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Identifying and collecting relevant literature related to the oral toxicity of furan and its methyl analogues, 2-methylfuran and 3-methylfuran

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Abstract

An extensive literature search to identify and collect all relevant literature on the oral toxicity of furan and its methyl analogues, 2-methylfuran and 3-methylfuran was performed in the two databases PubMed and Web of Science for four Areas. The literature search resulted for Area 1 (toxicokinetics) in 1,674 hits from PubMed and 2,318 hits from Web of Science; for Area 2 (oral toxicity in experimental animals) in 2,329 hits from PubMed and 3,914 hits from Web of Science; for Area 3 (*in vitro* and *in vivo* genotoxicity and mode of action) in 1,100 hits from PubMed and 2,290 hits from Web of Science; and for Area 4 (observations in humans) in 639 hits from PubMed and 1,073 from Web of Science. After removal of the duplicates, the total number of hits for Area 1 was 3,184, for Area 2 was 4,883, for Area 3 was 2,588, and for Area 4 was 1,295. The evaluation of all retrieved references for relevance by screening the title and abstract (if available) and applying eligibility criteria (inclusion/exclusion) resulted in a total number of relevant references for Area 1 of 33, for Area 2 of 44, for Area 3 of 75 (including two relevant references located in the Area 2 literature search), and for Area 4 of 5.

Key words: Furan, 2-methylfuran, 3-methylfuran, oral toxicity, extensive literature search

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Summary

The overall aim of this assignment was to identify and collect all relevant literature on the oral toxicity of furan and its methyl analogues, 2-methylfuran and 3-methylfuran to support preparatory work for the human risk assessment of these substances.

Initially, four tailored search strings were designed to retrieve all potentially relevant studies for the hazard identification and characterisation of furan and its methyl analogues. The four tailored search strings covered the following four areas:

- Area 1: Data on toxicokinetics (absorption, distribution, metabolism and excretion (ADME)) in experimental animals and humans and from *in vitro* studies.
- Area 2: Data on oral toxicity in experimental animals.
- Area 3: Data on *in vitro* and *in vivo* genotoxicity and mode of action (MoA).
- Area 4: Data on observations in humans (including epidemiological studies, case reports and biomarkers of exposure).

The search strings were tailored to the databases PubMed and Web of Science and consisted of two major steps each designed to search titles and abstracts in PubMed and Web of Science, as well as full text in PubMed. Combinations of search terms were used, starting with a broad search for each compound (furan, 2-methylfuran and 3-methylfuran) and its synonyms (step 1) and followed by an Area specific step with the addition of search terms relevant to each Area (step 2).

Then the four tailored search strings were employed to retrieve all relevant studies from the two databases. Data published since 1990 were retrieved for Area 1-3 and since 2004 for Area 4. All retrieved references were exported as separate files into EndNote™. Duplicate studies were then removed after combining the two EndNote™ files per Area into one single combined file per Area.

The literature search resulted for Area 1 in 1,674 hits from PubMed and 2,318 hits from Web of Science; for Area 2 in 2,329 hits from PubMed and 3914 hits from Web of Science; for Area 3 in 1,100 hits from PubMed and 2,290 hits from Web of Science; and for Area 4 in 639 hits from PubMed and 1,073 from Web of Science. After removal of the duplicates, the total number of hits for Area 1 was 3,184, for Area 2 was 4,883, for Area 3 was 2,588, and for Area 4 was 1,295.

All retrieved references were then evaluated for relevance by applying eligibility criteria (inclusion/exclusion). The selection for relevance was conducted by screening the title and abstract (if available) and all the retrieved references were ultimately sorted into one of the following two categories:

- Relevant to the research objectives: References ultimately evaluated to be relevant were included in this category. In case the relevance could not be evaluated because e.g. of missing or vague abstracts individual full texts were obtained if possible to evaluate if the study was truly relevant. If relevance remained uncertain, the references were also included in this category, as a conservative approach.
- Not relevant to the research objectives: References ultimately evaluated not to be in-scope were included in this category.

The results of the reference selection process were reported in summary tables (Excel files), one table per Area. The summary tables include all pertinent information for each of the references in the 'Relevant' category as identified by the eligibility criteria and which could be retrieved from the title and abstract (when available). The summary tables also include references in the 'Not relevant' category, including the reason for exclusion, but without any study details.

