHC 192, 1997)
References	EPA database

Products names	**Dicyclopentadienyl iron (ferrocene)** **Pentacarbonyl iron** **Ferox** **Ferrous picrate**
	www.epa.govt.nz/search-databases/Pages/ccid details.aspx?SubstanceID=2464 Pubchem pubchem.ncbi.nlm.nih.gov/summary/summary.cgi?cid=7611 Sigmaaldrich www.sigmaaldrich.com/catalog/DisplayMSDSContent.do Ferox fuel tabs site www.feroxfueltabs.com/ Powered by ferox www.poweredbyferox.com/ Peswiki peswiki.com/index.php/Directory:Ferox_Fuel_Additive OECD site: webnet.oecd.org/ccrweb/ChemicalDetails.aspx?ChemicalID=631521B8-5D4B-46E0-96F8-995E8742B217 American Conference of Governmental Industrial Hygienists (1986). Documentation of the Threshold Limit Values and Biological Exposure Indices. 5th ed. Cincinnati, OH: American Conference of Governmental Industrial Hygienists, p. 195 Armour, M.A (1991). Hazardous Laboratory Chemicals Disposal Guide. Boca Raton, FL: CRC Press Inc., p. 197. Bingham, E.; Cohrssen, B.; Powell, C.H. (2001).Patty's Toxicology Volumes 1-9 5th ed. John Wiley & Sons. New York, N.Y. p. V2 42. 40 CFR 355; U.S. National Archives and Records Administration's Electronic Code of Federal Regulations. Available from, as of November 1, 2004: www.gpoaccess.gov/ecfr Conversation between the author and Mr. David Naegli and Mr. Vernon Markworth (1993). Southwest Research Institute. Du, C.J., Kracklauer, J. and Kittelson, D.B (1998). Influence of an Iron Fuel Additive on Diesel Combustion, SAE Paper 980536. Duncan Seddon associates (2000). Octane enhancing petrol additives/products; literature review and analysis. Dresow B et al (1995). Hepatology 21 (4): 1099-105. Gerhartz, W. (exec ed.) (1989). Ullmann's Encyclopedia of Industrial Chemistry. 5th ed.Vol A1: Deerfield Beach, FL: VCH Publishers, 1985 to Present., p. VA14: 596. Green FJ (1990).The Sigma-Aldrich Handbook of Stains, Dyes and Indicators.

Acronyms	Details
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GHS	Globally Harmonized System of Classification and Labelling of Chemicals
IPPC	Integrated Pollution Prevention and Control
Kow	Octanol – water coefficient
LC50	median lethal concentration (concentration at which 50% of the sample population is eliminated)
LD50	median lethal dose (dose at which 50% of the sample population is eliminated)
LOAEL	Lowest Observed Adverse Effect Level (lowest dose that produced an adverse effect)
MFA	metallic fuel additives
MMT	methylcyclopentadienyl manganese tricarbonyl
NOAEL	No Observed Adverse Effect Level (usually expressed in mg/kg/day, it defines the dose of substance that produces no significant toxicological effects for a specific exposure pathway)

Products names	**Dicyclopentadienyl iron (ferrocene)** **Pentacarbonyl iron** **Ferox** **Ferrous picrate**
	Milwaukee, WI: Aldrich Chemical Company Inc. P. 367. International Labour Office (1998). Encyclopaedia of Occupational Health and Safety. 4th edition, Volumes 1-4 1998. Geneva, Switzerland: International Labour Office,p. 63.15. Investigation of Otto Engine Exhaust (1996). Resulting from the Combustion of Fuel with Added Ferrocene,"report Fraunhofer Institut für Toxikologie and Aerosolforschung. IUCLID Dataset, European Chemicals Bureau; Pentacarbonyliron (13463-40-6) (2000 CD-ROM edition). Available from, as of April 21, 2005: esis.jrc.ec.europa.eu/ Kirk-Othmer Encyclopedia of Chemical Technology. 4th ed. (1995). Volumes 1: New York, NY. John Wiley and Sons, 1991-Present., p. V14: 873. Lewis, R.J., Sr (Ed.). Hawley's Condensed Chemical Dictionary. 13th ed. New York, NY: John Wiley & Sons, Inc. 1997., p. 494. Lewis, R.J. (1996). Sax's Dangerous Properties of Industrial Materials. 9th ed. Volumes

Products names	**Dicyclopentadienyl iron (ferrocene)** **Pentacarbonyl iron** **Ferox** **Ferrous picrate**
	1-3. New York, NY: Van Nostrand Reinhold, p. 1946 Makeeva EP, Krivda GI (1980). Gig Tr Prof Zabol 9: 54-5 PubMed Abstract. Nikula, K.J, Sun, J.D, Barr, E.B (1993). Thirteen-Week, Repeated Inhalation Exposure of F344/N Rats and B6C3F! Mice to Ferrocene1, Inhalation Toxicology Research Institute. O'Neil, M.J. (ed.) (2001). The Merck Index - An Encyclopedia of Chemicals, Drugs, and Biologicals. 13th Edition, Whitehouse Station, NJ: Merck and Co., Inc., p. 916. Sittig, M. (1985.) Handbook of Toxic and Hazardous Chemicals and Carcinogens, 2nd ed. Park Ridge, NJ: Noyes Data Corporation, 1985., p. 523. Stolzenberg AM (1995). in Kirk-Othmer Encycl Chem Tech. 4th ed. NY, NY: John Wiley and Sons, 14: 873-902. Sun,J.D, Dahl,A.R,Gillett N.A (1991). Two-week, repeated inhalation exposure of F344/N Rats and B6C3F Mice to ferrocene , Inhalation Toxicology Research Institute. US patent 4,336,033: fuel compositions containing iron pentacarbonyl , Jun 22 1982. Valerio LG Jr, Petersen DR (2000). Exp Mol Pathol 68 (1): 1-12. WHO; Environ Health Criteria 192: Flame Retardants: A General Introduction p.25-6 (1997). Available from, as of September 15, 2004:www.inchem.org/documents/ehc/ehc/ehc192.htm Zeller, William H., and Westphal, T.E. (1992). Effectiveness of Iron-Based Additives for Diesel Soot Control, US Bureau of Mines, RI 9438, (fpc1.com/sci_ferrocene.php)

E. Chromium

For illustrative purposes only. This factsheet does not represent the assessment documents on the risk posed by individual substances following the methodology presented in the report. They aim to illustrate how information could be presented and some factsheet's sections are not necessarily relevantfor all the MFAs. They are based on the collection of available information but are not intended to be comprehensive and do not necessarily reflect the latest developments in the field of MFAs.

Product name	**Chromium salt**
Chemical names	**Cr salts of mono- and dialkylsalicylic acid or dodecyl sulfosuccinic acid**
Family compounds	Organometal
CAS	Chromium 7440-47-3 Chromium salt 16065-83-1

Acronyms	Details
BCF	Bioconcentration factor
CEC	Coordinating European Council
CLP	Classification Labelling and Packaging
DNEL	Derived No-Effect Level (DNELs are calculated by dividing the value of the health effect dose descriptor by an assessment factor (or safety factor) to allow for extrapolation to real human exposure situations)
DMEL	Derived Minimal Effect Level
EC50	half maximal effective concentration
GHS	Globally Harmonized System of Classification and Labelling of Chemicals
IPPC	Integrated Pollution Prevention and Control
Kow	Octanol – water coefficient
LC50	median lethal concentration (concentration at which 50% of the sample population is eliminated)
LD50	median lethal dose (dose at which 50% of the sample population is eliminated)
LOAEL	Lowest Observed Adverse Effect Level (lowest dose that produced an adverse effect)
MFA	metallic fuel additives
MMT	methylcyclopentadienyl manganese tricarbonyl
NOAEL	No Observed Adverse Effect Level (usually expressed in mg/kg/day, it defines the dose of substance that produces no significant toxicological effects for a specific exposure pathway)

Product name	**Chromium salt**
	Chromium (VI) 18540-29-9
EINECS	605-220-6
Chemical Formula	Cr
Classification / Labelling	No classification found
Chemical/Physical properties	Chromium is a metallic element that can exist in a variety of oxidation states 0, +2, +3 and +6 are the most common in environmental systems. Biologically, trivalent (III) and hexavalent (VI) chromium are most important. The divalent form is unstable in most compounds and is easily oxidized to the trivalent form by air (INCHEM, 1988). The environmental behavior of Cr is largely a function of its oxidation state. Hexavalent Cr compounds are considered toxic to a variety of terrestrial and aquatic organisms and are mobile in soil/water systems, much more so than trivalent Cr compounds. This is largely because of differing chemical properties: Hexavalent Cr compounds are strong oxidizers and highly soluble, while trivalent Cr compounds tend to form relatively inert precipitates at near-neutral pH. The trivalent state is generally considered to be the stable form in equilibrium

Product name	**Chromium salt**
	with most soil/water systems. For mor information on environmental behavior see Losi et al. Environmntal biochemistry of chromium, Reviews of Environmental Contamination and Toxicology, 1994, 136:91-121.
Major constituents	Chromium
Information on possible hazards	**HEALTH** **Behaviour in the body :** ■ After exposure to the chromium by inhation, the aerosol particule with a diameter of 2 µm are deposited in the upper respiratory tract (nose, pharynx) and the smaller particules penetrated to the trachea, bronchial tubes and alveoli (Nat'l Research Council Canada, 1976). ■ If the substance is absorbed, the trivalent chromium does not enter blood cells, but binds to plasma proteins such as transferrin and is transported to the liver. The hexavalent form of chromium does penetrate red blood cells, where it is reduced by glutathione to trivalent chromium, which binds to haemoglobin. Excess hexavalent chromium is taken up into the kidneys, spleen, liver, lungs and bone (Eperts group on Vitamins and Mineral 2003). **Health effects :** ■ Human toxic effects reported are after oral absorption of chromium. The first observed thing is that the toxicity of chromium varies depending on the valence state, with hexavalent (VI) chromium being generally more toxic than trivalent (III) chromium because of its low absorption (INCHEM, 1988). A study by Wasser et al., 1997 reported renal failure in a patient taking supplement of chromium trivalent but no adverse effects have been associated with chronic exposure to chromium (15 mg/kg by weight/day) (Cerulli et al., 1998 Jeejeebhoy, 1999). Higher doses of chromium (100 mg/kg by weight/day) are associated with reproductive and developmental effects. ■ A carcinogenic risk has been associated with occupational exposure to hexavalent chromium air levels (Norseth et al., 1981). An experiment on rat shows that at the end of the study the lung chromium retention was about 10 times higher for the rats exposed to chromium oxide versus sodium dichromate at an aerosol Cr-concentration of 100 µg/m^3. Primary lung tumors and malign tumor of the pharynx have been observed at the highest Cr-concentration (100 µg/m^3) (Glaser et al., 1986). **ENVIRONMENT** **Ecotoxicity values**

Acronyms	Details
BCF	Bioconcentration factor
CEC	Coordinating European Council
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DMEL	Derived Minimal Effect Level
EC50	half maximal effective concentration
GHS	Globally Harmonized System of Classification and Labelling of Chemicals
IPPC	Integrated Pollution Prevention and Control
Kow	Octanol – water coefficient
LC50	median lethal concentration (concentration at which 50% of the sample population is eliminated)
LD50	median lethal dose (dose at which 50% of the sample population is eliminated)
LOAEL	Lowest Observed Adverse Effect Level (lowest dose that produced an adverse effect)
MFA	metallic fuel additives
MMT	methylcyclopentadienyl manganese tricarbonyl
NOAEL	No Observed Adverse Effect Level (usually expressed in mg/kg/day, it defines the dose of substance that produces no significant toxicological effects for a specific exposure pathway)

Product name	**Chromium salt**

In the INCHEM (1988), the toxicity for most microorganisms is reported to occurs in the range of 0.05 - 5 mg chromium/kg of medium. The internal concentration of chromium depends on the species. In most groups of microorganisms, it ranges between the levels of 0.6 mg dry weight present in one litre of sample of microplankton from Monterey Bay, California, USA, and 21.4 mg/litre phytoplankton collected in the Pacific Ocean (Martin & Knauer, 1973).

Table 7: Toxicity values of chromium for fresh-water organism from the INCHEM,1988

Compound	category	Exposure	Toxicity range (mg/l)	Most sensitive species
Hexavalent chromium	Invertebrate	acute	0.067-59.9	scud
		Long-term	-	-
	vertebrate	Acute	17.6-249	Fathead minnow
		Long term	0.265-2.0	Rainbow

Product name	Chromium salt

				trout
Trivalent chromium	invertebrate	acute	2.0-64.0	cladoceran
		Long-term	0.066	cladoceran
	vertebrate	Acute	33.0-71.9	guppy
		Long term	1.0	Fathead minnow

Behaviour in the environment :

In the environment the atmosphere is a major pathway for long-range-transport of chromium to different ecosystems and depends on the meteorological factors, topography and vegetation (Nriagu et al., 1988; Spokes and Jickells, 1995). The size particles and the speciation of Cr are important factor for the fate of Cr in the environment. The transport within the terrestrial and water systems is greatly affected by chemical speciation: chemical forms of Cr and their affinity to chemical and photochemical redox transformations, precipitation/dissolution and adsorption/desorption processes occurring in individual compartments of the environment determine the biogeochemical cycle of this element. The efficient adsorption of metals by soils tends to limit the effect of atmospheric input of Cr. The dumping of industrial waste materials, however, significantly increases Cr concentration in soil, and is usually accompanied by groundwater contamination (Forstner, 1995). The hexavalent Cr is known as the most mobile Cr form in soil and water systems,whereas Cr(III) is generally not transported over great distances because of its low solubility and tendency to be adsorbed in the pH range typical for natural soils and waters.

