Study on the assessment of available evidence on toxicity, addictiveness and attractiveness of ingredients contained in tobacco and related products on the basis of information submitted by the industry in the context of reporting obligations introduced by Directive 2001/37/EC

Final Report

Database of Industry REsearch on the addictive and Carcinogenic additives in Tobacco (DIRECT)

EUREST Consortium

Biomedical Research Foundation of the Academy of Athens (BRFAA)

European Network for Smoking and Tobacco Prevention (ENSP)

Editors

C. Vardavas & P. Behrakis, on behalf of the contributing experts

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Study on the assessment of available evidence on toxicity, addictiveness and attractiveness of ingredients contained in tobacco and related products on the basis of information submitted by the industry in the context of reporting obligations introduced by Directive 2001/37/EC

European Regulatory Science on Tobacco (EUREST) Consortium

Led by the Biomedical Research Foundation of the Academy of Athens (BRFAA) in collaboration with the European Network on Smoking and Tobacco Prevention (ENSP)

On the DIRECT project

Database of Industry REsearch on the addictive and Carcinogenic additives in Tobacco (DIRECT)

Edited by Constantine Vardavas & Panagiotis Behrakis

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1. ABSTRACT

The report was prepared by the EUREST Consortium (**Eu**ropean **Re**gulatory **S**cience on **T**obacco) as part of the request for specific services No Chafea/2015/Health/02. The objective of the DIRECT project was to provide the Commission with an overview of assessment of available evidence on toxicity, addictiveness and attractiveness of ingredients contained in tobacco and related products on the basis of information submitted by the industry in the context of reporting obligations introduced by Directive 2001/37/EC. To address this objective, three work packages (WPs) were designed. The first WP aimed at providing an overview of the toxicological data submitted by tobacco product manufacturers and importers under Article 6 of the former Tobacco Products Directive 2001/37/EC13 in the period 2002-2014 either in electronic or paper form. To address this objective all submitted files were digitalised and an Optical Character Recognition (OCR) version of the data was created, while relevant metadata was extracted from each of the handled documents and subsequently incorporated into a fully searchable electronic database. This database was the final deliverable of WP1. The main purpose of WP2 was to carry out a detailed quantitative/qualitative assessment of submitted internal industry studies and documents not available in the public domain as identified in WP1 so as to assess the comprehensiveness and quality of evidence derived from the internal insert studies in light of regulatory needs.
Finally, the aim of WP3 was to develop the recommendations regarding studies to be carried out by the manufacturers in light of the enhanced reporting obligations foreseen for priority additives, and outline a template for the reporting of the reports in line with Article 6 of the TPD and on the basis of the results of WP2.

2. EXECUTIVE SUMMARY

Article 6 of the Tobacco Products Directive (TPD) includes provisions aiming to harmonise the reporting of ingredients in tobacco products for which enhanced reporting obligations shall apply for additives that in short may: (a) contribute to the toxicity or addictiveness of the products concerned; (b) result in a characterising flavour; (c) facilitate inhalation or nicotine uptake; or (d) lead to the formation of substances that have carcinogenic, mutagenic or reprotoxic (CMR) properties. For additives that meet this criteria and are included in a priority list – currently outlined in Commission Implementing Decision 2016/787, that European Union Member States (EU MS) shall require manufacturers and importers of cigarettes and roll-your-own tobacco containing such an additive to carry out comprehensive studies and submit them in the form of a report which may be peer reviewed by an independent scientific body.

Until now, information on the toxicological and addictive profile of tobacco product additives has been submitted in the form of accompanying documents as part of the annual reporting obligations of manufacturers and importers to competent EU MS authorities – an extensive data source which should be further utilised in the regulatory process.

In light of the above, the aim of the DIRECT project was to provide input to the Commission activities by providing supporting evidence for the priority additives indicated in Commission Implementing Decision 2016/787 and to aid the development of a uniform format and methodological checklist for studies that are to be performed under the obligations of TPD Article 6. To address these two aims, three work packages were designed.