The evaluation for relevance resulted in a total number of relevant references for Area 1 of 33, for Area 2 of 44, for Area 3 of 75 (including two relevant references located in the Area 2 literature search), and for Area 4 of 5.

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1. Introduction

1.1. Background and Terms of Reference as provided by the requestor

This contract was awarded by EFSA to:

Contractor: National Food Institute, Technical University of Denmark

Contract title: Identifying and collecting relevant literature related to the oral toxicity of furan and its methyl analogues, 2-methylfuran and 3-methylfuran

Contract number: RC/EFSA/BIOCONTAM/2016/02

1.1.1. Background as provided by EFSA

The Unit on Biological Hazard and Contaminants (BIOCONTAM Unit) supports the Panel on Contaminants in the Food Chain (CONTAM Panel), which provides scientific advice on contaminants in the food chain and undesirable substances such as natural toxicants, mycotoxins and residues of unauthorised substances.

In January 2016 EFSA received a mandate from the European Commission for a scientific opinion on the health risks related to the presence of furan and its methyl analogues in food. The mandate was allocated to the CONTAM Panel. A Working Group will be established to develop the draft opinion.

To support preparatory work for the hazard identification and characterization steps in the human risk assessment, EFSA wishes to outsource an extensive literature search (ELS) related to the toxicity of furan and its methyl analogues, 2-methylfuran and 3-methylfuran.

The contractor should ensure that all the steps for conducting the ELS are properly documented and reported.

The present Call is based on EFSA's 2016 Work Programme for Grants and operational Procurements Financing Decision found in Annex II of the Programming Document 2016-2018, available on the EFSA's website[1].

1.1.2. Objectives as provided by EFSA

The overall aim of the assignment is to identify and collect all relevant literature on the oral toxicity of furan and its methyl analogues, 2-methylfuran and 3-methylfuran to support preparatory work for the human risk assessment of these substances.

The three specific objectives in this assignment include:

Objective 1:

To design four tailored search strategies to retrieve all potentially relevant studies for the hazard identification and characterisation of furan and its methyl analogues, 2-methylfuran and 3-methylfuran. The four tailored search strategies will cover the following four areas:

- Area 1: Data on toxicokinetics (absorption, distribution, metabolism and excretion (ADME)) in experimental animals and humans and from *in vitro* studies.
- Area 2: Data on oral toxicity in experimental animals.
- Area 3: Data on *in vitro* and *in vivo* genotoxicity and mode of action (MoA).
- Area 4: Data on observations in humans (including epidemiological studies, case reports and biomarkers of exposure).

[1] http://www.efsa.europa.eu/sites/default/files/mb151203-a2.pdf

Objective 2:

To retrieve all potentially relevant studies for the hazard identification and characterisation of furan and its methyl analogues, 2-methylfuran and 3-methylfuran by execution of four extensive literature searches (ELSs) using the tailored search strings for the four areas developed under objective 1.

Objective 3:

To determine the relevance of the retrieved studies by screening titles and abstracts according to preselected eligibility criteria and prepare the outcome of the project for presentation to EFSA.

2. Methodologies

The methodology for systematic reviews including guidance for development and optimisation of a search strategy and for selecting relevant studies has been described by EFSA (2010). This methodology has been implemented as appropriate in the Tasks described below.

2.1. Objective 1

2.1.1. Task 1 Developing tailored search strategies and search strings for collecting relevant studies

Four tailored search strings on the four areas described below were developed for identifying all potentially relevant studies for the risk assessment of furan and its methyl analogues, 2-methylfuran and 3-methylfuran.

The four search strings are driven by the eligibility criteria for each Area (1-4) as provided by EFSA in the technical specifications which are copied in Appendix A of this external report. The search strings were tailored to the databases PubMed and Web of Science[2]. They consisted of two major steps each designed to search titles and abstracts in PubMed and Web of Science, as well as full text in PubMed. Combinations of search terms were used, starting with a broad search for each compound (furan, 2-methylfuran and 3-methylfuran) and its synonyms (step 1). The next step was Area specific with the addition of search terms relevant to each Area (step 2). The eligibility criteria contained both inclusion and exclusion criteria. Use of the Boolean operator "NOT" was avoided as a relevant reference can contain discussions on both relevant and excluded search terms. Instead exclusion criteria such as language (only English) and publication type (only peer reviewed primary research studies, systematic reviews and meta-analyses) were implemented in the search strategy.