Environmental effects :

- The main effects observed on microorganisms are inhibition of growth (at concentrations greater than 0.5 mg/litre in Chlorella cultures) and inhibition of various metabolic processes, such as photosynthesis or protein synthesis (EIFAC 1983).
- More studies have been performed with aquatic species than with free-living (non-parasitic) animals. Depending on the species, chromium can be less toxic for fish in warm water, but marked decreases in toxicity are found with increasing pH or water hardness; changes in salinity have little if any effect on its toxicity. Chromium can make fish more susceptible to infection; high concentrations can damage or accumulate in various fish tissues and in invertebrates such as snails and worms. Reproduction of *Daphnia* was affected by exposure to 0.01 mg

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EC50	half maximal effective concentration
GHS	Globally Harmonized System of Classification and Labelling of Chemicals
IPPC	Integrated Pollution Prevention and Control
Kow	Octanol – water coefficient
LC50	median lethal concentration (concentration at which 50% of the sample population is eliminated)
LD50	median lethal dose (dose at which 50% of the sample population is eliminated)
LOAEL	Lowest Observed Adverse Effect Level (lowest dose that produced an adverse effect)
MFA	metallic fuel additives
MMT	methylcyclopentadienyl manganese tricarbonyl
NOAEL	No Observed Adverse Effect Level (usually expressed in mg/kg/day, it defines the dose of substance that produces no significant toxicological effects for a specific exposure pathway)

Product name	**Chromium salt**
	hexavalent chromium/litre (EIFAC 1983). ■ Numerous other factors influence the availability of chromium and, therefore, its toxicity. These include the presence of other minerals and organic pollutants and the temperature of the environment.
Timing of action categorisation: **- distribution system additives** **- vehicle fuel system additives** **- additives sold in filling station**	
Function (category)	Antistatic : increase in fuel electrical conductivity (Teknik administration,

Product name	**Chromium salt**
	Chromium hex-Cem is a useful additive for reduction of the hot corrosion of alloys in gas turbines by sea salt contaminants. It is synergistic with Manganese fuel oil additives www.omgi.com/product-adv-fuel.html.
Concentration in gasoline (average)	The levels of antistatic used for treated the fuel is relatively low only 2-20 mg/kg (Gerlofs-Nijland et al., 2008)
Emissions in the environment during life cycle	No data found
Vehicle emissions impacts	No data found
Environmental exposure	A study by Merian et al. (1984) has compiled the global sources of chomium in the environment. Natural emissions such as volcanic emissions, biological cycle including extraction from soil by plants and weathering of rocks and soils represent 30 % of the emissions. The emissions due to human represent 70%: general ore and metal production (3%), form metal use (60%) and from coal burning and other combustion processes (7%).
Human exposure	The general population can be exposed to chromium through inhalation, absorption by food or water, or dermal contact. The level of chromium in air and water is generally low. In drinking water the level of chromium is usually low as well, but contaminated well water may contain the dangerous chromium(IV); hexavalent chromium.
References	Cerulli, J., Grabe, D.W., Gauthier, I., Malone, M., McGoldrick, M.D. (1998). Chromium picolinate toxicity. *Annals of Pharmacotherapy* 32, 428-431. EIFAC (1983). *Water quality criteria for european freshwaterfish. Report on chromium and freshwater fish,* European Inland Fisheries Advisory Commission, Working Party on Water Quality Criteria for European Freshwater Fish, 31 pp (EIFAC Technical Paper No. 43). Glaser U., Hochrainer D., Oldiges H. (1986). Carcinogenicity of sodium dichromate and chromium (VI/III) oxide aerosols inhaled by male wistar rats. Toxicology. Volume 42, Issues 2–3,Pages 219–232. Forstner, U. (1995). Land contamination by metals: global scope and magnitude of problem. In: Allen, H.E., Huang, C.P., Bailey, G.W., Bowers, A.R. (Eds.), Metal Speciation and Contamination of Soil. Lewis Publishers, Ann Arbor, pp. 1±24. INCHEM (1988). Environmental health criteria 61 : chromium. Jeejeebhoy, K.N. (1999). The role of chromium in nutrition and therapeutics and as a potential toxin. *Nutrition Reviews* 57, 329-335. Lenntech database www.lenntech.com/periodic/elements/cr.htm

Acronyms	Details
BCF	Bioconcentration factor
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CLP	Classification Labelling and Packaging
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DMEL	Derived Minimal Effect Level
EC50	half maximal effective concentration
GHS	Globally Harmonized System of Classification and Labelling of Chemicals
IPPC	Integrated Pollution Prevention and Control
Kow	Octanol – water coefficient
LC50	median lethal concentration (concentration at which 50% of the sample population is eliminated)
LD50	median lethal dose (dose at which 50% of the sample population is eliminated)
LOAEL	Lowest Observed Adverse Effect Level (lowest dose that produced an adverse effect)
MFA	metallic fuel additives
MMT	methylcyclopentadienyl manganese tricarbonyl
NOAEL	No Observed Adverse Effect Level (usually expressed in mg/kg/day, it defines the dose of substance that produces no significant toxicological effects for a specific exposure pathway)

Product name	**Chromium salt**
	Losi et al. Environmntal biochemistry of chromium, Reviews of Environmental Contamination and Toxicology, 1994, 136:91-121. Merian, E. (1984). Introduction on environmental chemistry and global cycles of arsenic, beryllium, cadmium, chromium, cobald, nickel, selenium, and their derivatives. *Toxicol.environ. Chem.*, **8**: 9-38. Nat'l Research Council Canada (1976). Effects of Chromium in the Canadian Envir p.94 NRCC No.15017. Nriagu, J.O., Nieboer, E. (1988). Chromium in Natural and Human Environments. Wiley Interscience, New York. Spokes, L.J., Jickells, T.D. (1995). Speciation of metals in the atmosphere. In: Ure, A.M., Davidson, C.M. (Eds.), Chemical Speciation in the Environment. Blackie Academic and Professional, Glasgow, pp. 137±168. US EPA (1980). *Ambient water quality criteria for chromium,* Washington DC, US Environmental Protection Agency, pp. A1-C48. Wasser, W.G. and Feldman, N.S. (1997). Chronic renal failure after ingestion of over-the-counter chromium picolinate. *Annals of Internal Medicine* 126, 410.

F. Copper compounds

For illustrative purposes only. This factsheet does not represent the assessment documents on the risk posed by individual substances following the methodology presented in the report. They aim to illustrate how information could be presented and some factsheet's sections are not necessarily relevantfor all the MFAs. They are based on the collection of available information but are not intended to be comprehensive and do not necessarily reflect the latest developments in the field of MFAs.

The two copper compounds listed as fuel additives are the copper acetate and the copper hydroxide. Specific information about these compounds used as fuel additives are not available but general information about copper compounds and copper acetate have been collected.

Product name	**Copper acetate** **Copper hydroxide**
Chemical names	Copper II acetate Copper II hydroxide
Family compounds	Transition metal
CAS	Copper element 7440-50-8 Copper acetate 142-71-2 Copper hydroxide 20427-59-2
EINECS	Copper acetate 205-553-3
Chemical Formula	C2H4O2.1/2Cu
Classification / Labelling	**Labelling according Regulation (EC) No 1272/2008 (CLP) for copper :** Acute Tox. 4 H302: harmful if swallowed Skin irrit. 2 H315 : causes skin irritation Eye Irrit. 2 : H319 : causes serious eye irritation Aquatic Acute 1 H400 : very toxic to aquatic life Aquatic Chronic 1 H410 : very toxic to aquatic life with long lasting effects
Chemical/Physical properties	■ Copper metal is soluble in nitric acid and hot sulphuric acid, very slightly soluble in hydrochloric acid and ammonium hydroxide and insoluble in water. Copper (II) (divalent) compounds vary in their water solubility (Sittig, 1985). ■ Copper (II) salts are readily reduced and therefore should be considered reactive with reducing agents, strong acids, alkali metals and finely powdered metals. The products of combustion of copper compound are mainly copper oxides and are likely to be harmful (Lenga, 1988).

Acronyms	Details
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DMEL	Derived Minimal Effect Level
EC50	half maximal effective concentration
GHS	Globally Harmonized System of Classification and Labelling of Chemicals
IPPC	Integrated Pollution Prevention and Control
Kow	Octanol – water coefficient
LC50	median lethal concentration (concentration at which 50% of the sample population is eliminated)
LD50	median lethal dose (dose at which 50% of the sample population is eliminated)
LOAEL	Lowest Observed Adverse Effect Level (lowest dose that produced an adverse effect)
MFA	metallic fuel additives
MMT	methylcyclopentadienyl manganese tricarbonyl
NOAEL	No Observed Adverse Effect Level (usually expressed in mg/kg/day, it defines the dose of substance that produces no significant toxicological effects for a specific exposure pathway)

Product name	**Copper acetate** **Copper hydroxide**
Major constituents	Copper
Information on possible hazards	**HEALTH** **Toxicity values :** Copper (II) Acetate: LD50 [oral, rat]; 710 mg/kg (INCHEM, 1998) **Behaviour in the body :** The biological half-life of copper element in human beings has been estimated to be about 4 weeks (Strickland et al., 1972; Dekaban et al., 1975). **Health effects :** ■ Occupational study by Mackinson et al., 1981 found that inhalation of copper acetate dust causes irritation of throat and lung and contact with solutions irritates eyes. The contact with solid compounds causes severe eye surface injury and irritation

Product name	**Copper acetate** **Copper hydroxide**

of skin (Mackinson et al., 1981).

- An experiment on rats during 16 months with diet suplemented with 5,000 ppm of copper has found that copper accumulates in the liver and kidneys. Similar depositions were seen in the liver, kidney, brain and the large and small bowel in rats exposed to 1250 ppm cupric acetate monohydrate in the drinking water for up to 902 days (US EPA, 1987). No liver necrosis (detected morphologically or by measurement of serum transaminases) has been observed after chronic poisoning of rats with copper acetate in drinking water for 30 days. But upon isolation and perfusion of the liver, reduced bile and bromsulfalein secreting capacities were found. Accumulation of copper in the hepatocytes may thus impair liver function before overt structural damage becomes evident (Gaeta et al., 1980).

ENVIRONMENT

Ecotoxicity values (copper compounds)

- Fish :
  - An LC50 value of 0.39 mg/l has been reported in acute toxicity study (96hr) in a static bioasssay on Pimephales promelas (fathead minnow) (Curtis et al., 1981).
  - In the US EPA report (1995) two other LC50 were reported. An acute toxicity study on Oncorhynchus kisutch (coho salmon) has found an LC50 value of 286 ug/l. The condition of the bioessay are not specified. An chronic toxicity study on *Salmo gairdneri* (rainbow trout; embryo, larvae) during 28 days has found an EC50 value of 5 ug/l .

- Algae :

  An acute toxicity study (growth rate bioassay) on Thalassiosira pseudonana (alga, saltwater) during 72 hrs has found an EC50 value of 5 ug/l (US EPA, 1985) and two chronic toxicity study during 14 and 21 days have found EC50 value of 85 ug/l on Selenastrum capricornatum (green alga) and 70 ug/l on Chlorella stigmatophora (alga, saltwater) (US EPA 1995).

- Aquatic invertebrates :

  A static bioassay has been conducted on Palaemonetes pugio during 96 hrs and a LC50 value of 37 mg/l has been found (Curtis et al., 1981).

Behaviour in the environment :

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Kow	Octanol – water coefficient
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Product name	**Copper acetate** **Copper hydroxide**
	■ In soil, copper is not expected to travel very far because the compounds strongly attaches to organic matter and minerals. It hardly ever enters groundwater. In surface water copper can travel great distances, either suspended on sludge particles or as free ions. Copper does not break down in the environment and because of that it can accumulate in plants and animals when it is found in soils (Lenntech database). **Environmental effects :** ■ On soils with an high concentration of copper the survival of plants is really low. Thus no much plant diversity is observed near copper-disposing factories. Copper negatively influences the activity of microorganisms and earthworms because of its effects on plants. Effects on animals in farm have been observed after contamination through the soils. For example sheep is the main specie concern because the effects of copper are manifesting at fairly low concentrations (Lenntech database). ■ The toxicity of copper compounds on aquatic species depends on

Product name	**Copper acetate** **Copper hydroxide**
	environmental factors (pH, hardness, dissolved organic carbon). Copper is an essential dietary element for some plants and animals but high concentrations of copper in water can be toxic to fish and other aquatic species. Elevated concentrations of copper in water are particularly toxic to many species of algae, crustaceans, annelids, cyprinids, and salmonids (Environmental Contaminants encyclopedia, 1997). Swartzman et al., (1990) have studied the effect of algal biomass on multispecies aquatic microcosm response to copper toxicity and have found that the effects of copper are strongly influenced by the density and species composition of the biota and the related differences in water chemistry at the time of copper addition.
Timing of action categorisation: **- distribution system additives** **- vehicle fuel system additives** **- additives sold in filling station**	Additives sold in filling station
Function (category)	The use of a copper diesel fuel additive in an emission control system improves particulate oxidation (Levin et al., 1990)
Concentration in gasoline (average)	No data found
Emissions in the environment during life cycle	No data found
Vehicle emissions impacts	No data found
Environmental exposure	No data found
Human exposure	No data found
References	Curtis MW, Ward CH (1981). J Hydrol (Amsterdam) 51 (1-4): 359-67. Dekaban AS, Aamodt R, Rumble WF, Johnston GS, O'Reilly S (1975). Kinky hair disease: a study of copper metabolism with use of 67Cu.Arch Neurol 32: 672-675.

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Product name	**Copper acetate** **Copper hydroxide**
	Environmental contaminants encyclopedia (1997).Copper Compilers editors: roy j. Irwin, national park service. Gaeta GB et al (1980). Boll-Soc Ital Biol Sper 56 (16): 1626-8. INCHEM (1998). Environmental Health Criteria 200. Copper. Lenga RE, ed (1988). Sigma-Aldrich library of chemical safety data, Milwaukee, Sigma-Aldrich Corporation, 4098 pp. Lenntech database www.lenntech.com/periodic/elements/cu.htm Levin, M., Koehler, D., and Saile, J. (1990). Copper Fuel Additives as a Part of a Particulate Emmission Control Strategy. SAE Technical Paper 901619. Mackison, F. W., R. S. Stricoff, and L. J. Partridge, Jr. (1981).(eds.). NIOSH/OSHA - Occupational Health Guidelines for Chemical Hazards. DHHS (NIOSH) Publication No. 81-123 (3 VOLS). Washington, DC: U.S. Government Printing Office. Nriagu JO (1979). The global copper cycle. In: Nriagu J.O. ed., Copper in the environment part 1: ecological cycling, New York John Wiley & Sons Inc pp. 1-17. Strickland GT, Beckner WM, Leu ML (1972). Absorption of copper in homozygotes

Product name	**Copper acetate** **Copper hydroxide**
	and heterozygotes for Wilson's disease and controls: isotope tracer studies with 67Cu and 64Cu. Clin Sci 43: 617-625. Swartzman L. Gordon, Frieda B. Taubb, James Meadorb, Chisheng Huanga, Andrew Kindigc (1990). Modeling the effect of algal biomass on multispecies aquatic microcosms response to copper toxicity. Aquatic Toxicology Volume 17, Issue 2, Pages 93–117. US EPA (1985).Ambient Water Quality Criteria Doc: Copper p.60 EPA 440/5-84-031 US EPA (1987).Health Issue Assessment: Copper p.33 EPA/600/8-87/001 Weast RC ed (1976-1977). Handbook of chemistry and physics, Cleveland, Ohio, CRC Press, pp. B109-B112.

G. Lead based fuel additives

For illustrative purposes only. This factsheet does not represent the assessment documents on the risk posed by individual substances following the methodology presented in the report. They aim to illustrate how information could be presented and some factsheet's sections are not necessarily relevantfor all the MFAs. They are based on the collection of available information but are not intended to be comprehensive and do not necessarily reflect the latest developments in the field of MFAs.

Lead fuel additives exist in five main compounds: tetraethyl lead, tetramethyl lead, ethyltrimethyl lead, diethyldimethyl lead and methyltriethyl lead. This factsheet illustrates information about each lead compound including but not limited to their chemical properties and potentialhazards.