Work package 1 addressed the issue of providing an overview on the toxicological data submitted by tobacco product manufacturers and importers during the period 2002-2014. As these were submitted in either electronic or paper form, the first aspect of the work was to create a digital version of all submitted documents and subsequently to extract metadata from these digital files. In short a total of 84,353 individual electronic files were copied or scanned onto the DG SANTE computer, the vast majority of which (76%) were not unique. After removing additional duplicates, confidential and or irrelevant files a total of approximately 8000 unique entries were coded and for each of these documents metadata was extracted. The metadata was designed to act as a checklist that could be used for the structured reporting and evaluation of each additive. They also enhanced searchability through a digital database that was created for the needs of this project.

Work package 2 aimed to perform a quantitative and qualitative overview of the evidence presented within the internal industry documents and assess the comprehensiveness and quality of evidence derived from the internal industry studies with regards to the priority additives. In short approximately 900 unique additives were identified, many of which belonged to "families" of additives (i.e. many different types of sugars), or were natural extracts in different forms.

Within the industry documents, it was noted that it was common practice to perform a battery of tests for all additives that included: a) a systematic review of published literature, b) a description of the physical and chemical properties of the additive, c) pyrolysis tests for the additive, d) in vitro tests and substantial in vivo tests. Notably, research on addictiveness and attractiveness was absent. A significant number of industry studies and conclusions were based on, and performed using, "reference cigarette" studies

with a high CMR threshold, additionallypyrolysis studies have been performed and reported.

Subsequently, the comprehensiveness of scientific evidence available within the DIRECT database was evaluated – for additives in the initial SCENIHR report and those in the final Commission Implementing Decision.

In short for these 15 additives:

- ✓ Titanium Dioxide: Was classified by IARC as a group 2b carcinogen.
- ✓ Maltol: Genotoxicity and cellular toxicity as well as the potential effect on increasing the concentrations of other constituents could not be ruled out.
- ✓ Diacetyl: The information available indicate that this could be a first level substance, and it is of interest to the scientific community due to recent inhalation studies.
- ✓ Geraniol: It can contain the relevant impurity methyl eugenol, a genotoxic carcinogen.
- ✓ Guaiacol:Tests on mammalian cells have indicated genotoxicity, while natural cytotoxic properties have also been noted.
- ✓ Fenugreek: Pyrolysis of the substance has indicated that carcinogenic or otherwise toxic compounds are produced.
- ✓ Fig: Produces carcinogenic or toxic substances during combustion and has been associated with chromosome damage in animal studies.
- ✓ Guar gum: May have mutagenic effects. Toxic agents are produced during pyrolysis.
- ✓ Carob bean and/or extract powder, gum: It promotes the increase of concentrations of several chemical substances in cigarette smoke and pyrolysis of the substance has indicated that carcinogenic or otherwise toxic compounds are produced.
- ✓ Propylene glycol: Reproductive concerns at high level exposure were raised. The possible carcinogen furan was identified during purge and trap tests. Carcinogens and toxic agents are produced during pyrolysis.
- ✓ D-sorbitol: showed mutagenic and reproductive toxicity. Toxic agents are produced during pyrolysis.
- ✓ Glycerol: Genotoxicity, cellular toxicity and tumorgenicity has been noted as also its potential effect on increasing the concentrations of other constituents.
- ✓ Cocoa: Several genotoxic and cardiovascular and irritating effects have been reported. Toxic agents are produced during pyrolysis.
- ✓ Liquorice: Found to promote reproductive, genotoxic and mutagenic effects. Toxic agents are produced during pyrolysis.
- ✓ Menthol: Found to produce some carcinogenicity, genotoxicity and cytotoxicity results.

Work package 3 aimed to develop recommendations regarding a) the methodology of studies to be carried out by the manufacturers in light of the enhanced reporting obligations foreseen for priority additives and b) identify the minimum checklist of contents to be provided for the studies to be requested under Article 6 of the TPD.
Within WP3 the types of tests performed by the industry for these 15 priority additives was evaluated and methodological drawbacks and key issues that should be taken into consideration were highlighted (for review studies, pyrolysis studies, in vitro, in vivo). Overall 4 checklists were created each with a number of internal subdomains that have to be addressed according to the different type of study. Other issues of peer review were also highlighted including but not limited to the importance of the independence of peer reviewers.