Step 1 was designed to capture titles and abstracts in PubMed and Web of Science, as well as full text in PubMed containing furan, 2-methylfuran or 3-methylfuran. This step included compound name and synonyms, e.g. for furan:

- Furan
- OR Divinylene oxide
- OR Furfuran
- OR Oxacyclopentadiene
- OR Oxole
- OR Tetrole
- OR …

[2] Including the following databases: Web of ScienceTM Core Collection, BIOSIS Citation IndexSM, CABI: CAB Abstracts®, Current Contents Connect®, Data Citation index SM, FSTA®- the food science resource, MEDLINE®, SciELO Citation Index and Zoological Recored®.

"OR" is a Boolean operator that expands the amount of references returned when used in a search string as just one of the search terms need to be present in the returned references.

Step 2 was designed to capture titles and abstracts in PubMed and Web of Science, as well as full text in PubMed containing Area specific search terms. This step could for Area 2 include:

- Oral
- OR gavage
- OR feed
- OR liver
- OR hepato*
- OR cancer
- OR carcino*
- OR …

"*" symbolises truncation and is used for finding singular and plural forms of words and various endings. Both PubMed and Web of Science use an asterisk as their truncation symbol.

Search terms were identified in collaboration with the entire project team to identify as many as possible. The search terms were combined and tested in the two databases to develop the most sensitive and appropriate search string.

The search strings were also tested by assessing whether it retrieved relevant papers already known to the project team (e.g. (Moser et al., 2009; Gill et al., 2010; Terrell et al., 2014; Churchwell et al., 2015)) as recommend in EFSA (2010).

2.2. Objective 2

2.2.1. Task 2 Execution of four extensive literature searches using the tailored search strings developed in task 1

The four tailored search strings developed in Task 1 and agreed upon by EFSA were employed to retrieve all relevant studies from the databases PubMed and Web of Science on furan and its methyl analogues, 2-methylfuran and 3-methylfuran.

Data published since 1990 were retrieved on toxicokinetics (ADME) in experimental animals, humans and *in vitro* (Area 1), oral toxicity in experimental animals (Area 2) and *in vitro* and *in vivo* genotoxicity and mode of action (Area 3). Data published since 2004 were retrieved on observations in humans (including epidemiological studies, case reports, biomarkers of exposure) (Area 4).

All references located in the extensive literature searches in PubMed and Web of Science were exported as separate files into EndNote™. Title, author, journal, year of publication and abstract were included for each study imported to EndNote™ and the number of hits resulting from each of the four tailored search strings in each of the two databases were recorded in a log file. Duplicate studies were then removed after combining the two EndNote™ files per Area into one single combined file per Area.

2.3. Objective 3

2.3.1. Task 3 Selection of all relevant studies retrieved by the extensive literature searches

All studies retrieved by the extensive literature searches and imported into the combined EndNote™ files, one file per Area (Task 2), were evaluated for relevance by applying eligibility criteria

(inclusion/exclusion) as described by EFSA in the technical specifications (see Appendix A of this external report) for each subject Area (1-4). The selection for relevance was conducted by screening the title and abstract (if available) and all the retrieved studies were ultimately sorted into one of the following two categories:

- Relevant to the research objectives: References ultimately evaluated to be relevant were included in this category. In case the relevance could not be evaluated because e.g. of missing or vague abstracts individual full texts were obtained if possible to evaluate if the study was truly relevant, as recommended by EFSA (2010). If relevance remained uncertain, the references were also included in this category, as a conservative approach.
- Not relevant to the research objectives: References ultimately evaluated not to be in-scope were included in this category.

To ensure a uniform understanding of the eligibility criteria in the four Areas, these were discussed in an internal meeting before all references were assessed for relevance.

According to the original protocol proposed by the Contractor, "*Each will be individually assessed by two reviewers in order to prevent the introduction of errors and personal bias. In the possible event of disagreements between reviewers a third member of the project team will assist in solving the specific issue as recommended by EFSA (2010).*" However, as a result of the very broad search strings for each Area, a huge number of irrelevant hits were retrieved in the ELS for each Area. It was therefore decided that one principal team member for each Area performed an initial sorting of the hits into one of the following three categories: 1) Relevant, 2) possibly relevant, and 3) not relevant. All the references considered as possibly relevant were then assessed by another principal team member for each Area and the references were included either in the 'Relevant' category or in the 'Not relevant' category. The project coordinator also assisted in the evaluation of the possibly relevant references. In case relevance still remained uncertain, the references were included in the 'Relevant' category, as a conservative approach.