Product name	**Lead based fuel additives**
Chemical names	■ **Tetramethyl lead:** Lead tetraethide Lead tetraethyl, PbEt4, TEL, Tel-TML, reacted, Tetra(methylethyl)lead, Tetraethyl lead, Tetraethyl lead liquid, Tetraethyllead solution, Tetraethyllead, liquid, Tetraethylplumbane, Tetraethylplumbium, [PbEt4], tetraethylplumbane (ACD/Name 4.0), ■ **Ethyltrimethyl lead:** Ethyl(trimethyl)plumbane, Ethyltrimethylplumbane, Trimethylethyllead ■ **Diethyldimethyl lead:** Diethyldimethylplumbane, Dimethyldiethyllead ■ **Methyltriethyl lead**: Methyltriethyllead, Methyltriethylplumbane, Triethylmethyllead, Triethylmethylplumbane

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Product name	**Lead based fuel additives**
Family compounds	■ Tetraethyl lead ■ Tetramethyl lead ■ Ethyltrimethyl lead ■ Diethyldimethyl lead ■ Methyltriethyl lead
CAS	■ Tetraethyl lead CAS 78-00-2 ■ Tetramethyl lead CAS 75-74-1 ■ Ethyltrimethyl lead CAS 1762-26-1 ■ Diethyldimethyl lead CAS 1762-27-2 ■ Methyltriethyl lead CAS 1762-28-3
EINECS	■ **Tetraethyl lead** 201-075-4 ■ Tetramethyl lead 200-897-0 ■ Ethyltrimethyl lead 217-169-3

Product name	**Lead based fuel additives**
	■ Diethyldimethyl lead 217-170-9 ■ Methyltriethyl lead 217-171-4
Chemical Formula	■ Tetraethyl lead $C_8H_{20}Pb$ ■ Tetramethyl lead $C_4H_{12}Pb$ ■ Ethyltrimethyl lead $C_5H_{14}Pb$ ■ Diethyldimethyl lead $C_6H_{16}Pb$ ■ Methyltriethyl lead $C_4H_{12}Pb$
Classification / Labelling	**EU Classification** Symbol: T+ = very toxic, N= dangerous for the environment R 61 May cause harm to the unborn child R 26 /27/28 Very toxic by inhalation, in contact with skin and if swallowed R33 danger of cumulative effects R 62 possible risk of impaired fertility R50/53 very toxic to aquatic organism , may cause long-term adverse effects in the aquatic environment S 53 avoid exposure obtain special instructions before use S45 Ion case of accident or if you feel unwell, seek medical advice immediately S60This material and its container must be disposed of as hazardous waste. S61 Avoid release to the environment Refer to special instructions /safety data sheets **UN Classification** UN Hazard Class: 6.1 UN Pack Group: I (INCHEM)
Chemical/Physical properties	**Tetraethyl lead:** Insoluble in water; slightly soluble in benzene, petroleum ether, alcohol; flammable, moderate fire risk (Sax & Lewis 1987). In combustion of alkyl lead unstable relatively soluble lead halogenades are formed.
Major constituents	Lead
Information on possible hazards	**HEALTH** Toxicity values: **Tetraethyl lead (TEL)** ■ Workers: □ Systemic effects following acute exposure: □ Dermal DN(M)EL 3.13 mg/kg bw/day □ Inhalation DN(M)EL 0.68 mg/m3

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Product name	**Lead based fuel additives**
	▫ Systemic effects following long-term exposure: ▫ Dermal DN(M)EL 0.00067 mg/kg bw/day ▫ Inhalation DN(M)EL 0.00058 mg/m3 ■ General population: ▫ Systemic effects following acute exposure:Dermal DN(M)EL 1.56 mg/kg bw/day ▫ Inhalation DN(M)EL 0.34 mg/m³ ▫ Oral DN(M)EL Exposure based waiving ▫ Systemic effects following long-term exposure:Dermal DN(M)EL 0.00033 mg/kg bw/day ▫ Inhalation DN(M)EL 0.00083 mg/m³ ▫ Oral DN(M)EL 0.00033 mg/kg bw/day ■ Results from a study conducted by Schroeder (1972) suggest the oral LD50 of TEL to be 14.18 mg/kg by weight. The research was based on a sample group of 16 rats in four equal groups in which each group received a different dose level of TEL. All animals

Product name	Lead based fuel additives
	displayed neurological signs including lethargy, irritability, ataxia, violent trembling and aggressiveness. For the groups that received the two highest doses of TEL, rats began to die rapidly after day 6. By the end of the 14-day study no rats survived and the.LD100 was 16.9 mg/kg bw. ■ In experiments by Cremer et al. (1961) TEL inhalation exposure tests were carried out in a glass chamber. The research was based on 7 sample groups of 12 -20 rats in which each group received a different dose level of TEL. All rats displayed behaviour changes, signs of mild poisoning and some had cyanosis at lower dose rates. All rats dosed at 0.37 mg/l and below survived whereas deaths were observed at the 0.77 mg/l dose rate with an LC50 of 0.85 mg/l. All rats dosed at the highest three dose levels of TEL died andhe LC100 was reported as 1.58 mg/l ■ A repeat oral toxicity study carried out on groups of male rats, concluded that the first signs of toxicological effects due to TEL were observed at a dose rate of 0.2 mg/kg by weight/d (Franklin et al., 1987). **Behaviour in the body:** **Lead compounds** ■ Lead is suggested in the HSDB database to be absorbed in humans and animals following inhalation or ingestion (percutaneous absorption is minimal in humans). Depending upon chemical speciation, particle size, and solubility in body fluids, up to 50% of the inhaled lead compound may be absorbed.Blood lead (PbB) levels are used as a measure of body burden and absorbed (internal) doses of lead. The relationship between blood lead levels and the concentration of lead at sources of exposure is curvilinear (HSDB database). ■ Compared to the skin's low ability to absorb inorganic lead compoundsalkyl lead compounds are easily absorbed by the skin to such a degree that there is high toxicity among handlers of leaded gasoline(Doull et al, 1980). **Health effects:** **Lead compounds** ■ Early exposure effects associated to lead fuel additives are generally those of hydrocarbon abuse. These include anorexia, nausea, vomiting, diarrhea, delirium, nervous irritability, headache, restlessness, pallor, tremor, euphoria, lethargy, insomnia, slurred speech and blurred vision. After the initial effects of asthenia, weakness, fatigue, headache, nausea, vomiting, diarrhea, anorexia and insomnia, the "tetraethyl lead triad" of central nervous system involvement (including ataxia, tremor and

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Product name	Lead based fuel additives
	hypotonia), bradycardia and decreased body,temperature may be noted (INCHEM, 2008). ■ Illness resulting from acute exposure to lead fuel additives may persist for days or weeks, with intervals of quietude readily triggered into over-activity by any type of disturbance. The cause of death, according to the authors, is direct damage to the brain (encephalopathy) involving capillary dysfunction, cerebral oedema, and interference with cerebral metabolism. Muscle damage is confirmed by elevated serum creatine phosphokinase and ransient elevation of transaminases in liver and proteinuria were described. Chronically erythrocytes with basophilic stippling are described in some cases. However substrates of the haem synthesis, such as erythrocyte protoporphyrin may be normal. Other clinical effects include pallor of the face, loss of body weight in chronic exposure (INCHEM, 2008). ■ From all of the data collected on the carcinogenic effects of lead compounds one can conclude that there is limited evidence of carcinogenicity in humans from inorganic and organic lead compounds. However, there is sufficient evidence carcinogenicity in animals from inorganic and inorganic lead compounds. Inorganic

Product name	**Lead based fuel additives**
	lead compound are probably carcinogenic to humans (Group 2A). Organic lead compounds are not classifiable by carcinogenicity to humans (Group 3). The working group noted that organic lead compounds are partially metabolized into ionic lead in both humans and animals. Depending on the extent to which ionic lead, is present in the body, ionic lead mayexert the toxicities associated with inorganic lead (IARC 2006). **Tetraethyl lead (TEL)** ■ The central nervous system is the main organ system affected by tetraethyl lead (TEL). The effects of TEL may be experienced in conjunction with the effects of the solvent. The exposure-onset interval varies inversely with the dose of TEL; symptoms can begin within hours after exposure, butusually commence within 1-5 days and up to as long as 14 days. Symptoms that begin within 24 hours of exposure usually indicate high levels of exposure or reflect intoxication (due to gasoline) (INCHEM, 2008). ■ In one example of high exposure to TEL, four men cleaned a tank which previously held leaded aviation gasoline. Their exposure to the leaded fuel was shortly followed by illness, notably cognitive impairment.. Furthermore, the workers displayed elevated blood lead levels ranging from 645- 925 ug/L and lead was found predominantly in the lipid blood fraction. Urinary coproporphyrin was slightly raised in one case. Erythrocyte protoporphyrin was slightly raised in the three more severe cases. Blood delta aminolevulinic acid dehydratase activity was markedly reduced. The rate of urinary lead excretion was increased by administering D-penicillamine and all men recovered in a few weeks (Beattie et al, 1972 ;INCHEM, 2008). ■ There are also several cases of organolead compound poisoning associated with gasoline sniffing that produced lead blood levels higher than 1000 ug/L. Signs of organic lead poisoning, mostly neurological symptoms, were detected in children and adolescents who sniffed gasoline for periods ranging from 6 months to 5 years. Blood delta aminolevulinic acid dehydratase activity was reduced. Treatment with chelating agents resulted in symptomatic improvement (Keenlyside, 1984; INCHEM, 2008).TEL at dose levels of 1-100 µg/plate in ethanol proved to be non mutagenic in an Ames test on Salmonella typhimurium TA 98, TA 100 and TA 1537 (Mortelmans et al., 1986) **ENVIRONMENT** **Ecotoxicity values:** Lead compounds □ PNEC aqua (freshwater) 0.027 µg/L

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Product name	**Lead based fuel additives**
	☐ PNEC aqua (marine water) 0.0027 µg/L ☐ PNEC aqua (intermittent releases) 0.27 µg/L ☐ PNEC STP 0.5 µg/L ☐ PNEC soil 0.93 µg/kg soil dw ☐ PNEC oral 0.6 µg/kg food **Behaviour in the environment:** **Lead compounds** ■ The production and use of lead and lead compounds as an anti-knock agent in fuels may result in their release to the environment through various waste streams. ■ When released into the air, the vapor pressures of lead compounds indicate that they exist in a vapor state in the atmosphere. Once in vapor-phase, the lead compounds reactwith photochemically-produced hydroxyl radicals and begin to degrade. The half-life for this reaction in air is estimated to be 10- 22 hours (Bidleman, 1988 ; Wang et al., 1996 ; Atkinson, 1994 ; Harrison et al., 1978)

Product name	Lead based fuel additives
	■ The lead compounds also undergo direct photolysis in the environment and have half-lives ranging from 2.3-34 hours for the structurally similar substances tetramethyl and tetraethyl lead. ■ If released to soil, organic matter in the soil will facilitate the mobility of lead compounds because possibilities exist for inhibited mobility by sorption to soil organic matter and for enhanced mobility by the formation of soluble chelate complexes with soluble organic anions. Volatilization from moist soil surfaces is expected to be an important fate process based upon an estimated Henry's Law constant of 0.35 atm-cu m/mole. The compounds may volatilize from dry soil surfaces based upon its vapor pressure. However, adsorption to soil is expected to attenuate volatilization. After a leaded gasoline spills onto soil, the nonpolar nature of gasoline acts as a solvent capable of transporting lead alkyl compounds through the soil (Rhue et al., 1992; Wang et al., 1996) ■ Data on the biodegradation of lead compounds is not available. ■ If released into water, organic matter in suspended solids and sediment may influence the mobility of lead compounds. The volatilization half-lives of lead compounds, calculated with the compounds' estimated Henry's Law constants, for a model river and model lake are 4.9 hours and 6.6 days, respectively. However, volatilization from water surfaces is expected to be attenuated by adsorption to suspended solids and sediment in the water column. The volatilization half-life from a model pond is about 27 days when adsorption is considered. The lead compounds are expected to undergo hydrolysis in the environment based on half-lives ranging from 14 hours to 8 days for the structurally similar substances tetraethyl lead and tetramethyl lead (Rhue et al.,1992; Lyman et al., 1990 ; Wang et al., 1996 ; Franke et al., 1994 ; Maddock et al., 1990 ;Wong et al., 1981 ; Tiravanti et al., 1979) **Environmental effects** ■ Lead compounds and aquatic life ■ Lead compounds are very toxic to aquatic organisms. Biomagnification of lead compounds may occur along the food chain, for example affecting mollusks and fish. An estimated BCF range for all lead compounds is 500- 600 and according to a classification scheme, this BCF range suggests that the potential for lead bioconcentration in aquatic organisms is high provided that thecompounds are not metabolized by the organisms (SRC) (Wang et al., 1996; Meylan et al.,1999; Franke et al., 1994). **Tetraethyl lead (TEL) and aquatic life** ■ Environmental effects of TEL have been observed in fish, invertebrates and algae. The key values from the short-term study

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Product name	Lead based fuel additives
	or studies, for each of these groups, are: ▫ LC50 (marine water fish): 0.23 mg/l over 96 hours ▫ LC50 (marine water invertebrates): 0.027 mg/l over 96 hours ▫ LC50 (marine water algae):0.1 mg/l over 96 hours ▫ LC50 values for the degradation products are also quoted: Triethyl lead chloride - 1.7 mg/l over 96 hours Inorganic lead degradation product - 180 mg/l over 96 hours. ■ Furthermore, the study shows that the order of toxicity of the materials tested is as follows:- R4 (ethyl) » R3 (ethyl) > Inorganic lead. The toxicity of inorganic lead compounds to aquatic animals was originally thought to be due to coagulation film anoxia (Westfall, 1945). This phenomena, which was first reported for lead by Carpenter in 1949 involves the formation, by the action of the toxicant, of a veil like film of coagulated mucus on the body surface of the fish. If this film of mucous affects the gill tissues, the fish suffers acute respiratory distress and dies from lack of oxygen. It

Product name	**Lead based fuel additives**
	was thought that this process was a common cause of metal toxicity. This type of mucous film was not detected during this study and one can conclude that the mechanism of acute toxicity for alkyl lead compounds cannot be due to this cause. Oher workers (Jackim, 1970) have indicated that direct action of the metal on enzyme systems may be responsible for their toxic effects, and such enzymatic responses may be involved in the case of the alkyl lead compounds. (ECHA database)
Timing of action categorisation: **- distribution system additives** **- vehicle fuel system additives** **- additives sold in filling station**	Depending on the considered additve
Function (category)	■ Gasoline additive ■ Anti-knock agents in aviation fuels
Concentration in gasoline (average)	■ Maximum allowable lead content in gasoline: 0.013 g/L in US (Mike Davis prsonnal communication) ■ Composition of tetramethyl lead (TML)-CB as additive to gasoline: TML: 51 wt %; ethylene dibromide: 18 wt %; ethylene dichloride: 19 wt %; dye, stabilizer, kerosene, and inerts: 12 wt % (Verschueren, 1996).
Emissions in the environment during life cycle	The end products of exhaust fumes were reported by (Ter Haar & Bayard 1971) to be lead carbonate, lead oxides and lead oxycarbonate.
Vehicle emissions impacts	When burned, tetraethyl leaded fuels can produce other alkyllead compounds (such as ethyltrimethyl lead) (HSDB database).
Environmental exposure	
Human exposure	■ Monitoring data indicates that the general population may be exposed to ethyltrimethyl lead via inhalation of ambient air and dermal contact with this compound and products containing ethyltrimethyl lead, such as leaded gasoline (NIOSH, 2008). ■ Occupational exposure to ethyltrimethyl lead may occur through inhalation and dermal contact with this compound at workplaces where ethyltrimethyl lead is produced or used (SRC) (NIOSH, 2008).

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Product name	**Lead based fuel additives**
	■ The use of lead additives in on-road automotive gasoline is no longer permitted in the United States; however lead additives are still used in leaded aviation gasoline. When burned, tetraethyl leaded fuels can produce other alkyllead compounds (such as ethyltrimethyl lead) (USEPA, 1999; Rhue et al., 1992)
References	Atkinson R (1994). Gas-phase Tropospheric Chemistry of Organic Compounds. J Phys Chem Ref Data. Monograph 2. p. 150. Beattie AD, Moore MR & Goldberg A (1972). Tetraethyl lead poisoning. Lancet 2 (7766): 12-15. Bidleman TF (1988). Environ Sci Technol 22: 361-367. Branica M Konrad Z eds (1980). Oxford, UK: Pergamon Press Cremer, J.E., Callaway, S. (1961). Further studies on the toxicity of some tetra and trialkyl lead compounds. British Journal of Industrial Medicine Vol 18, pp 277-282. Doull, J., C.D. Klaassen, and M. D. Amdur (eds.). (1980). Casarett and Doull's Toxicology. 2nd ed. New York: Macmillan Publishing Co., p. 415. Franke C et al (1994). Chemosphere 29: 1501-14.