RÉSUMÉ DU RAPPORT

L'article 6 de la directive sur les produits du tabac (TPD) comprend des dispositions visant à harmoniser la transmission des informations sur les ingrédients contenus dans les produits du tabac, pour lesquelles un système de déclaration approfondie et obligatoire doit être appliqué pour les additifs qui pourraient : (a) contribuer à la toxicité ou à la dépendance du produit concerné ; (b) résultant d'un arôme essentiel ; (c) facilitant l'inhalation ou l'absorption de la nicotine ; (d) menant à la création de substances avec des propriétés cancérigènes, mutagènes ou toxiques pour la reproduction (CMR). Pour les additifs qui répondent à ces critères et sont inclus dans la liste d'ingrédients prioritaires - actuellement dans la décision d'exécution (UE) 2016/787 de la Commission, qui souligne que les Etats Membres de l'Union Européenne doivent exiger aux fabricants et importateurs de cigarettes et de tabac à rouler contenant un tel additif de réaliser des études poussées et de les soumettre sous la forme d'un rapport qui puisse être examiné par les pairs d'un organisme scientifique indépendant.

Jusqu'à présent, les informations sur le profil addictif et toxicologique des additifs des produits du tabac ont été soumises sous la forme de documents d'accompagnement, faisant partie des obligations de déclarations annuelles des fabricants et des importateurs envers les autorités compétentes des Etats Membres de l'Union Européenne – une vaste source de données qui devrait être davantage utilisée dans le processus de réglementation.

Compte tenue de ce qui est susmentionné, l'objectif du projet DIRECT est d'apporter des éléments aux activités de la Commission, en fournissant des preuves à l'appui pour les additifs prioritaires indiqués dans la décision d'exécution (UE) 2016/787 de la Commission et d'aider le développement d'un format uniformisé et d'une liste de vérification (une check-list) méthodologique pour les études qui doivent être réaliser en vertu des obligations de l'article 6 de la Directive sur les Produits du Tabac. Pour répondre aux deux objectifs, trois modules de travail ont été crés.

Le module de travail 1 répond à la question de fournir un aperçu sur les données toxicologiques soumises par les fabricants et importateurs de produits du tabac pendant la période entre 2002 et 2014. Comme celles-ci avaient été soumises sous forme électronique ou papier, le premier aspect du travail était de créer une version numérique de tous les documents soumis et ensuite d'extraire les métadonnées de ces fichiers numériques. En résumé, un total de 84 353 fichiers numériques ont été copiés ou scannés sur l'ordinateur de la DG SANTE, dont la majeure partie (76%) n'était pas unique. Après avoir supprimé les doublons, les fichiers confidentiels et/ou non-pertinents, un total d'environ 8000 entrées uniques ont été codifiées et pour chacun de ces documents, les métadonnées ont été extraites. Les métadonnées étaient conçues pour agir comme une check-list qui peut être utilisée comme une méthode de compte rendue et d'évaluation de chaque additif. Elles ont augmenté aussi la facilité de recherche, grâce à une base de données entièrement consultable créée pour les besoins de ce projet.

Le module de travail 2 vise à produire un aperçu quantitatif et qualitatif des preuves présentées dans les documents internes de l'industrie et évaluer l'exhaustivité et la qualité des preuves issues des études internes de l'industrie en ce qui concerne les additifs prioritaires. En somme, près de 900 additifs uniques ont été identifiés, dont la plus part

appartenant à des « familles » d'additifs (par exemple de nombreux types de sucres), ou étant des extraits naturels sous des formes variées.

Dans les documents de l'industrie, il a pu être remarqué qu'il était une pratique courante d'effectuer une série d'épreuves pour tous les additifs, comprenant : a) un examen systématique de la littérature scientifique publiée, b) une description des propriétés physiques et chimiques de l'additif, c) des analyses pyrolytiques pour l'additif, d) des tests in vitro et des tests in vitro substantiels. La recherche sur la dépendance et l'attractivité est notamment absente. Un nombre conséquent d'études et de conclusions de l'industrie étaient basées et menées sur des études de « cigarettes témoins » avec un seuil de CMR élevé. De plus, des études pyrolytiques étaient effectuées et communiquées.

Par conséquent, l'exhaustivité des preuves scientifiques disponibles au sein de la base de données de DIRECT a été évaluée – pour les additifs dans le rapport initial SCENIHR et ceux dans la décision d'exécution de la Commission.