This deviation from the original protocol is not considered to invalidate the outcome of the selection for relevance of the studies retrieved from the ELSs as both the principal team members for each Area have an extensive experience within the specific Area and as the project coordinator has an extensive experience within all four Areas.

The results of the reference selection process were reported in summary tables, one table per Area. The information included in the summary tables ensures that all eligibility criteria of the studies were considered. Additional fields for relevance (answered by yes/no based on the eligibility criteria), the person(s) responsible for the screening and comments were also included in the summary tables.

To ensure a uniform reporting in the four summary tables, five representative references within each Area were assessed by all principal team members and discussed in an internal meeting before all references were reported in the summary tables.

2.3.2. Task 4 Preparation of EndNote™ files, summary tables and reference lists

EndNote™ files

All references found relevant for the risk assessment of furan and its methyl analogues, 2-methylfuran and 3-methylfuran within Area 1-4 were collected in a single EndNote™ file including all indexed fields per reference (i.e. title, author, publication year, journal and abstract).

Summary tables

Summary tables (Excel files) were prepared, one table for each Area.

Reference lists

All relevant references were collected in a reference list (see Appendix B).

3. Results

3.1. Objective 1

3.1.1. Task 1 Developing tailored search strategies and search strings for collecting relevant studies

The search strings that resulted in the largest number of potentially relevant studies on furan and its methyl analogues, 2-methylfuran and 3-methylfuran within Area 1-4 were submitted to EFSA on 8 April 2016 (email) as part of Deliverable 1. The proposed search strings were discussed with EFSA at the kick-off meeting on 11 April, revised and agreed on 15 April (email). The agreed search strings for Area 1-4 are presented below.

In the proposed search strings, "OR" is the Boolean operator that expands the amount of references returned when used in a search string as just one of the search terms need to be present in the returned references. "*" symbolises truncation and is used for finding singular and plural forms of words and various endings. Both PubMed and Web of Science use an asterisk as their truncation symbol.

Step 1:

The search strings agreed for step 1 are as follows:

Furan:
(Furan OR Furane OR Furfuran OR Furfurane OR Tetrole)

2-Methylfuran:
(2-Methylfuran OR 2-Methylfurane OR 5-Methylfuran OR 5-Methylfurane OR Silvan OR Sylvan)

3-Methylfuran:
(3-Methylfuran OR 3-Methylfurane)

Step 2:

The Area specific search strings agreed for step 2 are as follows:

Area 1: Data on toxicokinetics (ADME) in experimental animals and humans and from *in vitro* studies.
(Furan OR Furane OR Furfuran OR Furfurane OR Tetrole OR Silvan OR Sylvan OR 2-Methylfuran OR 2-Methylfurane OR 3-Methylfuran OR 3-Methylfurane OR 5-Methylfuran OR 5-Methylfurane) AND (absor* OR tissue* OR metaboli* OR excret* OR kinetic* OR toxicokinetic* OR pharmacokinetic* OR degrad* OR biotrans*)

Area 2: Data on oral toxicity in experimental animals.
(Furan OR Furane OR Furfuran OR Furfurane OR Tetrole OR Silvan OR Sylvan OR 2-Methylfuran OR 2-Methylfurane OR 3-Methylfuran OR 3-Methylfurane OR 5-Methylfuran OR 5-Methylfurane) AND (oral OR diet* OR gavage OR feed OR food OR organ* OR tissue* OR cancer* OR carcino* OR tumor* OR tumour* OR tox* OR immun* OR teratogen* OR rat OR mouse OR mice OR rabbit*)

Area 3: Data on *in vitro* and *in vivo* genotoxicity and MoA.
(Furan OR Furane OR Furfuran OR Furfurane OR Tetrole OR Silvan OR Sylvan OR 2-Methylfuran OR 2-Methylfurane OR 3-Methylfuran OR 3-Methylfurane OR 5-Methylfuran OR 5-Methylfurane) AND (genotox* OR mode OR action OR mechanism* OR muta* OR DNA OR damage OR repair OR clastogen* OR aneugen* OR chromosom*)

Area 4: Data on observations in humans (including epidemiological studies, case reports and biomarkers of exposure).
(Furan OR Furane OR Furfuran OR Furfurane OR Tetrole OR Silvan OR Sylvan OR 2-Methylfuran OR 2-Methylfurane OR 3-Methylfuran OR 3-Methylfurane OR 5-Methylfuran OR 5-Methylfurane) AND