Product name	**Lead based fuel additives**
	Franklin, C.A., Yagminas, A.P., Golman, A.P., Villineuve, D.C., Little, P.B., Valli, V.E.O. (1987). Toxicological assessment of alkyllead and inorganic lead: a multidisciplinary approach Trace Subst. Environ. Health Vol 21, pp 286-296. Gerhartz, W. (exec ed.) (1990). Ullmann's Encyclopedia of Industrial Chemistry. 5th ed.Vol A1: Deerfield Beach, FL: VCH Publishers, 1985 to Present., p. VA15: 254. Harrison RM, Laxen PD (1978). Environ Sci Technol 12: 1384-92. IARC (2006). Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Man. Geneva: World Health Organization, International Agency for Research on Cancer, 1972-PRESENT. (Multivolume work). Available at: monographs.iarc.fr/index.php p. V87 377. INCHEM, IPCS; International Program for chemical safety (1994). Poisons Information Monograph 320: Lead, organic. Available from, as of February 4, 2008: www.inchem.org/documents/pims/chemical/organlea.htm Keenlyside RA (1984). The gasoline-sniffing syndrome. In: Grandjean P & Grandjean E, eds. Biological effects of organolead compounds. Boca Raton, Florida, CRC Press, p. 219-225. Lyman WJ et al (1990). Handbook of Chemical Property Estimation Methods. Washington, DC: Amer Chem Soc pp. 15-1 to 15-29. Maddock BG, Taylor D (1981). Lead in the Marine Environment. p. 233-62. Meylan WM et al (1999). Environ Toxicol Chem 18: 664-72 Mortelmans, K., Haworth, S., Lawlor, T., Speck, W., Tainer, B., Zeiger, E. (1986). Environ. Mutagen. Vol 8, pp 1-119. NIOSH; NOES. National Occupational Exposure Survey conducted from 1981-1983. Estimated numbers of employees potentially exposed to specific agents by 2-digit standard industrial classification (SIC). Available at www.cdc.gov/noes/ as of Jan 23, 2008. Rhue RD et al (1992). Crit Rev Environ Control 22: 2403-11. Sax, N.I. & Lewis, R.J.Sr. (1987). Hawley's condensed chemical dictionary. Eleventh edition. Van Nostrand Reinhold Company. New York. pp. 1288. Schroeder, T., Avery, D.D., Cross, H.A (1971). The LD50 value of tetraethyl lead Experimentia 28, 425-426. Ter Haar, G.L. & Bayard, M.A. (1971). Composition of airborne lead particles. Nature 232: 553 - 554. Tiravanti G, Boari G (1979). Environ Sci Technol 13: 849-54. USEPA; Great Lakes Binational Toxics Strategy. Draft Report on Alkyl-lead: Sources, Regulations and Options. October 1999. Available at: www.epa.gov/bns/Lead/steplead.html as of Jan 31, 2008. Verschueren, K (1996). Handbook of Environmental Data on Organic Chemicals. 3rd ed. New York, NY: Van Nostrand Reinhold Co.,.p. 1699.

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DMEL	Derived Minimal Effect Level
EC50	half maximal effective concentration
GHS	Globally Harmonized System of Classification and Labelling of Chemicals
IPPC	Integrated Pollution Prevention and Control
Kow	Octanol – water coefficient
LC50	median lethal concentration (concentration at which 50% of the sample population is eliminated)
LD50	median lethal dose (dose at which 50% of the sample population is eliminated)
LOAEL	Lowest Observed Adverse Effect Level (lowest dose that produced an adverse effect)
MFA	metallic fuel additives
MMT	methylcyclopentadienyl manganese tricarbonyl
NOAEL	No Observed Adverse Effect Level (usually expressed in mg/kg/day, it defines the dose of substance that produces no significant toxicological effects for a specific exposure pathway)

Product name	**Lead based fuel additives**
	Wang Y et al (1996). Appl Organomet Chem 10: 773-8.

H. Magnesium oxide

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Product name	**Magnesium oxide**
Chemical names	Magnesium oxide
Family compounds	Alkaline earth
CAS	1309-48-4
EINECS	215-171-9
Chemical Formula	MgO
Classification / Labelling	**Notified classification and labeling according to the CLP criteria for magnesium oxide** Aquatic Chronic 1 H410 Very toxic to aquatic life with long lastings effects Skin Irrit 2 H315 causes skin irritation Skin sens 1 H317 may cause an allergic skin irritation Eye Irrit 2 H319 causes serious eye irritation
Chemical/Physical properties	The magnesium oxide is a hygroscopic, fine white powder which can reacts violently with strong acids. It is used with most non-metals and almost every acid. Magnesium reacts only slightly or not at all with most of the alkalis and many organic substances, like hydrocarbons, aldehides, alcohols, phenols, amines, esters and most of the oils. It used as a catalyst allow promoting organic reactions of condensation, reduction, addition and dehalogenisation.
Major constituents	
Information on possible hazards	**HEALTH** **Toxicity values :** **Behaviour in the body :** The elimination of magnetic dust has been studied by Reichrtova et al., 1992 on Wistar rats after a single exposure (6 hr) and repeated exposure to dust (200 hr). The data show that inhaled dust is gradually dissolved in the body. The magnesium content was evaluated in the reticulo-endothelial organs (liver and spleen) 25 days after the last exposure and was found to increase by 20.1% in the spleen and by 15.6% in the liver. A histological exam of internal organs confirmed that the dust was retained in the lungs (without fibrotic changes), that particles were present in the spleen (sinusoid

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Product name	**Magnesium oxide**
	macrophages). No signs of pulmonary fibrosis were found even after 6 months after the last exposure (Reichrtova et al., 1992). **Health effects :** ■ Occupational exposure to an unspecified concentration magnesium oxide dust revealed slight irritation of the eyes and nose (American Conference of governmental Industrial hygienists, 2001). ■ Human exposure studies to freshly generated magnesium oxide fume at low concentrations (410 to 580 mg/cu) during 1 to 9 min show only slight reactions. Inhalation of magnesium oxide produced a febrile reaction and a leukocytosis, similar to other metal fume fever, in the exposed subjects analogous to that caused by inhalation of zinc oxide (American Conference of governmental Industrial hygienists, 2001). ■ In vitro toxicity test have been conducted by Ge et al., 2011 in order to study the magnesium oxide nanoparticles

Product name	**Magnesium oxide**
	toxicity to cells and organs. The morphology and size of MgO nanoparticles were analysed by the transmission electron microscope (TEM) and nanoparticle size analyser. MTT[123] assay was used to evaluate the cytotoxicity of MgO nanoparticles. The data of the MTT assay show no cytotoxicity of low concentration (below 200 ug/mL) of MgO. At higher concentrations a decrease in growth has been observed (Ge et al., 2011). **ENVIRONMENT** No data have been found about ecotoxicity of magnesium.
Timing of action categorisation: **- distribution system additives** **- vehicle fuel system additives** **- additives sold in filling station**	
Function (category)	To lessen the effects of corrosion and deposits. The magnesium additive is used in fuel boilers in order to eliminate contaminants of fuels such as vanadium, sodium and sulphur with a reaction with the magnesium. These contaminants cause both corrosion and hard slag deposits. Sulfur combustion can cause acid corrosion problems (Liquid Mineral group Inc.).
Concentration in gasoline (average)	No data found
Emissions in the environment during life cycle	
Vehicle emissions impacts	
Environmental exposure	Magnesium oxide occurs in nature as the mineral periclase but the production and use of magnesium compounds in various field result in their release to the environment through various waste streams (Patnaik, 2003).
Human exposure	No data found

[123](3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl-2 H-tetrazolium bromide)

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Product name	**Magnesium oxide**
References	American Conference of Governmental Industrial Hygienists (2001). Documentation of Threshold Limit Values for Chemical Substances and Physical Agents and Biological Exposure Indices for 2001. Cincinnati, OH, p. 2. Ge S et al (2011). IET Nanobiotechnol. 5 (2): 36. Liquid Mineral group Inc.: www.liquidminerals.com/framebl.htm. Patnaik P (2003). Handbook of Inorganic Chemicals. New York, NY: McGraw-Hill p. 529. Reichrtova E, Takac L (1992). J Hyg Epidemiol Microbiol Immunol 36 (4): 235-244.

I. Methylcyclopentadienyl Manganese Tricarbonyl (MMT®)

For illustrative purposes only. This factsheet does not represent the assessment documents on the risk posed by individual substances following the methodology presented in the report. They aim to illustrate how information could be presented and some factsheet's sections are not necessarily relevantfor all the MFAs. They are based on the collection of available information but are not intended to be comprehensive and do not necessarily reflect the latest developments in the field of MFAs.

Product name	**Methylcyclopentadienyl Manganese Tricarbonyl (MMT®)**
Chemical names	■ (1-Methyl-2,4-cyclopentadien-1-yl)manganese tricarbonyl ■ (methylcyclopentadienyl)manganese tricarbonyl ■ (methylcyclopentadienyl)tricarbonylmanganese ■ 2-(Methylcyclopentadienyl)manganesetricarbonyl ■ 2-Methylcyclopentadienyl manganese tricarbonyl ■ 2-Methylcyclopentadienylmanganese tricarbonyl ■ Manganese methyl cyclopentadienyl tricarbonyl ■ Manganese, (methylcyclopentadienyl)tricarbonyl- ■ Manganese, tricarbonyl methylcyclopentadienyl ■ Manganese, tricarbonyl(2-methylcyclopentadienyl)- ■ Manganese, tricarbonyl(methyl-2,4-cyclopentadienyl)- ■ Manganese, tricarbonyl(methyl-pi-cyclopentadienyl)- ■ Manganese, tricarbonyl(methyl-pi-cyclopentadienyl)- (8CI) ■ Manganese, tricarbonyl[(1,2,3,4,5-.eta.)-1-methyl-2,4 ■ Manganese, tricarbonylmethylcyclopentadienyl ■ Methyl cyclopentadienyl manganese tricarbonyl ■ Methylcyclopentadienyl manganese tricarbonyl ■ Methylcymantrene ■ Pi-(methylcyclopentadienyl)manganese tricarbonyl ■ Pi-methylcyclopentadienylmanganese tricarbonyl ■ Tricarbonyl(2-methylcyclopentadienyl)manganese ■ Tricarbonyl(eta(5)-methylcyclopentadienyl)manganese ■ Tricarbonyl(methylcyclopentadienyl)manganese
Family compounds	■ MMT®

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LOAEL	Lowest Observed Adverse Effect Level (lowest dose that produced an adverse effect)
MFA	metallic fuel additives
MMT	methylcyclopentadienyl manganese tricarbonyl
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Product name	**Methylcyclopentadienyl Manganese Tricarbonyl (MMT®)**
	■ Antiknock-33 ■ HiTec 3000 ■ Combustion improver -2 ■ AK-33X ■ Ecotane ■ Greenburn
CAS	12108-13-3
EINECS	235-166-
Chemical Formula	$C_9H_7MnO_3$
Classification / Labelling	Not available yet
Chemical/Physical properties	MMT® has a boiling point of 231.67 ° C and a vapor pressure of 7.3 mm Hg at 100°C. The water solubility at 25°C is 29 mg/L. The octanol/water partition coefficient Log

Product name	**Methylcyclopentadienyl Manganese Tricarbonyl (MMT®)**
	Kow=3.7. MMT® is a liquid thus the melting point is not applicable (EPA, 2008).
Major constituents	Manganese
Information on possible hazards	**HEALTH** **Toxicity values:** ■ Workers Systemic effects of long-term exposure: □ Dermal DN(M)EL 0.057 mg/kg bw/day □ Inhalation DN(M)EL 0.201 mg/m³ ■ General population Systemic effects of long-term exposure: □ Dermal DN(M)EL 0.029 mg/kg bw/day □ Inhalation DN(M)EL 0.036 mg/m³ □ Oral DN(M)EL 0.013 mg/kg bw/day(ECHA database) □ LD50: 140-795 mg/kg (Dermal, Rabbit) (Verschueren, 1983), LD50: 58 mg/kg (Oral, Rat) (Gong et al., 2003), LC50: 247 mg/m3 over 1 hour (Inhalation, Rat) (Verschueren, 1983) **Behaviour in the body:** *General behaviour* U.S. Public Health Service in collaboration with U.S. Environmental Protection Agency (EPA) has produced a report on the toxicoloical profile of manganese. In the report, the authors conclude that: ■ Manganese is an essential nutrient and is associated with toxic effects on the nervous, respiratory, and reproductive systems at elevated levels of exposure (ATSDR 2008). ■ As a cellular toxicant Mn can impair transport systems, enzyme activities, and receptor functions (ATSDR 2008). ■ Mn is well known as a central nervous system toxicant, particularily of the globus pallidus of the basal ganglia (ATSDR 2008). *Transportation in the organism* Based on dosimetry studies and pharmacokinetic modelling, Nong et al concluded that inhaled manganese can be absorbed from the respiratory tract and transported to the brain before the liver can metabolise and remove it (Nong et al. 2008). *In the brain*

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Product name	**Methylcyclopentadienyl Manganese Tricarbonyl (MMT®)**
	In the brain Mn is taken up by dopaminergic neurons, the neurons associated with movement initiation. *Nervous system* ■ Most common health problems in workers exposed to high levels of manganese concern nervous system (ATSDR 2012). ■ Both divalent and trivalent manganese induce ROS in the rat brain (Ali et al. 1995). For an overview of the influence of redox Mn chemistry and neuridegenrative consequences see Hami and Bondy 2004. ■ According to the report by ATSDR (2008), the scientific community generally accepts that the manganese ion, Mn(II), enhances the autoxidation or turnover of various intracellular catecholamines, leading to increased production of free radicals, reactive oxygen species, and other cytotoxic metabolites, along with a depletion of cellular antioxidant defense mechanisms, leading to oxidative damage and selective destruction of dopaminergic neurons (ATSDR 2008). ■ In addition to dopamine, manganese is thought to perturb other

Product name	Methylcyclopentadienyl Manganese Tricarbonyl (MMT®)

neurotransmitters, such as GABA and glutamate. In order to produce oxidative damage, manganese must first overwhelm the antioxidant enzyme manganese superoxide dismutase (ATSDR 2008)

- The neurotoxicity of Mn(II) has also been linked to its ability to substitute for Ca(II) under physiological conditions. The ATSDR report concludes that it can enter mitochondria via the calcium uniporter and inhibit mitochondrial oxidative phosphorylation. It may also inhibit the efflux of Ca(II), which can result in a loss of mitochondrial membrane integrity. Mn(II) has been shown to inhibit mitochondrial aconitase activity to a significant level, altering amino acid metabolism and cellular iron homeostasis (ATSDR 2008).

Health effects:

- Manganese has been suggested to be able to cause behavioral changes and other nervous system effects, which include movements that may become slow and clumsy.
- Carcinogenicity: not been found carcinogenic acoording to US EPA (Class D).
- The health risks associated with MMT® gasoline combustion products have been related primarily to low-level, chronic exposure to particulate inorganic Mn rather than the organomanganese additive itself. MMT in air has a very short half-life in the presence of sunlight, quickly degradating to manganese particulate. As a result, ambient exposures to MMT have been characterised as "extremely low" (Health Canada 1994).