En résumé, pour les 15 additifs :

- ✓ Le dioxyde de titane : classifié par le CIRC (le Centre International de Recherche sur le Cancer) comme appartenant au group 2b des cancérigènes.
- ✓ Le maltol : la génotoxicité et la toxicité cellulaire ainsi qu'un effet potentiel sur l'augmentation de la concentration des autres composants ne pouvaient pas être exclues.
- ✓ Le diacétyle : les informations disponibles indiquent qu'il pourrait être une substance de premier niveau, et qu'il est d'intérêt pour la communauté scientifique à cause des récentes études sur l'inhalation.
- ✓ Geraniol: Il peut contenir l'impureté méthyl eugénol, une substance cancérogène génotoxique.
- ✓ Le guaiacol: les tests sur les cellules de mammifères ont indiqué une génotoxicité, tandis que les propriétés cytotoxiques naturelles ont aussi été remarquées.
- ✓ Le fenugrec : la pyrolyse de la substance a indiqué que des composés cancérogènes ou autrement toxiques sont produits.
- ✓ La figue : elle produit des substances cancérigènes ou toxiques durant la combustion et a été associée aux dommages chromosomiques dans les études animales.
- ✓ La gomme de guar : elle pourrait avoir des effets mutagènes. Des agents toxiques sont produits pendant la pyrolyse.
- ✓ La fève de caroube et/ou poudre d'extrait, gomme : elle favorise l'augmentation de la concentration de plusieurs substances chimiques dans la fumée de cigarette et la pyrolyse de la substance a indiqué que des composés cancérigènes ou autrement toxiques sont produits.
- ✓ Le propylène glycol : des inquiétudes ont été émises concernant sa reprotoxicité liée à un niveau d'exposition élevé. Le furanne, probablement cancérigène, a été identifié durant les tests de purge et de piégeage. Des agents cancérigènes et toxiques sont produits pendant la pyrolyse.
- ✓ Le D-sorbitol : il présente une toxicité mutagène et une reprotoxicité. Des agents toxiques sont produits pendant la pyrolyse.
- ✓ Le glycérol : la génotoxicité, la toxicité cellulaire et la tumorigénicité ont été remarquées ainsi que ses incidences possibles sur l'augmentation des concentrations d'autres composants.
- ✓ Le cacao : plusieurs effets génotoxiques, cardiovasculaires et irritants ont été signalés. Des agents toxiques sont produits pendant la pyrolyse.
- ✓ La réglisse : il a été démontré qu'elle favorise l'augmentation des effets reprotoxiques, génotoxiques et mutagéniques. Des agents toxiques sont produits pendant la pyrolyse.

- ✓ Le menthol : Des résultats sur la cancérogénicité, la génotoxicité et la cytotoxicité ont été produits.

Le module de travail 3 vise à développer des recommandations concernant a) la méthodologie des études effectuées par les fabricants compte tenu des exigences en matière de production de rapports envisagées pour les additifs prioritaires et b) identifier la check-list minimale des contenus qui doivent être fournis pour les études, qui devra être requise en vertu de l'article 6 de la TPD.

Au sein du module de travail 3 les types de tests réalisés par l'industrie du tabac pour ces 15 additifs prioritaires ont été évalués et les problèmes méthodologiques ainsi que les points principaux qui doivent être pris en compte ont été soulignés (pour les études de synthèse, de pyrolyse, in vitro, in vivo). En tout, 4 check-lists ont été créées, chacune avec un nombre de sous-domaines internes qui doivent être abordés selon les différents types d'études. D'autres questions concernant la critique des pairs ont été aussi soulignées y compris - mais pas limité à – l'importance de l'indépendance des pairs examinateurs.

3. INTRODUCTION

Directive 2001/37/EC of the European Parliament and of the Council on the approximation of the laws, regulations and administrative provisions of the EU MS concerning the manufacture, presentation and sale of tobacco products, was adopted on 5 June 2001[1]. Within this directive, EU MS required manufacturers and importers of tobacco products to report on the ingredients used in such products, and provide relevant toxicological information. So as to facilitate and homogenize these reporting obligations a practical guide on the reporting of tobacco product ingredients was developed in 2006 that included three reporting formats[2]: One with full ingredient information for national regulators (Table 1), a second for the submission of available toxicological information (Table 2) and a third with information for the public (Table 3). As defined in this practical guide, Table 2 was intended as a "tick-box", where manufacturers or importers would specify which type of toxicological data is available and subsequently submit the toxicological information as an accompanying document. These accompanying documents were the main target of the DIRECT project.