(epidemio* OR biomarker* OR exposure* OR case* OR poison* OR cohort* OR cross-sectional OR random* OR work*)

3.2. Objective 2

3.2.1. Task 2 Execution of four extensive literature searches using the tailored search strings developed in task 1

The number of hits resulting from each of the four tailored search strings in each of the two databases PubMed and Web of Science were recorded in a log file:

OBJECTIVE: Log file for the four tailored search strings to retrieve all relevant data on furan and its methyl analogues, 2-methylfuran and 3-methylfuran.						
Date of search	Substance name	Databases & Search Engines	Search terms	Limitations applied to search	No of 'hits'	Comments & follow-up actions
April 14, 2016	Furan	PubMed	(Furan OR furane OR furfuran OR furfurane OR tetrole OR silvan OR sylvan OR 2-methylfuran OR 2-methylfurane OR 3-methylfuran OR 3-methylfurane OR 5-methylfuran OR 5-methylfurane) AND (absor* OR tissue* OR metaboli* OR excret* OR kinetic* OR toxicokinetic* OR pharmacokinetic* OR degrad* OR biotrans*)	Year: 1990-Language: English	1,674	AREA 1 Has been exported to EndNote™
April 14, 2016	Furan	PubMed	(Furan OR furane OR furfuran OR furfurane OR tetrole OR silvan OR sylvan OR 2-methylfuran OR 2-methylfurane OR 3-methylfuran OR 3-methylfurane OR 5-methylfuran OR 5-methylfurane) AND (oral OR diet* OR gavage OR feed OR food OR organ* OR tissue* OR cancer* OR carcino* OR tumor* OR tumour* OR tox* OR rat OR mouse OR mice OR rabbit* OR immun* OR teratogen*)	Year: 1990-Language: English	2,329	AREA 2 Has been exported to EndNote™

Date of search	Substance name	Databases & Search Engines	Search terms	Limitations applied to search	No of 'hits'	Comments & follow-up actions
April 14, 2016	Furan	PubMed	(Furan OR furane OR furfuran OR furfurane OR tetrole OR silvan OR sylvan OR 2-methylfuran OR 2-methylfurane OR 3-methylfuran OR 3-methylfurane OR 5-methylfuran OR 5-methylfurane) AND (genotox* OR mode OR action OR mechanism* OR muta* OR DNA OR damage OR repair OR clastogen* OR aneugen* OR chromosom*)	Year: 1990-Language: English	1,100	AREA 3 Has been exported to EndNote™
April 14, 2016	Furan	PubMed	(Furan OR furane OR furfuran OR furfurane OR tetrole OR silvan OR sylvan OR 2-methylfuran OR 2-methylfurane OR 3-methylfuran OR 3-methylfurane OR 5-methylfuran OR 5-methylfurane) AND (epidemio* OR biomarker* OR exposure* OR case* OR poison* OR cohort* OR cross-sectional OR random* OR work*)	Year: 2004-Language: English	639	AREA 4 Has been exported to EndNote™
April 18, 2016	Furan	Web of Science	(Furan OR furane OR furfuran OR furfurane OR tetrole OR silvan OR sylvan OR 2-methylfuran OR 2-methylfurane OR 3-methylfuran OR 3-methylfurane OR 5-methylfuran OR 5-methylfurane) AND (absor* OR tissue* OR metaboli* OR excret* OR kinetic* OR toxicokinetic* OR pharmacokinetic* OR degrad* OR biotrans*)	Year: 1990-Language: English	2,318	AREA 1 Has been exported to EndNote™