ENVIRONMENT
Ecotoxicity values:

- PNEC aqua (freshwater) 0.21 µg/L
- PNEC aqua (marine water) 0.021 µg/L
- PNEC aqua (intermittent releases) 2.1 µg/L
- PNEC soil 31.02 µg/kg soil dw

Behaviour in the environment:

In an environmental assessment, Lynham et al. conclude that since MMT® has a low vapour pressure and a short half-life in sunlight, it is unlikely that significant concentrations of MMT® could occur in the environment as a result of its use as a gasoline additive, but manganese particles remain and do not disappear in combination with sunlight (Lynam et al., 1990).

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Product name	**Methylcyclopentadienyl Manganese Tricarbonyl (MMT®)**
	Environmental effects: ■ In a study by Zayed, roadside plants, soils and urban animal tissues have all shown elevated manganese levels related to traffic (Zayed, 2001). ■ One North American study showed that MMT® in gasoline will produce a slow increase in Mn concentrations in soil near a busy Canadian intersection, but a doubling of this concentration would take 95- 256 years (Bhuie at al 2005) ■ NICNAS (2003), in their report conclude thatMMT® is toxic to aquatic animals, and therefore should not be released into the stormwater, sewers or natural waterways. ■ The 48-hours acute toxicity of MMT® to Daphnia magna has been studied under static system conditions. The 48-hours EC50 was 0.83 mg/L using the binomial method with 95% CL of 0.70 and 0.99 mg/l. Using the classification range of Reg (EC) 1272/2008, MMT® is classified for acute category 1 'H400: Very toxic for aquatic organisms' and additionally of 'H410: Very toxic to aquatic life with long lasting effects' since the substance is not

Product name	**Methylcyclopentadienyl Manganese Tricarbonyl (MMT®)**
	readily biodegradable. This study is classified as acceptable and satisfies the guideline requirements for an acute toxicity study with Daphnia magna. ■ EC50 (48h) = 0.83 mg/l (Binomial) CI 95% 0.70 and 0.99 mg/l ■ NOEC (48h) = 0.29 mg/l (ECHA database)
Timing of action categorisation: **- distribution system additives** **- vehicle fuel system additives** **- additives sold in filling station**	■ Gasoline additive ■ Distribution system additives ■ Additives sold in filling station (or in shops selling car parts and accessories)
Function (category)	■ Anti-valve seat recession additive ■ Anti-Knock additive ■ Octane number enhancer ■ Combustion emission reducer (or combustion improver)
Concentration in gasoline (average)	■ In the USA, the maximum allowable MMT® concentration in gasoline is 8.3 mg Mn/L (60 Fed. Reg.36.414. July 17 1995)). ■ In Canada, the maximum allowable MMT® concentration in gasoline is 18mg Mn/L (CAN/CGSB-3.5-2004) ■ In Europe, the article 8ª of Fuel Quality Directive set limits at maximum of 6.0 mg Mn/L as of 1 January 2011, and at maximum of 2 mg Mn/L after 1 January 2014. (Directive 2009/30/EC)
Emissions in the environment during life cycle	■ Combustion of MMT® results in the emission of fine Mn particulates (0.5-1 µm) mainly in the form of manganese sulphate and manganese phosphate (Zahyed et al. 1999) ■ The contribution of direct emissions from motor vehicles to the atmospheric background manganese has been suggested to be around 50% at 25 meter from the source and less than 8% at 250 meter (Loranger et al., 1995). ■ Gerlofs-Nijland et al has estimated that only 1 to 5 percent of the manganese consumed in the fuel is emitted as a respirable particulate (Gerlofs-Nijland et al. 2008) ■ Gerlofs-Nijland et al also concluded that it is impossible to distinguish between directly emitted Mn from automobiles, Mn

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	enriched road dust, and the naturally occurring Mn in crustal material (Gerlofs-Nijland et al. 2008) ▪ A survey of ambient air concentrations of fine (PM2.5) manganese in rural sites in U.S. national parks and in urban sites in California indicated that from 1988 to 1993, ambient concentrations of manganese ranged from 1 ng/m3 in rural sites to 3 ng/m3 in urban sites (Wallace and Slonecker 1997)
Vehicle emissions impacts	▫ The US Environmental Proetction Agency (EPA) has determined that MMT® when used in gasoline at a concentration of 8.3 mg Mn/L does not cause or contribute to the failure of vehicle emission control systems. Based on a statistical study carried out by the EPA on vehicles using fuel containing 8.3 mg Mn/L of MMT®, the EPA concluded "[a]pplication of this test to the full mileage range of HC emissions data from Ethyl's tests of 1992 and 1993 vehicles results in a failure to discern any 'real' emission increase at all – that is, no increase that we may not reasonably attribute to sampling error rather than to an additive effect on HC in the sampled vehicle population." 59 Fed. Reg. 42238 (August 17,

Product name	**Methylcyclopentadienyl Manganese Tricarbonyl (MMT®)**
	1994). ■ Ambient levels of airborne manganese worldwide are reported by Pfeifer et al to range from 0.5-15 ng/m3 for remote areas, from <10-30 ng/m3 for non-polluted urban and rural areas, and 10–70 ng/m3 for large urban centres without major point sources. Air concentrations in areas close to point sources may, according to these studies, reach up to several thousand milligrams/m3. (Pfeifer et al., 2004).
Environmental exposure	MMT® can remain present in both air and water. For example, MMT® was found in most samples of water and storm runoff collected along highways where MMT® was in use (Yang & Chau, 1999, Gulson et al. 2006; Cohen et al. 2005)).
Human exposure	■ Humans can be exposed to MMT® via oral contact and inhalation (ATSDR 2008). □ The EPA has established that lifetime exposure to 0.3 mg/L manganese is not expected to cause any adverse effects (ATSDR 2012). ■ The FDA has determined that the manganese concentration in bottled drinking water should not exceed 0.05 mg/L. ■ The Occupational Health and Safety Administration (OSHA) has established a ceiling limit (concentration that should not be exceeded at any time during exposure) of 5 mg/m^3 for manganese in workplace air. ■ In another study, NICNAS (2003) finds that MMT® causes mild skin and eye irritation
References	ACGIH (American Conference of Governmental Industrial Hygienists) (1993). Threshold Limit Values for Chemical Substances and Physical Agents and Biological Exposure Indices. Ali SF, Duhart H, Newport G, Lipe G, Slikker W. Manganese-induced reactive oxygen species: Comparison between Mn+2 and Mn+3. Neurodegeneration. Volume 4, Issue 3, September 1995, Pages 329–334 ATSDR - Agency for Toxic Substances and Disease Registry (2012). Availability of Final Toxicological Profiles of priority hazardous substances by Agency for Toxic Substances and Disease Registry. Ref: 77 Fed. Reg. 74,192 (December 13, 2012). Final report available for Manganese at: www.atsdr.cdc.gov/ToxProfiles/tp.asp?id=102&tid=23 ATSDR - Agency for Toxic Substances and Disease Registry (2008). Toxicological profile for manganese. U.S. Public Health Service in collaboration with U.S. Environmental Protection Agency (EPA). ATSDR - Agency for Toxic Substances and Disease Registry (2001). Minimal Risk

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NOAEL	No Observed Adverse Effect Level (usually expressed in mg/kg/day, it defines the dose of substance that produces no significant toxicological effects for a specific exposure pathway)

Product name	**Methylcyclopentadienyl Manganese Tricarbonyl (MMT®)**
	Levels (MRLs) for Hazardous Substances. U.S. Public Health Service in collaboration with U.S. Environmental Protection Agency (EPA) Bhuie AK, Ogunseitan OA, White RR, Sain M, & Roy DN (2005). Modeling the environmental fate of manganese from methylcyclopentadienyl manganese tricarbonyl in urban landscapes. Science of the Total Environment 339(1-3), 167-178 Cohen DD; Gulson BL; Davis JM; Stelcer E; Garton D; Hawas O; Taylor A (2005) Fine-particle Mn and other metals linked to the introduction of MMT into gasoline in Sydney, Australia: results of a natural experiment. Atmospheric Environment 39: 6885-6896 Davis JM (2001) Manganese, rhenium. In: Patty's Toxicology, Fifth edition, Vol. 3, E. Bingham, B. Cohrssen, and C. Powell, eds., John Wiley and Sons, New York , pp. 129-168 Dorman, D.C., Struve, M.F., Clewell III, H.J., Andersen, M.E (2006) Application of pharmacokinetic data to the risk assessment of inhaled manganese. *NeuroToxicology* 27: 752-764 Gerlofs-Nijland ME, Groenewegen L and Cassee FR (2008) Health effects of addition and combustion of fuel additives Quick scan and deepening of a selective additive set. RIVM Letter Report 630160001/2008

Product name	**Methylcyclopentadienyl Manganese Tricarbonyl (MMT®)**
	Gulson B; Mizon K; Taylor A; Korsch M; Stauber J ; Davis JM; Louie H; Wu M; Swan H (2006) Changes in manganese and lead in the environment and young children associated with the introduction of methylcyclopentadienyl manganese tricarbonyl in gasoline – preliminary results. Environmental Research 100: 100-114 Hamai D and Bondy S. Oxidative Basis of Manganese Neurotoxicity. Annals of the New York Academy of Sciences Volume 1012, Redox-Active Metals in Neurological Disorders pages 129–141, March 2004 US EPA (US Environmental Protection Agency) (2008). Integrated Risk Information System: Manganese (CASRN 7439-96-5). www.epa.gov/ncea/iris/subst/0373.htm, accessed on July 8, 2008. Lynam DR, Pfeifer GD, Fort BF, Gelbcke AA (1990) Environmental assessment of MMT fuel additive. *Science of the Total Environment* 93: 107-114 Minjares, R. J. (2009). Methylcyclopentadienyl Manganese Tricarbonyl (MMT): A Science and Policy Review Authors. Science, (January) Nong A, Taylor MD, Clewell HJ, Dorman DC, Andersen ME (2008) Manganese Tissue Dosimetry in Rats and Monkeys: Accounting for Dietary and Inhaled Mn with Physiologically based Pharmacokinetic Modeling. Toxicological Sciences 108: 22-34 Pfeifer, G. D., Roper, J. M., Dorman, D., & Lynam, D. R. (2004). Health and environmental testing of manganese exhaust products from use of methylcyclopentadienyl manganese tricarbonyl in gasoline. The Science of the total environment, 334-335, 397-408. doi:10.1016/j.scitotenv.2004.04.043 Tapin, D., Kennedy, G., Lambert, J., Zayed, J (2006) Bioaccumulation and locomotor effects of manganese sulphate in Sprague-Dawley rats following subchronic (90 days) inhalation exposure. *Toxicol Appl Pharmacol* 211: 166-174 U.S. Environmental Protection Agency (1993, December). Inhalation reference concentration (RfC) for manganese. In: IRIS (Integrated Risk Information System) [Database Online]. Available from www.epa.gov.ngispgm3/iris/index.html World Health Organization Regional Office for Europe. (2000). Chapter 6.8 Manganese, WHO Air Quality Guidelines for Europe, 2nd Edition, 2000 (CD ROM Version). Copenhagen, Denmark. Yang, F., & Chau, Y. K. (1999). Determination of methylcyclopentadienyl manganese tricarbonyl (MMT) in aqueous samples by SPME-GCAED. Analyst, 124, 71-73 Zayed J, Hong B and L'Esperance G (1999) Characterization of manganese containing particles collected from the exhaust emissions of automobiles running with MMT additive. *Environmental Science & Technology* 33: 3341-3346. Zayed, J. (2001) Use of MMT in Canadian gasoline: health and environmental issues. American Journal of Industrial Medicine, 39, 425-433.

Acronyms	Details
BCF	Bioconcentration factor
CEC	Coordinating European Council
CLP	Classification Labelling and Packaging
DNEL	Derived No-Effect Level (DNELs are calculated by dividing the value of the health effect dose descriptor by an assessment factor (or safety factor) to allow for extrapolation to real human exposure situations)
DMEL	Derived Minimal Effect Level
EC50	half maximal effective concentration
GHS	Globally Harmonized System of Classification and Labelling of Chemicals
IPPC	Integrated Pollution Prevention and Control
Kow	Octanol – water coefficient
LC50	median lethal concentration (concentration at which 50% of the sample population is eliminated)
LD50	median lethal dose (dose at which 50% of the sample population is eliminated)
LOAEL	Lowest Observed Adverse Effect Level (lowest dose that produced an adverse effect)
MFA	metallic fuel additives
MMT	methylcyclopentadienyl manganese tricarbonyl
NOAEL	No Observed Adverse Effect Level (usually expressed in mg/kg/day, it defines the dose of substance that produces no significant toxicological effects for a specific exposure pathway)

J. Perovskite compounds

For illustrative purposes only. This factsheet does not represent the assessment documents on the risk posed by individual substances following the methodology presented in the report. They aim to illustrate how information could be presented and some factsheet's sections are not necessarily relevantfor all the MFAs. They are based on the collection of available information but are not intended to be comprehensive and do not necessarily reflect the latest developments in the field of MFAs.

Perovskite compounds, composed of calcium titanate nanoparticles (calcium titanium oxide $CaTiO_3$) and other metallic elements (La, Li, Cr), are used as metallic fuel additives (Catalysis today, 2006). No specific data is available about perovskite nanoparticles, but titanium nanoparticles such as titanium dioxide are used in several other fields. Thus, the information in this factsheet is about titanium nanoparticles, specifically titanium dioxide.

Product name	**La-perovskite** **Li-perovskite** **Cr-perovskite**
Chemical names	Calcium titanate/ Calcium titanium oxide
Family compounds	Transition metal
CAS	Perovskite 37226-56-5 / 12049-50-2 / 98246-90-3/ 12194-71-7 Titanium dioxide 13463-67-7
EINECS	308-763-4 234-988-1
Chemical Formula	$CaTIO_3$
Classification / Labelling	**Labelling according to Regulation (EC) No 1272/2008 (CLP) for titanium dioxide :** Acute Tox. 4 H332 : harmful if inhaled Carc.2 H351 : suspected of causing cancer The titanium dioxide (TiO_2) has been classified, according to the International Agency for Research on Cancer (IARC), as possibly carcinogenic to humans (Group 2B) (IARC 2010).
Chemical/Physical properties	Titanium dioxide is generally found as a white to slightly-coloured amorphous powder or platelet. Most titanium dioxide in the anatase form is produced as a white powder, whereas various rutile grades are often off-white and can even exhibit a slight colour, depending on the physical form affecting light reflectance. Titanium dioxide may be coated with small amounts of alumina and silica to improve technological properties. Titanium dioxide is insoluble in water, hydrochloric acid, dilute sulfuric acid, and organic solvents. It dissolves slowly in hydrofluoric acid and hot concentrated sulfuric acid. It is almost insoluble in aqueous alkaline media. Titanium dioxide is often found in the environment in ionic form and has a low vapour pressure (Kirk-Othmer, 1997).
Major constituents	Titanium (Ti)
Information on possible hazards	**HEALTH** **Toxicity values :** No data found **Behaviour in the body :** Titanium is present in the human body in low amounts. It has been estimated that humans take in about 0.8 mg Ti/day mainly with food, but the majority of titanium is not absorbed and is directly evacuated (WHO, 1982).