In line with market, scientific and international developments it became necessary to update the reporting obligations of manufacturers and importers, and hence within the revised TPD reporting of tobacco product ingredients is regulated in Article 5, while certain additives can be placed on a priority list for enhanced reporting obligations. According to Article 6, enhanced reporting obligations shall apply to certain additives contained in cigarettes and roll-your-own tobacco that are included in a priority list of additives that may meet one of the following requirements:

a. Contributes to the toxicity or addictiveness of the products concerned, and whether this has the effect of increasing the toxicity or addictiveness of any of the products concerned to a significant or measurable degree;
b. Results in a characterising flavour;
c. Facilitates inhalation or nicotine uptake; or
d. Leads to the formation of substances that have CMR properties, the quantities thereof, and whether this has the effect of increasing the CMR properties in any of the products concerned to a significant or measurable degree.

For additives on the priority additive list, EU MS shall require manufacturers and importers of products containing an additive that is included in the priority list to carry out comprehensive studies that shall examine for each additive whether it has any of the properties specified above. Those studies shall take into account the intended use of the products concerned and examine in particular the emissions resulting from the combustion process involving the additive concerned. The studies shall also examine the interaction of that additive with other ingredients contained in the products concerned.

[1] Directive 2001/37/EC of the European Parliament and of the Council on the approximation of the laws, regulations and administrative provisions of the Member States concerning the manufacture, presentation and sale of tobacco products, OJ L 194, 18.7.2001.

[2] Reporting on tobacco product ingredients. PRACTICAL GUIDE See http://ec.europa.eu/health/ph_determinants/life_style/Tobacco/Documents/practical_guidance_en.pdf

Subsequently these comprehensive studies shall be submitted to the Commission and to the competent authorities of those EU MS where a tobacco product containing this additive is placed on the market.

With the above in mind, the main purpose of the DIRECT project was to use the wealth of "Table 2 type accompanying data" submitted by manufacturers and importers to EU MS so as to:

- ✓ To assist the Commission in establishing the priority list of additives,
- ✓ To assist in the identification of the appropriate types of studies including corresponding methodologies and
- ✓ To aid developing a uniform format for reports to be submitted by the manufacturers and importers.

An overview of the methodological approach, findings and conclusions per WP is presented below. Additional detail and scientific documentation is presented in the Annexes to this report.

4. METHODOLOGY AND FINDINGS PER WORK-PACKAGE

4.1 WP1– Detailed Methods and Results

This work package primarily supported the work that was to be performed under WP2 and WP3, as it provided an overview on the toxicological data submitted by tobacco product manufacturers and importers under Article 6 of the former TPD[3] during the period 2002-2014 and that were submitted in either electronic or paper form. Within WP1, two tasks were performed:

- Creation of an optical character recognition (OCR) version & extraction of relevant data from storage media.
- Extraction of the metadata from the files and compilation of a fully searchable additive database.

4.1.1 Creating an OCR version & extraction of relevant data from storage media

The first aspect of WP1 was to create an OCR version of all documents of supporting toxicological information submitted to the EU MS during the period 2002-2014.

- ✓ Prior to the handling of the documents, experts who were to obtain access (even limited) to the raw data signed additional and individual confidentiality for, verifying amongst others that the information that they may view must be kept strictly confidential and may not be disseminated or released in any form and manner. In addition to the above, the experts were trained on how to identify and separate toxicological data from ingredient data.
- ✓ During Task 1.1, the information in paper form was physically screened by BRFAA experts, in the presence of a DG SANTE policy officer. At this initial transfer stage the first level of data separation took place (Step 1), with the hand separation of

[3] Directive 2001/37/EC of the European Parliament and of the Council on the approximation of the laws, regulations and administrative provisions of the Member States concerning the manufacture, presentation and sale of tobacco products, OJ L 194, 18.7.2001,

Table 1, Table 2 and Table 3 paper documents and the transfer of Table 2 information only, to a separate cabinet. Following this step, Table 1 and Table 3 data in paper form were not further handled by BRFAA researchers.