Date of search	Substance name	Databases & Search Engines	Search terms	Limitations applied to search	No of 'hits'	Comments & follow-up actions
April 18, 2016	Furan	Web of Science	(Furan OR furane OR furfuran OR furfurane OR tetrole OR silvan OR sylvan OR 2-methylfuran OR 2-methylfurane OR 3-methylfuran OR 3-methylfurane OR 5-methylfuran OR 5-methylfurane) AND (oral OR diet* OR gavage OR feed OR food OR organ* OR tissue* OR cancer* OR carcino* OR tumor* OR tumour* OR tox* OR rat OR mouse OR mice OR rabbit* OR immun* OR teratogen*)	Year: 1990- Language: English	3,914	AREA 2 Has been exported to EndNote™
April 18, 2016	Furan	Web of Science	(Furan OR furane OR furfuran OR furfurane OR tetrole OR silvan OR sylvan OR 2-methylfuran OR 2-methylfurane OR 3-methylfuran OR 3-methylfurane OR 5-methylfuran OR 5-methylfurane) AND (genotox* OR mode OR action OR mechanism* OR muta* OR DNA OR damage OR repair OR clastogen* OR aneugen* OR chromosom*)	Year: 1990- Language: English	2,290	AREA 3 Has been exported to EndNote™
April 18, 2016	Furan	Web of Science	(Furan OR furane OR furfuran OR furfurane OR tetrole OR silvan OR sylvan OR 2-methylfuran OR 2-methylfurane OR 3-methylfuran OR 3-methylfurane OR 5-methylfuran OR 5-methylfurane) AND (epidemio* OR biomarker* OR exposure* OR case* OR poison* OR cohort* OR cross-sectional OR random* OR work*)	Year: 2004- Language: English	1,073	AREA 4 Has been exported to EndNote™

For Area 1, 1,674 hits resulted from the ELS in PubMed and 2,318 hits in Web of Science. For Area 2, 2,329 hits resulted from the ELS in PubMed and 3,914 hits in Web of Science. For Area 3, 1,100 hits resulted from the ELS in PubMed and 2,290 hits in Web of Science. For Area 4, 639 hits resulted from the ELS in PubMed and 1,073 hits in Web of Science.

After removal of the duplicates, the total number of hits for Area 1 was 3,184, for Area 2 was 4,883, for Area 3 was 2,588, and for Area 4 was 1,295.

The results of the ELS and an initial selection of potentially relevant studies on furan and its methyl analogues, 2-methylfuran and 3-methylfuran for Area 1-4 were submitted to EFSA on 11 May (emails) as Deliverable 2 and then uploaded to the DMS on 13 May.

For each of Area 1-4, three EndNote files were submitted: one including all hits from PubMed (named: My EndNote Library_AREA X_PubMed.enlx), one including all hits from Web of Science (named: My EndNote Library_AREA X_Web of Science.enlx), and one including the combined hits from PubMed and Web of Science with duplicate records removed (named: My EndNote Library_AREA X.enlx).

In the combined EndNote files, one file per Area, all hits were separated into 4 folders and named as follows:

- 'Relevant': Containing hits initially evaluated to be of relevance for this procurement
- 'Maybe relevant': Containing hits where relevance initially was considered uncertain, as a conservative approach. Hits in this folder were afterwards sorted into either the 'relevant' or 'not relevant' following further scrutiny before submission of the draft final deliverable.
- 'Not relevant': Containing hits initially evaluated not to be in-scope for this procurement
- 'Trash': Containing the removed duplicates

For Area 2 a 5th folder contained 3 hits initially considered of relevance for Area 3; these were further scrutinized before submission of the draft final deliverable.

3.3. Objective 3

3.3.1. Task 3 Selection of all relevant studies retrieved by the extensive literature searches

A proposal for the information to be included in the summary tables for each area (Excel file) was submitted to EFSA on 8 April (email) as part of Deliverable 1. The proposed summary tables were discussed with EFSA at the kick-off meeting on 11 April. EFSA had a number of suggestions for revisions which were agreed and reflected in the revised version of the summary tables submitted to EFSA on 15 April (email).

According to the tender specifications, the summary tables should only include the relevant studies. However, for transparency reasons, it was agreed at the kick-off meeting also to include the non-relevant studies (including the reason for exclusion), but without any study details.

The total number of relevant references for Area 1 was 33, for Area 2 44, for Area 3 75 (including two relevant references located in the Area 2 literature search), and for Area 4 5.

3.3.2. Task 4 Preparation of EndNote™ files, summary tables and reference lists

The EndNote™ files, the summary tables and the reference lists were submitted to EFSA on 31 May (uploaded to the DMS) as part of the draft final deliverable.

The final protocol and project plan implemented by the Contractor to carry out the project was also submitted to EFSA on 31 May (uploaded to the DMS and by email) as part of the draft final deliverable.