Acronyms	Details
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LOAEL	Lowest Observed Adverse Effect Level (lowest dose that produced an adverse effect)
MFA	metallic fuel additives
MMT	methylcyclopentadienyl manganese tricarbonyl
NOAEL	No Observed Adverse Effect Level (usually expressed in mg/kg/day, it defines the dose of substance that produces no significant toxicological effects for a specific exposure pathway)

Product name	**La-perovskite** **Li-perovskite** **Cr-perovskite**
	Health effects : ■ Titanium and titanium dioxide are considered to have low toxicity. Laboratory rats exposed to titanium dioxide via inhalation developed small-localized areas of dark-colored dust deposits in their lungs following exposure. Excessive titanium exposure in humans may result in slight changes to the lungs (Clayton et al., 1982; Friberg et al., 1986; Trochimowicz et al., 1988). ■ Exposure to titanium dioxide nanoparticles can produce oxidative damage to lung cells. With increased titanium exposure, TiO_2 nanoparticles accumulate and increase the reactive oxygen species (ROS) production in the lungs, resulting in severe pulmonary edema, inflammatory response and pneumonocyte apoptosis for 90 days (Sun et al., 2012). ■ Liao et al. (2008) proposed a model-based approach to assess inhalation risk levels of workers in titanium dioxide (TiO_2) production and manufacturing factories. The risk level-based

Product name	**La-perovskite** **Li-perovskite** **Cr-perovskite**
	analytical schemes were present for investigations of job-related airborne nano/fine TiO2 dust exposures. A Hill model124 was used to reconstruct dose-response function based on data from rats exposed by chronic inhalation to poorly soluble fine and nanosized particles. A physiologically based lung model was used to predict impacts of TiO2 on alveolar surface and interstitial granuloma, respectively. The findings illustrate that titanium dry/wet treatment and ore handlers in US and maintenance mechanics in EU factories were unlikely to experience substantial lung cancer risks. (Liao et al., 2008). ■ The titanium dioxide (TiO2) has been classified according to the International Agency for Research on Cancer (IARC) as possibly carcinogenic to humans (Group 2B) (IARC 2010). **ENVIRONMENT** **Ecotoxicity values :** No data found **Behaviour in the environment :** ■ In the ambient atmosphere, titanium compounds exist in the particulate phase. Particulate titanium compounds may be removed from the air by wet and dry deposition. In soil, titanium compounds are immobile and do not volatilize from moist or dry soil based due to their ionic character and low vapor pressures. If released into water, soluble titanium ions are easily hydrolyzed into hydrated titanium oxides and basic insoluble oxo salts. Volatilization from water surfaces is not expected to be an important process because dissolved titanium compounds are ionic and ions do not volatilize (WHO, 1982; Cotton et al., 1980). **Environmental effects :** Titanium dioxide nanoparticles in aquatic organims have a very low, direct toxicity but may have sub-lethal effects on the immune system (Jovanovic et al., 2012)
Timing of action categorisation: **- distribution system additives** **- vehicle fuel system additives**	No categorisation found

[124]Goutelle S., Maurin M., Rougier F.(2008) The Hill equation : a review of its capabilities in pharmacological modelling.

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LD50	median lethal dose (dose at which 50% of the sample population is eliminated)
LOAEL	Lowest Observed Adverse Effect Level (lowest dose that produced an adverse effect)
MFA	metallic fuel additives
MMT	methylcyclopentadienyl manganese tricarbonyl
NOAEL	No Observed Adverse Effect Level (usually expressed in mg/kg/day, it defines the dose of substance that produces no significant toxicological effects for a specific exposure pathway)

Product name	**La-perovskite** **Li-perovskite** **Cr-perovskite**
- additives sold in filling station	
Function (category)	■ CSatalyst ■ Active for simultaneous NOx-soot removal reaction (Wang et al., 2005)
Concentration in gasoline (average)	No data found
Emissions in the environment during life cycle	No data found
Vehicle emissions impacts	No data found

Product name	**La-perovskite** **Li-perovskite** **Cr-perovskite**
Environmental exposure	No data found
Human exposure	Monitoring data indicates that the general population may be exposed to titanium compounds via inhalation of ambient air, ingestion of food, and dermal contact with consumer products containing titanium compounds (SRC) (WHO, 1982).
References	Catalysis Today (2006).Volume 114, Issue 1 Pages 31-39. Chatterjee R (2008). Environ Sci Technol 42: 7733. Cotton FA, Wilkinson G (1980) Advanced Inorganic Chemistry. 4th ed. NY, NY: John Wiley and Sons pp. 694-708. Friberg, L., Nordberg, G.F., Kessler, E. and Vouk, V.B. (1986) (eds). Handbook of the Toxicology of Metals. 2nd ed. Vols I, II.: Amsterdam: Elsevier Science Publishers B.V., p. V2 601. Jovanovic J. Palic D. (2012). Immunotoxicology of non-functionalized engineered nanoparticles in aquatic organisms with special emphasis on fish—Review of current knowledge, gap identification, and call for further research. Aquatic Toxicology 118-119 141-151. Karn B et al (2004). eds; p. 23 in Nanotechnolgy and the Environment. ASC Symp Ser 890. Washington, DC: Amer Chem Soc. Kirk-Othmer (1997). Kirk-Othmer Encyclopedia of Chemical Technology, 4th ed, Vol. 24. John Wiley and Sons, New York, pp. 233-250. Koehler AR et al., (2008). J Cleaner Production 16(8-9): 927-37. Liao CM, Chiang YH, Chio CP (2008). Model-based assessment for human inhalation exposure risk to airborne nano/fine titanium dioxide particles. Sci Total Environ 407 (1): 165-77 NIOSH. (2009) Safety and Health Topic. Nanotechnology. Washington , DC: Center for Disease Control. Available at www.cdc.gov/niosh/topics/nanotech/. Sun Q, Tan D, Zhou Q, Liu X, Cheng Z, Liu G, Zhu M, Sang X, Gui S, Cheng J, Hu R, Tang M, Hong F. (2012). Oxidative damage of lung and its protective mechanism in mice caused by long-term exposure to titanium dioxide nanoparticles. J Biomed Mater Res Part A 2012:00A:000–000. Tanaka H., Taniguchi M., Kajita N., Uenishi M., Tan I., Sato N., Narita K., Kimura M., Proceding of CAPoC6, vol. 3, Brussels, 2004, p. 605. Trochimowicz HJ et al (1988). J Appl Toxicol 8 (6): 383-35. Wang Hong; Zhao Zhen, Xu Chun-ming, Liu Jian (2005). Nanometric La(&-x)Kx MnO" Perovskite-type oxides- highly active catalysts for the combustion of diesel soot particle under loose contacts condition.Catalysis Letters Vol.102, Nos.3-4. WHO (1982). Environmental Health Criteria. Titanium. Geneva, Switzerland: WHO

Acronyms	Details
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GHS	Globally Harmonized System of Classification and Labelling of Chemicals
IPPC	Integrated Pollution Prevention and Control
Kow	Octanol – water coefficient
LC50	median lethal concentration (concentration at which 50% of the sample population is eliminated)
LD50	median lethal dose (dose at which 50% of the sample population is eliminated)
LOAEL	Lowest Observed Adverse Effect Level (lowest dose that produced an adverse effect)
MFA	metallic fuel additives
MMT	methylcyclopentadienyl manganese tricarbonyl
NOAEL	No Observed Adverse Effect Level (usually expressed in mg/kg/day, it defines the dose of substance that produces no significant toxicological effects for a specific exposure pathway)

Product name	**La-perovskite** **Li-perovskite** **Cr-perovskite**
	24: 1-68.

K. Potassium compounds

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Two potassium compounds are used as metallic fuel additives: potassium acetate (KOAc) and 1,2-bis(2-ethylhexyloxycarbonyl) ethane sulphonate potassium salt. Most of the information collected and presented in this factsheet is about potassium acetate since little information is available on 1,2-bis(2-ethylhexyloxycarbonyl) ethanesulphonate potassium salt.

Product name	**Potassium acetate KOAc** **1,2-bis(2-ethylhexyloxycarbonyl)ethanesulphonate potassium salt**
Chemical names	■ Potassium acetate ; acetic acid, potassium salt ■ 1,2-bis(2-ethylhexyloxycarbonyl)ethanesulphonate potassium salt
Family compounds	**Alkaline metal salts**
CAS	Potassium acetate: 127-08-2 1,2-bis(2-ethylhexyloxycarbonyl)ethanesulphonate potassium salt: 7491-09-0
EINECS	Potassium acetate: 204-822-2 1,2-bis(2-ethylhexyloxycarbonyl)ethanesulphonate potassium salt: 231-308-5
Chemical Formula	Potassium acetate: $C_2H_4O_2K$ 1,2-bis(2-ethylhexyloxycarbonyl)ethanesulphonate potassium salt: $C_{20}H_{37}KO_7S$
Classification / Labelling	**Regulation (EC) No 1272/2008 Annex VI: potassium element** □ Water-react 1 H260: In contact with water releases flammable gases which may ignite spontaneously. □ Skin Corr. 1B H314: Causes severe skin burns and eye damage. □ Skin irrit. 2 H315: Causes skin irritation □ Eye irrit. 2 H319: Causes serious eye irritation
Chemical/Physical properties	Potassium acetate is colorless and lustrous compound rapidly deliquesc crystals or white powder or flakes.Potassium acetate is soluble in alcohol and is not soluble in ether nor is it ignitable. The chemical physical properties of the 1,2-bis(2 ethylhexyloxycarbonyl) ethanesulphonate potassium salt are not available.
Major constituents	Potassium
Information on possible hazards	**HEALTH** **Toxicity values (ECHA database):** ■ Workers □ Systemic effects of acute exposure: □ Dermal DN(M)EL 86.14 mg/kg body weight/day

Acronyms	Details
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DMEL	Derived Minimal Effect Level
EC50	half maximal effective concentration
GHS	Globally Harmonized System of Classification and Labelling of Chemicals
IPPC	Integrated Pollution Prevention and Control
Kow	Octanol – water coefficient
LC50	median lethal concentration (concentration at which 50% of the sample population is eliminated)
LD50	median lethal dose (dose at which 50% of the sample population is eliminated)
LOAEL	Lowest Observed Adverse Effect Level (lowest dose that produced an adverse effect)
MFA	metallic fuel additives
MMT	methylcyclopentadienyl manganese tricarbonyl
NOAEL	No Observed Adverse Effect Level (usually expressed in mg/kg/day, it defines the dose of substance that produces no significant toxicological effects for a specific exposure pathway)

Product name	**Potassium acetate KOAc** **1,2-bis(2-ethylhexyloxycarbonyl)ethanesulphonate potassium salt**
	☐ Inhalation DN(M)EL 1265.65 mg/m³ ☐ Systemic effects of long-term exposure: ☐ Dermal DN(M)EL 14.36 mg/kg bw/day ☐ Inhalation DN(M)EL 1265.65 mg/m³ ■ General population ☐ Systemic effects of acute exposure: ☐ Dermal DN(M)EL 43.07 mg/kg bw/day ☐ Inhalation DN(M)EL 624.2 mg/m³ ☐ Oral DN(M)EL 43.07 mg/kg bw/day ☐ Systemic effects of long-term exposure: ☐ Dermal DN(M)EL 7.18 mg/kg bw/day ☐ Inhalation DN(M)EL 624.2 mg/m³ ☐ Oral DN(M)EL 6 mg/kg bw/day

Product name	**Potassium acetate KOAc** **1,2-bis(2-ethylhexyloxycarbonyl)ethanesulphonate potassium salt**

- (ECHA database, potassium acetate)

- In a study on the health effects of potassium acetate, single oral toxicity was estimated by the gastric intubation of groups of five non-fasted Carworth-Wistar rats, four to five weeks of age and 90 to 120 grams in weight: The rats were reared in the laboratory and were administered potassium acetate doses of 3.25g/kg (2.48-4.26). The observation period was 14 days and resulted in a potassium acetate LD50 of 3.25 g/kg (2.48-4.26) (ECHA database).
- Calcium acetate, which shares the same functional group as potassium acetate, has a 4-hour exposure LC50 value higher than 5.6 mg/L. At the dose no mortality was observed nor any changes during the pathology observations realized at the end of the 14-day study. According to the aforementioned tests, potassium acetate is considered a non-toxic substance.

Behaviour in the body:
Health effects:

- Inhalation of potassium dust or mists can irritate the eyes, nose, throat and lungs and cause sneezing, coughing and a sore throat. Increased exposure to potassium may cause a build-up of fluid in the lungs, called pulmonary edema,.and in severe cases can cause death. Furthermore, skin and eye contact with potassium can cause lung irritation, possible development of bronchitis, and severe burns leading to permanent damage; prolonged exposure to fumes can create sores on the inner nose and nasal septum (Pohanish, 2002).
- Direct contact with potassium metal may be corrosive and cause skin and eye burns, as concluded by O'Neil (2001).

ENVIRONMENT
Ecotoxicity values (ECHA database)

- PNEC aqua (freshwater) 0.46 mg/L
- PNEC aqua (marine water) 0.046 mg/L
- PNEC STP 0.862 g/L
- PNEC sediment (freshwater) 0.00185 mg/kg sediment dw
- PNEC sediment (marine water) 0.000185 mg/kg sediment dw
- PNEC soil 0.00185 mg/kg soil dw
- PNEC oral No potential for bioaccumulation (ECHA database)

Behavior in the environment:

- Potassium's photo transformation in air has been studied:

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Kow	Octanol – water coefficient
LC50	median lethal concentration (concentration at which 50% of the sample population is eliminated)
LD50	median lethal dose (dose at which 50% of the sample population is eliminated)
LOAEL	Lowest Observed Adverse Effect Level (lowest dose that produced an adverse effect)
MFA	metallic fuel additives
MMT	methylcyclopentadienyl manganese tricarbonyl
NOAEL	No Observed Adverse Effect Level (usually expressed in mg/kg/day, it defines the dose of substance that produces no significant toxicological effects for a specific exposure pathway)

Product name	**Potassium acetate KOAc** **1,2-bis(2-ethylhexyloxycarbonyl)ethanesulphonate potassium salt**
	Calculation by EPI-Suite, EPA (USA) v3.20 / AopWin v1.92 estimate. The half life of the potassium acetate in the air is 253.700 days (12-hr day; 1.5E6 OH/cm3 (ECHA database). ■ The biodegradability of potassium acetate in water was determined in a study with a non-adapted activated sludge for the test item over a test period of 28 days in the EU Method C.4-A DOC-Die-Away test (screening test). At 7 days, the biodegradation of potassium acetate in water reached 86% and at 28 days 99% and is thereby considered by ECHA as readily biodegradable (ECHA database) ■ The calculated bioaccumulation factor for potassium acetate is 3.162 (BCFWIN v3.00) and the Log BCF from regression-based method is 0.500 (ECHA database). ■ According to literature reviews, potassium salts arereadily biodegradable in aerobic conditions whereas a lack of information is available regarding the biodegradation of potassium salts in anaerobic conditions (Videncenter for jordforurening, 2006).