- ✓ The information in paper form was then scanned in the SANTE premises and a fully searchable OCR version of each paper document was obtained. Prior to the scanning of these documents, they were once again checked by a BFRAA expert on a page-by-page basis.
- ✓ With regards to the data submitted in electronic format, all relevant CDs/USBs were opened and Table 2 data was extracted from these. During data handling it was noted that a percentage of files that were already in electronic format (mainly on CDs) were encrypted or locked. Access codes for these documents were obtained from submitters, via DG SANTE and unlocked files were then stored on a DG SANTE computer. The extraction process of information from locked CDs, was done in the presence of a DG SANTE Policy Officer.
- ✓ In total during the first database entry period, 84,353 individual electronic files were copied or scanned within a DG SANTE computer and organised by year, EU MS and submitter (manufacturer/importer).
- ✓ The files on the DG SANTE computer included a substantial number of copies of absolutely identical files, as identified through an IT document comparison programme. The duplicate files were identified (n=64,379) and were removed with the use of a data handling software.
- ✓ All files that were marked as "confidential" and contained names of tobacco industry representatives or scientists (n=7,013) were unlinked from the DIRECT database of files and placed within a separate version of the Database (the full Commission version).
- ✓ Out of 12,961 files left within Task 1.1, we proceeded with the entering of 4,849 unique files into the database. We excluded 5,031 files containing links to pdfs already included, another 1,556 files containing personal data of scientists or company representatives, 593 files containing references we already had in pdfs and 858 files which were not useful as they were cover letters, empty tables or were not written in English.
- ✓ Files which contained references to multiple substances were split into multiple entries so that each additive would be a unique entry. In total, an additional 219 files with multiple substances content were processed, with approximately 1000 new files then added to the database.
- ✓ During the second database entry period (November –December 2015), 8,669 files were handled. Duplicates were removed and approximately 4,000 unique files remained. From the remaining files, 1,070 files marked as confidential and 1,035 files with personal names were finally added to the database. The rest of the files not included were mostly empty tables, cover letters, and documents not in English, damaged files, and locked files.
- ✓ The final product of this task was that two versions of the dataset were created, a full version with all pdf files linked to each database entry that the Commission will keep internally (the Commission version) and a second version (a "lite" DIRECT database version) where metadata was incorporated but pdf files were removed, for use among the DIRECT project experts.

4.1.2 Extraction of metadata and compilation of a fully searchable database

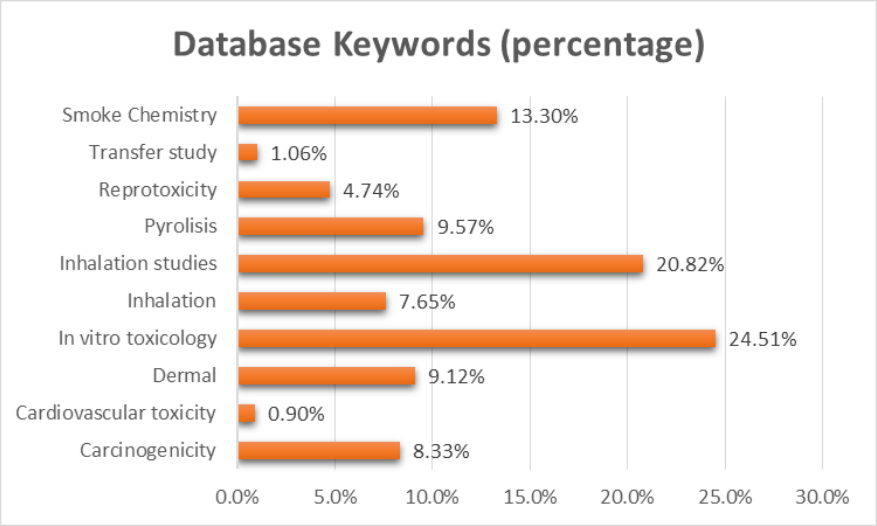
The next aspect of the project was to identify, extract and then incorporate all of the metadata fields (keywords) from each document, and link the full text pdf of the original document within an electronic database system. The purpose hence was to compile a digital inventory of the relevant material submitted to DG SANTE and identify within the submitted material, internal industry studies not available in the public domain.

Within DIRECT the metadata was extracted for the below record fields (keyword domains), which was designed to act as a checklist that could be used for the structured reporting for each additive, so as to enhance searchability through the database. These keywords were selected to facilitate categorisation.