EndNote™ files

For each of Area 1-4, three EndNote files were submitted: One file per Area including all hits from PubMed (named: My EndNote Library_AREA X_PubMed.enlx) which are identical to the files submitted as part of Deliverable 2; one file per Area including all hits from Web of Science (named: My EndNote Library_AREA X_Web of Science.enlx) which are identical to the files submitted as part of Deliverable 2; and one file per Area including the combined hits from PubMed and Web of Science (named: My EndNote Library_AREA X_deliverable 3.enlx).

In the combined EndNote files, one file per Area, all hits were separated into 2 folders and named as follows:

- 'Relevant': Containing all the references evaluated to be of relevance for the research objectives, including the references of uncertain relevance
- 'Not relevant': Containing all the references evaluated not to be in-scope for the research objectives

For Area 2, a 3rd folder contains hits of relevance for Area 3.

Summary tables

Summary tables (Excel files) were prepared, one table for each Area 1-4. The summary tables include all pertinent information for each of the references in the 'Relevant' category as identified by the eligibility criteria described by EFSA in the technical specifications (see Appendix A of this external report) which could be retrieved from the title and abstract (when available). The summary tables also include references in the 'Not relevant' category, including the reason for exclusion, but without any study details. All references included in the 'Relevant' category appear on a green background; all references included in the 'Not relevant' category appear on a white background.

Reference lists

All relevant references were collected in a reference list (Word file), one file per Area. The reference lists are included in Appendix B.

4. Conclusions

An extensive literature search to identify and collect all relevant literature on the oral toxicity of furan and its methyl analogues, 2-methylfuran and 3-methylfuran was performed in the two databases, PubMed and Web of Science, for four Areas.

The literature search resulted for Area 1 (toxicokinetics) in 1,674 hits from PubMed and 2,318 hits from Web of Science; for Area 2 (oral toxicity in experimental animals) in 2,329 hits from PubMed and 3,914 hits from Web of Science; for Area 3 (*in vitro* and *in vivo* genotoxicity and mode of action) in 1,100 hits from PubMed and 2,290 hits from Web of Science; and for Area 4 (observations in humans) in 639 hits from PubMed and 1,073 from Web of Science.

After removal of the duplicates, the total number of hits for Area 1 was 3,184, for Area 2 was 4,883, for Area 3 was 2,588, and for Area 4 was 1,295.

The evaluation of all retrieved references for relevance by screening the title and abstract (if available) and applying the eligibility criteria (inclusion/exclusion) as described by in the technical specifications (see Appendix A of this external report) for each subject Area (1-4) resulted in a total number of relevant references for Area 1 of 33, for Area 2 of 44, for Area 3 of 75 (including two relevant references located in the Area 2 literature search), and for Area 4 of 5.

References

EFSA (European Food Safety Authority), 2010. Application of systematic review methodology to food and feed safety assessments to support decision making. EFSA Journal 2010;8(6):1637, 90 pp. doi:10.2903/j.efsa.2010.1637

Appendix A – Tables Regarding Eligibility Criteria as provided by EFSA in the technical specifications

Table 1A: Eligibility criteria for the selection of studies in humans

Study design	In	Cross-sectional studies Cohort studies Case-control studies (retrospective and nested) Case series/Case reports[(c)]
	Out	Animal studies *In vitro* studies
Study characteristics:	In	Any study duration Any number of subjects
	Out	-
Population	In	All populations groups, all ages, males and females Study location: all countries
	Out	-
Exposure/ intervention	In	All routes of exposure (dietary, dermal, inhalation, transplacental exposure) Studies in which levels of the following target compounds have been measured in human tissues (including by bioassays), OR Studies in which the total exposure to the following target compounds has been estimated[(a)] – furan – 2-methylfuran – 3-methylfuran
	Out	Studies on compounds other than furan, 2-methylfuran and 3-methylfuran
Specific outcome of interest	In	All endpoints, including hormone levels
	Out	Studies on gene expression only Studies on drug metabolising enzyme activity/levels only
Language	In	English
Time	In	From 2004 onwards
Publication type	In	Peer-reviewed primary research studies (i.e. studies generating new data) Systematic reviews, reviews and meta-analyses[(b)]
	Out	Expert opinions, editorials, and letters to the editor PhD Theses Extended abstracts, conference proceedings

(a): Although these studies will not serve for the hazard characterisation, they are informative and serve as supporting information.
(b): Systematic reviews, reviews and meta-analysis will be included and used as background information for the hazard characterisation.
(c): Case series/case report studies will be included to inform the hazard identification.