Product name	**Potassium acetate KOAc** **1,2-bis(2-ethylhexyloxycarbonyl)ethanesulphonate potassium salt**
	Environmental effects: ■ An acute toxicity test (96 hours static) using zebrafish (Brachydanio rerio) has been performed with 50% water solution of potassium acetate in accordance with OECD Guideline 203, "Fish Acute Toxicity Test". The measured 96-hour- LC50 value for the test substance was found to be >992.7mg/L and >496.35 mg/L for Potassium Acetate (ECHA database). ■ The results for the study of acute toxicity (OECD guideline test 202) of the 50% water solution of potassium acetate in *Daphnia magna* were: □ Nominal EC0 (24h) = 564 mg/L and measured EC0 (48h) = 564 mg/L (282 mg/L of Potassium acetate). □ Nominal EC50 (24h) > 919 mg/L and measured EC50 (48h) > 919 mg/L (> 459.5mg/L of Potassium acetate). The 560 mg/L treatment group showed no changes compared to the control group. In groups with 1000 mg /L, immobility occurred in only one of 20 animals. To determine the matter content were taken after 0 and 48 hours water samples. The analysis values were averaged over 80% of target concentration. In the test, all control parameters were within the recommended range (ECHA database). ■ An acute toxicity test (72 hours) on Skeletonema costatum has been performed on the 50% water solution of potassium acetate based on ISO 10253 "Water Quality Marine Algal Growth Inhibition Test with Skeletonema costatum and Phaeodactum tricornutum". The 72-hour EC50 value for the test substance was found to be >1000 mg/L (for Potassium acetate was > 500 mg/L). The NOEC value was estimated to 1000 mg/L (500 mg/L for Potassium acetate). In the test all of the control parameters were within the recommended ranges (ECHA database).
Timing of action categorisation: **- distribution system additives** **- vehicle fuel system additives** **- additives sold in filling station**	Additives sold in filling stations
Function (category)	■ Produce discernible ion signals in a combustion engine ■ Freeze protection ■ Anti-valve seat recession

Acronyms	Details
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MFA	metallic fuel additives
MMT	methylcyclopentadienyl manganese tricarbonyl
NOAEL	No Observed Adverse Effect Level (usually expressed in mg/kg/day, it defines the dose of substance that produces no significant toxicological effects for a specific exposure pathway)

Product name	**Potassium acetate KOAc** **1,2-bis(2-ethylhexyloxycarbonyl)ethanesulphonate potassium salt**
Concentration in gasoline (average)	■ The maximum concentration of 1,2-bis(2 ethylhexyloxycarbonyl) ethanesulphonate potassium salt in fuel products is 100 mg/L (Videncenter for jordforurening, 2006). ■ No data found for the potassium acetate.
Emissions in the environment during life cycle	No data found
Vehicle emissions impacts	No data found
Environmental exposure	No data found
Human exposure	Humans can be exposed to potassium compounds via accidental ingestion or dermal contact (MSDS factsheet).
References	ECHA database

Product name	**Potassium acetate KOAc** **1,2-bis(2-ethylhexyloxycarbonyl)ethanesulphonate potassium salt**
	apps.echa.europa.eu/registered/data/dossiers/DISS-9d870180-b549-01e1-e044-00144f67d249/AGGR-ccca23d6-8a95-4df7-b43b-5820e57ecfe8_DISS-9d870180-b549-01e1-e044-00144f67d249.html#L-29543715-f50c-4368-86a2-9ea48fc764cd Material Safety Datasheet: Potassium acetate www.sciencelab.com/msds.php?msdsId=9927397 O'Neil, M.J. (ed.) (2001). The Merck Index - An Encyclopedia of Chemicals, Drugs, and Biologicals. 13th Edition, Whitehouse Station, NJ: Merck and Co., Inc, p. 1366. Pohanish, R.P. (2002). Sittig's Handbook of Toxic and HazardousChemicals and Carcinogens (4th Edition)William Andrew Publishing/Noyes. Online version Available from: www.knovel.com/knovel2/Toc.jsp?BookID=421&VerticalID=0 Videncenter for jordforurening, (Denmark) (2006) Fuel additives A risk screening of additives to gasoline and diesel Contamination of soil, soil air and groundwater Teknik og Administration Nr. 3 2006

L. Platinum Group Metals (PGM)

For illustrative purposes only. This factsheet does not represent the assessment documents on the risk posed by individual substances following the methodology presented in the report. They aim to illustrate how information could be presented and some factsheet's sections are not necessarily relevantfor all the MFAs. They are based on the collection of available information but are not intended to be comprehensive and do not necessarily reflect the latest developments in the field of MFAs.

In the stated forms (CAS 7440-16-6, 7440-05-3, 7440-06-4), Rhodium, Palladium and Platinum are insoluble to fuel, but they are presented for informative purposes because existing literature indicated the possible use of this metal in MFAs.

Product name	**Platinum group metals**
Chemical names	■ Rhodium ■ Palladium ■ Platinum
Family compounds	Platinum group metals
CAS	■ Rhodium 7440-16-6 ■ Palladium 7440-05-3 ■ Platinum 7440-06-4
EINECS	Not available

Acronyms	Details
BCF	Bioconcentration factor
CEC	Coordinating European Council
CLP	Classification Labelling and Packaging
DNEL	Derived No-Effect Level (DNELs are calculated by dividing the value of the health effect dose descriptor by an assessment factor (or safety factor) to allow for extrapolation to real human exposure situations)
DMEL	Derived Minimal Effect Level
EC50	half maximal effective concentration
GHS	Globally Harmonized System of Classification and Labelling of Chemicals
IPPC	Integrated Pollution Prevention and Control
Kow	Octanol – water coefficient
LC50	median lethal concentration (concentration at which 50% of the sample population is eliminated)
LD50	median lethal dose (dose at which 50% of the sample population is eliminated)
LOAEL	Lowest Observed Adverse Effect Level (lowest dose that produced an adverse effect)
MFA	metallic fuel additives
MMT	methylcyclopentadienyl manganese tricarbonyl
NOAEL	No Observed Adverse Effect Level (usually expressed in mg/kg/day, it defines the dose of substance that produces no significant toxicological effects for a specific exposure pathway)

Product name	**Platinum group metals**
Chemical Formula	■ Rhodium Rh ■ Palladium Pd ■ Platinum Pt
Classification / Labelling	Not available
Chemical/Physical properties	■ Platinum group elements (PGEs) is a group of metals that includes platinum (Pt), palladium (Pd) and rhodium (Rh). The chemical properties of these rare metals make them superb catalysts. Furthermore, the PGEs arehighly resistant to oxidation and present in lowabundance in the Earth's crust (Wedepohl, 1995). ■ Platinum (Pt) is a lustrous silvery-white, malleable, and ductile metal. Its density is one of the highest among the member of group 10 of the periodic table of the elements. Platinum is unaffected in the aquatic and atmospheric compartment but will dissolve in hot *aqua* regia, in hot concentrated phosphoric and sulphuric acids, and in molten alkali. It is highly resistant to corrosion and tarnishing and in the atmospheric compartment, platinum will not oxidize no

Product name	Platinum group metals
	matter how strongly it is heated (Lenntech database). ■ Rhodium (Rh) metal is lustrous and silvery-white. Its melting point is higher than platinum and its density is lower than platinum. It is highly resistant in the water and atmospheric compartment (up to 600°C). It is insoluble in most acids, including aqua regia, but is dissolved in hot concentrated sulfuric acid and it is attacked by molten alkalis. A dust explosion of rhodium is possible if rhodium in powder or granular form is mixed with air. Additionally, Rhodium reacts with oxygen difluoride causing fire hazard (Lenntech database). ■ Palladium (Pd) is a lustrous silver-white metal. It has a face-centered cubic crystalline structure and at ordinary temperatures is strongly resistant to corrosion in air and to the action of acids. It is attacked by hot acids, and it dissolves in aqua regia. Palladium can form many compounds and several complex salts and has a great ability to absorb hydrogen up to 900 times its own volume (Lenntech database).

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Product name	**Platinum group metals**
Major constituents	PGM
Information on possible hazards	**HEALTH** ■ Platinum (Pt): When assessing the health effects of Pt, a clear distinction must be made between elemental (i.e. metallic) Pt and halogenated Pt compounds. Concerning the toxicology of finely dispersed Pt particles, almost no data is available. There is epidemiological evidence that the sensitizing potential of Pt compounds is restricted to halogenated compounds (Linnett et al., 1999). The acute toxicity of Pt compounds depends on their solubility; in animal experiments, soluble Pt salts aremore toxic than insoluble Pt compounds such as PtO, PtO and PtCl . **Toxicity values :** ■ Based on the conclusions from a longitudinal study by Merget et al. 1999., Pt concentrations below 10 ng/m3 soluble Pt or below 100 ng/m3 total Pt may be defined as safe. In a more conservative approach, a NOEL of 1.5 ng/m3 for soluble Pt, as derived from that workplace study, has been calculated. Hence, automotive Pt

Product name	Platinum group metals
	emissions with halogenated Pt salts (comprising only 1 or 0.1%) would result in NOELs of 150 and 1500 ng/m3 of total Pt. A safety factor of 10, to account for the potentially higher susceptibility of sensitive groups, was applied and theguidance values of 15 and 150 ng/m3 of total catalyst-borne Pt respectively were derived. **Bioavailability and behaviour in the body :** ■ Toxic effects of metallic Pt emitted from automobile exhaust converters are expected only if the Pt compounds are bioavailable. Platinum found in plants and animals, according to tests by Vaughan and Florence (1992), appears to be bioavailable and therefore can be found in the human body via oral ingestion of contaminated food. An average dietary intake of 1.44 µg Pt per day for adults (male: 1.73 µg day-1; female: 1.15 µg day-1) has been calculated. The natural levels of Pt significantly fluctuate in various human body fluidsPt values of 0.8-6.9 ng.l-1 and 0.56 µg.l-1 for blood, and 0.5-15 ng.l-1 and 0.18 µg.l-1 for urine have been reported (Vaughan and Florence, 1992). ■ In experiments, a model of platinum particles emitted by a three-way catalytic converter equipped engine.The bioavailability of Pt from these particles and the form of Pt species in vivo were assessed. An in vitro solubility test showed that 10 % of Pt content from the model substance was soluble in physiological NaCl solutions. (Artelt et al., 1998). ■ For comparison, particles with aerodynamic diameters <10 µm have been estimated by DFG (1999) to be inhalable, but are mainly deposited in the upper respiratory tract. Particles <10 µm reach the tracheobronchial region with a likelihood of >50%, whereas particles < 4 µm are mainly respirable, i.e. deposit in the alveolar region of the human lung (DFG, 1999). ■ In some short-term animal tests by Artelt et al., (1998), Pt was detected in all the studied tissues (lungs, kidney, liver, spleen, stomach, adrenal glands) and body fluids. The contribution of the swallowed Pt (via oral application) to the Pt content of the matrices studied was very low; therefore, its contribution to the overall bioavailability was considered negligible (Artelt et al., 1998). ■ In another study (Artelt et al., 1999b), the PGM compounds were applied to rats via tracheal instillation, inhalation, and feeding. Pt was found in the bloodstream, urine and feces as well as the liver, spleen, kidney, adrenals, stomach, and femur. Based on the Pt content in body fluids and all organs (except for the lungs and faeces), it was calculated that up to 16 % of the Pt was retained in the lungs 1 day after intratracheal instillation. Additionally, on average 30 % of the Pt retained was finely dispersed and deposited during the 90-day inhalation exposure. Furthermore this study

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Product name	Platinum group metals
	reported that greater than 90 % of the bioavailable Pt was bound to high molecular weight compounds (80-800 kDa), most likely proteins. **Health effects :** ■ Some in vitro studies suggest that Pd(II), Pt(II) and Rh(III) complexes are able to inhibit a variety of cellular functions, which can be attributed to their capacity to form strong complexes with various organic and inorganic ligands. Platinum based treatments are used in chemohrapy but those rgimen have ben showed to be particularly toxic to patients (D'Addario et al. 2005). Numerous older studies demonstrate that PGEs can affect cellular fluidity, membrane integrity, permeability, interfere with protein synthesis (Binet and Volfin, 1977; Wataha et al., 1995), inhibit mitochondrial enzyme production and alter the structure of the mitochondrial lipid bilayer (Rosen et al., 1992). Their ability to impact cell viability, cellular processes and functions has also been suggested in more recent in vitro studies. Frazzoli et al. (2007) investigated the potential of $PdCl_2$, $PtCl_2$ and $RhCl_3$ to interfere with aerobic respiration at a cellular level using suspended yeast cells (Saccharomyes cerevisiae). Metal concentrations in found by the authors closely correlated with

Product name	Platinum group metals
	acute respiration inhibition. The lowest experimental doses found to induce an adverse effect were 161 ng.g–1 for Pd, 120 ng.g–1 for Pt and 60 ng.g–1 for Rh. The results of this test indicate that Rh was more toxic (i.e. EC50%, steepness of curve) than Pd and Pt (Frazzoli et al., 2007). ■ The acute oral toxicity of 1-5 µm Pt particles in rats was reported as very low(WHO, 1991). In an experiment that examined the effects of PtO, PtCl, and finely dispersed Pt on the popliteal lymph-node assay of mice, none of the chemicals induced an immune response (Schuppe et al., 1993) . In another study, no clear allergic reaction to Pt was reported (according to the WHO's conclusions) from workplaces with exposure to metallic Pt. However, according to a study conducted by Cleare in 1977, metallic Pd can cause contact dermatitis. In Cleare's experiments, workers in the Pt industry who were highly sensitive to tetra- and hexachloro platinates were skin-prick tested with extracts of particulate exhaust samples and no positive responses were observed (Cleare, 1977). ■ According to the WHO's analysis of, (1991) several soluble Pt compounds showed mutagenic effects in bacterial systems as well as in mammalian cells, but not in vivo tests on Drosophila or in micronucleus tests on mice. The cytotoxic effects of the platinum complexes (ED50), in tests conducted by XXX occurred at concentrations of 0.2 mM. The analogous palladium salts tested were three times less toxic (ED50 = 0.6 mM), while the rhodium salts proved to be 30 times less toxic (ED50 = 6 mM). The toxicity levels of a metal's various complexes did not differ significantly from each other thereby indicating that the metal itself is responsible for inducing toxic effects. Using the Ames test, the spontaneous mutation rates for four tester strains exposed to platinum complexes increased by factors of 3- 20. The analogous rhodium compounds proved to be considerably less mutagenic, and palladium demonstrated no mutagenic potential. Since all four tester strains contain different mutations, the authors (who?) conclude that the mutagenic potential of platinum and rhodium complexes appear to be based on a variety of mechanisms that damage DNA (WHO, 1991; Bunger, 1997; Gebel et al., 1997). ■ The relevant end-point for humans is the sensitizing effect of some halogenated Pt compounds. No scientific reports were identified on health effects related to non-occupational exposure of allergenic Pt compounds. In several occupational cases and epidemiological studies (Rosner and Merget, 1990 ; Dhara, 1984), it was suggested that exposure to halogenated Pt salts can cause respiratory sensitization. The Health and Safety Executive (1990) lists eye watering, sneezing, tightness of chest, wheezing, breathlessness, cough, eczematous and urticarial skin lesions, and mucus

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Product name	Platinum group metals
	membrane inflammation as typical symptoms of Pt salt sensitization. In addition, some Pt complexes can bind to the nitrogen and sulfur in proteins and can potentially reduce enzymatic activity (Helmers et al., 1994). ■ A study has also indicated that PGM compounds have lymphocyte proliferation and cytokine release effects (Boscolo et al., 2004). ■ Platinum compounds, especially soluble salts, can be toxic. Chronic industrial exposure to these compounds has been suggested to be responsible for the development of Platinosis, an allergic reaction characterized by respiratory and cutaneous hypersensitivity (Brubaker et al., 1975). Employees exposed to platinum compounds during the production and recycling of Pt-based catalytic converters showed Pt levels in urine and blood up to 100 times higher than non-exposed control individuals (Zereini and Alt, 1999). ■ Pd salts have been suggested to have a lower genotoxicity in bacteria and mammalian cells compared to elemental Pt, according to sudies by Gebel (et al., 1997) ; Migliore (et al., 2002). ■ Rhodium compounds are rarely encountered by the general population and there are almost no cases of humans affected by this

Product name	Platinum group metals
	element (Murdoch and Pepsu 1987). The health effects of rhodium exposure have not been investigated, therefore utmost care must be taken (Lenntech database). There is no evidence that other PGMs show a higher potency than Pt salts. There is a striking difference between Pt and Pd, since metallic Pd can cause contact dermatitis. However, this potential cannot be projected to the respiratory sensitizing potential of Pd and its salts. A study described immediate type sensitizations to Pd only in refinery workers sensitized to Pt, and limited cross-reactivity between both metals. This study showed a low prevalence of sensitizations to platinum group metals other than Pt (Murdoch and Pepys 1987). **ENVIRONMENT** **Ecotoxicity values :** No data found **Behaviour in the environment :** ■ If released into air, the WHO (1991) suggests that platinum compounds exist solely in the particulate phase in the ambient atmosphere. Particulate-phase platinum compounds may be removed from the air by wet and dry deposition (WHO, 1991). ■ If released into soil, platinum compounds are expected to be mobile only in extremely acidic soil or soil with high chloride levels. The compounds will not volatilize from moist or dry soil surfaces based upon their ionic character and low vapor pressures (WHO, 1991). ■ If released into water, organic matter may bind with dissolved platinum, which may precipitate or concentrate platinum compounds in suspended solids and sediments. Bacteria may transform water soluble platinum compounds into methylplatinum compounds. Volatilization from water surfaces is not expected to be an important fate process because dissolved platinum compounds are ionic and ions are not expected to volatilize (WHO, 1991 ; Cotton et al., 1980 ; Renner et al., 1991). ■ A study investigated the solubility of Pd and Pt blacks (fine metal powders) in aqueous solutions of biogenic substances. These finely dispersed materials resembled the state of PGMs in catalytic converters. The authors concluded from this study that the finely dispersed Pt significantly dissolved in the presence of adenosine triphosphate (the well-known bioactive compound of the living organisms) as well as in the human body (Freiesleben et al., 1993). ■ Some estimates of the Pt concentration in roadside soil approached 270 ng km-1 (Zereini et al., 2001b). An examination of these Pt particulates showed that around 99% was in the metallic state with around 1% oxidized, presumably in the form of Pt4+ (Schlögl et al., 1987; Artelt et al., 2000). Early experiments also suggest the

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Product name	Platinum group metals
	evolvement of volatile Pt(IV) oxide when heating Pt metal at 500°C while in contact with air or oxygen (Balgord, 1973). **Environmental effects :** ■ Biological half-lives for platinum are rather short which, according to Renner et al. (1991), suggest that the potential for bioconcentration in aquatic organisms is low (SRC). In four marine algal species, BCFs ranged from 5,000 to 10+5 (Renner et al., 1991). ■ An experiment on zebra mussels studied the bioavailability of the PGM and their capacity to bioaccumulate. This experiment suggests that all the three catalyst emitted metals were bioaccumulated by mussels and that the respective increases from least to greatest Rh<Pt<Pd (Sures et al., 2002). ■ Plants can, as suggested by Ek (et al 2004), take up and accumulate soluble species of PGE, especially Pd. Furthermore,PGE deposition in species with low molecular weight can occur in the roots via sulfur binding (Ek et al., 2004). ■ Rhodium, according to the Lenntech database, is a rare naturally occurring element and therefore its effect on the environment can

Product name	**Platinum group metals**
	be assumed to be nil (Lenntech database). ■ Palladium has been suggested by the Lenntech database to have little environmental impact. It is present at low levels in some soils, and the leaves of trees have been found to contain 0.4 ppm. Some plants, such as the water hyacinth, are killed by low levels of palladium salts but most plants tolerate it and their growth is affected at levels above 3 ppm. (Lenntech database)
Timing of action categorisation: - distribution system additives - vehicle fuel system additives - additives sold in filling station	■ Additive sold in filling station
Function (category)	Vehicle exhaust catalyst
Concentration in gasoline (average)	■ Rh in catalysts is present in smaller quantities than Pt. Pd has increasingly substituted Pt in automotive catalysts (Merget et al., 2000). ■ A vehicle exhaust catalyst contains around 1-3 g of PGM, corresponding to approximately 1.8 mg cm-3 PGM of the catalyst (Ravindra et al ., review).
Emissions in the environment during life cycle	■ The amount and rate of PGM emissions from catalytic converters are affected by the speed of the automobile, type of engine, type and age of the catalyst, and kind of fuel additives (Artelt et al., 1999a; Ely et al., 2001, Ravindra et al., 2004). Emissions can be intensified by unfavorable operating conditions such as misfiring, and excessive heating, which may even destroy the converter (Schäfer and Puchelt, 1998). ■ According to studies by Artelt et al. (1999a) Pt is emitted from automotive catalytic converters in particulate form, mainly in the oxidation state (elemental Pt). The nanocrystalline Pt particles are attached to µm-sized aluminum oxide particles. The majority of emissions is comprised of Pt-loaded particles with sizes >10.2 µm. between 11-36% of the particles were found to be <3.14 µm (Artelt et al., 1999a). ■ The PGM emission rate, in studies by Palacios et al, ranged from 65-180ng km-1 depending on whether it was calculated in motor experiments or on the base of environmental concentrations.

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Product name	**Platinum group metals**
	Samples were collected following the 91,441 EUDC driving cycle for light-duty vehicle testing (Palacios et al., 2000a, 2000b). ■ The Pt concentration emitted in astudy by Artelt ranged from 7 -123 ng m-3; these values correspond to emission factors of 9-124 ng km-1 (Artelt et al., 1999a).
Vehicle emissions impacts	■ The introduction of three-way catalysts has reduced the emissions of carbon monoxide (CO), unburned hydrocarbons (HC) and nitrogen oxides (NOx) by 90%. PGM are the active components of the catalysts: platinum (Pt) and palladium (Pd) (which oxidizes CO to CO_2 and HC to H_2O) and rhodium (Rh) (which reduces NOx) (Barefoot, 1997).
Environmental exposure	■ Rhodium is mainly used with platinum in catalysts in both the automobile chemical industries (Habashi, 1997). However, sources of PGM other than automobile catalysts are not considered important when assessing environmental contamination. ■ Zereini et al suggest that the highest concentrations of PGM can be expected on, or very close to, highly frequented motorways. This

Product name	**Platinum group metals**
	finding is supported by a study that found Pt concentrations in roadside dust samples, in which a decreasing tendency was found in the following order: close to motorways 308 µg/kg; city sites 257 µg/kg; parking garages 189 µg/kg; and roadway tunnels 141 µg/kg (Zereini et al., 1997) ■ The use of platinum compounds in automobile catalytic converters results in its release into the environment. Most of the PGMs, released from catalytic converters, have been suggested to be in particulate form (Pt>95 %, Pd>85 %, and Rh>90 %) and are dispersed into the environment at a rate of a few ng PGM per km per car (König et al., 1992; Moldovan et al., 1999, 2002).
Human exposure	■ Monitoring data indicates that the general population may be exposed to platinum compounds via inhalation of roadside air containing platinum compounds (SRC) (WHO, 1991). Palladium exposure through inhalation of Pd from automobile catalyst emissions is expected to be low (about 2.2 ng person/ day). However, in a worst case air pollution scenario of 57 ng/m 3 the average daily intake would reach 1254 ng/person (Melber et al., 2002). ■ Occupational exposure occurs during the mining and processing of platinum. However, the most common occupational exposure to soluble platinum compounds is through inhalation in platinum refining and catalyst manufacturing. ■ The prevalence and incidence of allergic reactions resulting from Pt salt exposure in Pt refineries and catalyst productions are still high, although exposure was reported below the occupational threshold limit value (TLV) for soluble Pt in two refineries. Based on epidemiological studies by Merget et al. 1988 and Bolm-Audorff et al. 1992 in these plants, exposure to soluble Pt was approximately 0.1 µg/m3 and did not exclude sensitisation.
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MMT	methylcyclopentadienyl manganese tricarbonyl
NOAEL	No Observed Adverse Effect Level (usually expressed in mg/kg/day, it defines the dose of substance that produces no significant toxicological effects for a specific exposure pathway)

Product name	Platinum group metals
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Product name	**Platinum group metals**
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Product name	**Platinum group metals**
	1:44-49.

N. Zirconium salt

For illustrative purposes only. This factsheet does not represent the assessment documents on the risk posed by individual substances following the methodology presented in the report. They aim to illustrate how information could be presented and some factsheet's sections are not necessarily relevantfor all the MFAs. They are based on the collection of available information but are not intended to be comprehensive and do not necessarily reflect the latest developments in the field of MFAs.

Zirconium salts are used as fuel additives. Little specific information are available, thus general information about zirconium element and zirconium compounds have been collected in this factsheet.

Product name	**Zirconium salt**
Chemical names	■ Zirconium hexanoate ■ Zirconium 2-ethylhexyloctanoate

Product name	**Zirconium salt**
	■ 2-ethylhexanoic acid, zirconium salt ■ Hexanoic acid, 2-ethyl-, zirconium salt ■ Zirconium 2-ethylhexanoate ■ 2-Ethylhexanoic acid metal salt ■ 2-ethylhexanoic acid, zirconium salt
Family compounds	Transition metal
CAS	22464-99-9
EINECS	245-018-1
Chemical Formula	$C_{16}H_{30}O_4Zr$
Classification / Labelling	**Labelling according Regulation (EC) No 1272/2008 (CLP) for zirconium salt :** Skin Irrit. 2 H315: causes skin irritation Eye Irrit. 2 H319 : causes serious eye irritation STOT SE 3 H335 : may cause respiratory irritation Acute tox. 4 H332 : harmful if inhaled Aquatic chronic 4 H413 : May cause long lasting harmful effects to aquatic life
Chemical/Physical properties	One characteristic of zirconium salt and other metal carboxylates is that they readily dissociate from an ion pair into free metal and free acid. They are found as partially dissociated products in the ambient environment (i.e. neutral pH). The transport and bioavailability of the metals and acids are determined by their solubility in environmental media and biological fluids which is determined by environmental parameters such as pH (US EPA, 2005).
Major constituents	Zr
Information on possible hazards	**HEALTH** **Toxicity values :** Acute toxicity values: Oral, inhalation and dermal LD50 or LC50 values are >5000 mg/kg (rat), >8.8 mg/L (1 hr., rat), and >5000 mglkg (rabbit), respectively (US EPA, 2005). **Behaviour in the body :** Zirconium salts are slowly absorbed from injection sites and cause local irritation. If zirconium salt are injected intravenously on rodent insoluble colloidal polymers are

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Product name	Zirconium salt
	formed and are phagocytized by macrophages. Excretion is mainly through feces owing to poor alimentary absorption of orally ingested zirconium salts and to accumulation of soluble zirconium salts in liver with their subsequent return to alimentary tract by the bile. A mechanism of zirconium homeostasis is apparently present in man (Venugopal et al.1978). **Health effects :** ■ Animals (rodents) acutely poisoned by zirconium compounds show progressive depression and decrease in activity until death. The time of death varies from a few hours to a few days following administration of the compounds; few deaths occur later than 5 days after administration. No signs characteristic of zirconium poisoning has been observed (Clayton et al., 1981-1982). ■ Zirconium can produce hypersensitivity and granulomatous skin disease in humans. Granulomas occur after dermal contact with zirconium salts. Granulomas caused by soluble salts tend to disappear in a few months. Those caused by insoluble zirconium salts persist for years (Sullivan et al., 1999). ■ Case of pulmonary fibrosis have been reported by Bingham et al.(2001) after long term exposure to zirconium salt in workers. Several criteria

Product name	**Zirconium salt**
	have been taken into account for the diagnosis. The history of exposure and the latency period (15 years) before the onset of symptoms is a key criteria. Chest roentgenograms allow seeing the progression of pulmonary fibrosis. **ENVIRONMENT** **Ecotoxicity values** **Behaviour in the environment :** The principal valence state of zirconium is +4 and the only stable valence in aqueous solution. The aqueous chemistry of zirconium is characterized by a high degree of hydrolysis and formation of polymeric species and various complex ions. Zirconium forms very stable oxides (Anonymous, 1998). Zr_4+(aq) ion is only present in very dilute solutions (approx. 10-4 M) and at low pH (1-2)(2). Zirconium compounds would not volatilize from aqueous solution due to their ionic character (SRC). Ionic zirconium compound would not be expected to bioconcentrate in aquatic organisms (SRC) (Cotton et al., 1999). **Environmental effects :** ■ Using bioassays on bacteria (Photobacterium phosphoreum), microscopic algae (Selenastrum capricornutum), and fish (Salmo gairdneri), a study confirmed the hypothesis that zirconium element has low toxicity. The toxic effects noted by the Microtox test may have been attributed to pH rather than specifically to zirconium. Fish assays also confirmed the low toxicity of zirconium. Mutagenicity (fluctuation test) and genotoxicity (SOS Chromotest) assays failed to show any DNA-related effects linked to this metal. Only the algal assays (ATP energy stress) demonstrated genuine toxicity at zirconium concentrations between 1.3 and 2.5 mg/L (Bingham et al., 2001). ■ No reliable ecotoxicity data on hexanoic acid, 2-ethyl, zirconium salt are available. The dissociation product 2-ethyl hexanoic acid is moderately toxic to fish, invertebrates, and algae. Zirconium poses slight to moderate toxicity to fish, but appears to be somewhat more toxic to algae (EPA, 2005).
Timing of action categorisation: **- distribution system additives** **- vehicle fuel system additives** **- additives sold in filling station**	No categorisation found
Function (category)	Reduce the amount of particulate matter formed during the combustion of residual

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Product name	Zirconium salt
	fuel oil (US patent 1983).
Concentration in gasoline (average)	No data found
Emissions in the environment during life cycle	No data found
Vehicle emissions impacts	No data found
Environmental exposure	No data found
Human exposure	Occupational exposure to zirconium compounds may occur through inhalation and dermal contact with these compounds at workplaces where zirconium or zirconiumcompounds are produced or used (SRC). Mean zirconium concentration in the interior of highway trooper patrol cars monitored for 25 days during August, September, and October of 2001 was 2.0

Product name	**Zirconium salt**
	ng/cu m^3; ambient and roadside concentrations were each 1.8 ng/cu m^3 (Riediker et al., 2003).
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NOEC	No Observed Effect Concentration
PBT	persistent, bioaccumulative and toxic
PEC	predicted environmental concentration
PNEC	Predicted No Effect Concentration (concentration below which no effect is expected in the environment)
SDS	chemical safety data sheet
vPvB	very persistent, very bioaccumulative

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Regarding the sampling strategy for monitoring in air:

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Regarding the tests used in evaluating hazards:

The OECD protocols (e.g. from 410 to 413) to test the toxicity for humans of a specific substance. For instance, regarding emission inhalation the OECD 412 test can be a reference point.

Regarding the development of exposure scenarios:

ECHA website provides concrete examples through the guidance developed for REACH: echa.europa.eu/web/guest/guidance-documents/guidance-on-reach

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CAA Alternative Tier 2 test program for MMT designed to collect critical manganese emissions, personal exposure, and pharmacokinetic data (all test reports and correspondence related to the Alternative Tier 2 Testing for MMT can be found in the Federal Docket Management System (FDMS) at www.regulations.gov as an existing guidance for exposure assessment identified by docket number EPA-HQ-OAR-2004-0074).

Regarding risk characterisation (many other examples exist in the literature):

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Steiner et al. (2012) investigated the risks from Cerium dioxide nanoparticles with diesel exhaust: Cerium dioxide nanoparticles can interfere with the associated cellular mechanistic response to diesel exhaust exposure ; and

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Reach dossiers

The following dossiers are available on the ECHA website: MMT, pentacarbonyl iron, cerium dioxide, tetraethyl lead, potassium acetate.

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