Table 1B: Eligibility criteria for the **toxicity in experimental animals**

Study design	In	Experimental animal studies (e.g. rats, mice, monkeys, guinea pig, mini pigs, rabbit, hamster, dog, cat, mink, pigs)
	Out	Studies on transgenic animals Human studies *In vitro* studies
Study characteristics:	In	Any study duration Any number of animals
	Out	-
Population	In	Any experimental animal study, all ages, males and females
	Out	-
Exposure/ intervention	In	Route of administration: Oral (feeding, gavage studies) Exposure regime: single or repeated administration Number of doses: any Compounds: – furan – 2-methylfuran – 3-methylfuran
	Out	Route of administration: dermal, inhalation, subcutaneous, intraperitoneal, intramuscular Studies on compounds other than furan, 2-methylfuran and 3-methylfuran
Specific outcome of interest	In	All endpoints
	Out	Studies on enzyme induction only (e.g. CYP modulation) Studies on gene expression only Studies on co-administration of pro-carcinogens (CON A, DMBA, NKK) only Studies on -omics profiles Studies on the protective effects of certain substances against methyl/2-methyl/3-methyl toxicity
Language	In	English
Time	In	From 1990 onwards
Publication type	In	Peer-reviewed primary research studies (i.e. studies generating new data) Systematic reviews, reviews and meta-analyses[(a)]
	Out	Expert opinions, editorials, and letters to the editor. PhD Theses Extended abstracts, conference proceedings

(a): Systematic reviews, reviews and meta-analysis will be included and used as background information.

Table 1C: Eligibility criteria for the **Toxicokinetics**

Study design	In	Experimental animal (e.g. rats, mice, monkeys, guinea pig, mini pigs, rabbit, hamster, dog, cat, mink, pigs), human and *in vitro* studies in relation to: • absorption • distribution • metabolism • excretion
	Out	-
Study characteristics:	In	Any study duration Any number of animals
	Out	-
Population	In	Any experimental animal (all ages, males and females), human or *in vitro* study
	Out	-
Exposure/ intervention	In	Route of administration: Oral (feeding, gavage studies), inhalation, subcutaneous, intraperitoneal, intramuscular Compounds: – furan – 2-methylfuran – 3-methylfuran Number of doses: any Exposure regime: single or repeated administration
	Out	Dermal application Studies on compounds other than furan, 2-methylfuran and 3-methylfuran
Specific outcome of interest	In	Any outcome in relation to absorption, distribution, metabolism and excretion
	Out	-
Language	In	English
Time	In	From 1990 onwards
Publication type	In	Peer-reviewed primary research studies (i.e. studies generating new data) Systematic reviews, reviews and meta-analyses[(a)]
	Out	Expert opinions, editorials, and letters to the editor. PhD Theses Extended abstracts, conference proceedings

(a): Systematic reviews, reviews and meta-analysis will be included and used as background information.

Table 1D: Eligibility criteria for the **genotoxicity and mode of action**

Study design	In	Experimental animal studies (e.g. rats, mice, monkeys, guinea pig, mini pigs, rabbit, hamster, dog, cat, mink, pigs) and *in vitro* studies In relation to: • genotoxicity, • mode of action Including studies on transgenic animals[(a)]
	Out	-
Study characteristics:	In	Any study duration Any number of animals
	Out	-
Population	In	Any experimental animal (all ages, males and females) or *in vitro* study
	Out	-
Exposure/ intervention	In	Route of administration: Oral (feeding, gavage studies), inhalation, subcutaneous, intraperitoneal, intramuscular. Compounds: – furan – 2-methylfuran – 3-methylfuran Number of doses: any Exposure regime: single or repeated administration
	Out	Dermal application Studies on compounds other than furan, 2-methylfuran and 3-methylfuran
Specific outcome of interest	In	Genotoxicity and mechanistic studies
	Out	-
Language	In	English
Time	In	From 1990 onwards
Publication type	In	Peer-reviewed primary research studies (i.e. studies generating new data) Systematic reviews, reviews and meta-analyses[(b)]
	Out	Expert opinions, editorials, and letters to the editor. PhD Theses Extended abstracts, conference proceedings

(a): It is considered that studies on transgenic animals are helpful in terms of mechanism of action.
(b): Systematic reviews, reviews and meta-analysis will be included and used as background information. These types of publications will not go through the data extraction process.

Appendix B – Identified relevant references for each area

AREA 1

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AREA 3

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AREA 4

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