Keywords within the DIRECT Database	
Title	The title of the document
Scanned ID	The automated ID as
Company	The company that provided the information
Year	The year the document was submitted
EU Member State (MS)	The MS to which the data was submitted
Publicly available	Checkbox if the document is publicly available
Ingredient name	The name of the additive
Ingredient CAS	The CAS of the additive
REACH registration	If the ingredient is registered under REACH
Type of toxicity test performed	Checkbox if the document contains such research
Pyrolysis studies	Checkbox if the document contains such research
Transfer studies	Checkbox if the document contains such research
Smoke chemistry	Checkbox if the document contains such research
In vitro toxicology	Checkbox if the document contains such research
Dermal exposure studies	Checkbox if the document contains such research
Inhalation research	Checkbox if the document contains such research
Carcinogenicity studies	Checkbox if the document contains such research
Cardiovascular toxicity	Checkbox if the document contains such research
Inhalation studies	Checkbox if the document contains such research
Reprotoxicity studies	Checkbox if the document contains such research

The distribution of database keywords as catalogues within the DIRECT database is depicted on the next page in **Figure 1**. In vitro toxicity (24%), Inhalation studies (21%)

and Smoke chemistry (13%) were the most frequently used keywords related to the types of studies available in the DIRECT database.



4.1.3 Synopsis of WP1 findings

- ✓ The paper information available was scanned in house and a fully searchable OCR version of each paper document was created.
- ✓ A total of 84,353 individual electronic files were copied or scanned onto the DG SANTE computer within Task 1.1 of WP1.
- ✓ The vast majority of documents submitted to EU MS (76%) were not unique, but found multiple times within the paper and digital files. These files included a substantial number of copies of absolutely identical files, as identified through an IT document comparison programme. Potentially confidential files were separated first and then the duplicates (64,379) were removed with the use of software.
- ✓ Approximately 8000 unique entries were coded and for each of these documents metadata was extracted. Two versions of the DIRECT dataset were created, a full version with all pdf files linked to each database entry that the Commission will keep internally and a second version (a lite version) where metadata was incorporated but pdf files were removed, for use among the DIRECT project experts.
- ✓ In vitro toxicity (24%), Inhalation studies (21%) and Smoke chemistry (13%) were the most frequently used keywords related to the types of studies available in the DIRECT database.

4.2 WP2- Detailed Methods and Results

The aim of WP2 was to assess the list of additives that are suitable/recommended to be added to the priority list of additives in line with Article 6 of TPD 2014/40/EU. The two approaches used were:

- ✓ To perform a quantitative and qualitative overview of the evidence presented within the internal industry documents.
- ✓ To assess the comprehensiveness and quality of evidence derived from the internal industry studies with regards to the priority additives.

4.2.1 Quantitative/qualitative assessment of the evidence presented

The aim of this task was to perform a quantitative and qualitative assessment of the data that was incorporated into the DIRECT database that would aid potential regulatory actions.

- ✓ To aid the process of evaluating the additives within the database, a "DIRECT Database Additive Checklist" was created, within which additives would receive a score of 0-10 depending on the availability of the types of performed studies within the DIRECT database. This checklist was used to shortlist additives for which more data was available in the DIRECT database, and hence this was used as a proxy of the quantity of industry research on the additives and wass not an assessment method for the submitted additives, nor does this score reflect the toxicity of the substance.
- ✓ Overall within the DIRECT database, 19 additives had a score of 10/10; 38 a score of 9/10 and 78 a score of 8/10. The majority of additives had a score <5/10 indicating a large gap in the evidence base, while interestingly 108 additives had a score of 0 indicating that they were noted however no toxicological information for these additives was provided.
- ✓ Based on our scoring within the database, 12/15 of the priority additives noted in the Annex of the Commission Implementing Decision[4] 2016/787 had a score of either 9/10 or 10/10 indicating the existence of a plethora of studies performed by the industry for these additives.
- ✓ Approximately 900 unique additives were noted within the DIRECT database. It is important to state that these unique additives included many groups of "families" of substances (i.e. many different types of sugars, different types of silica, natural extracts in different forms etc.)
- ✓ Within the industry documents, and as outlined in WP1 through the metadata extraction, it was noted that it was common practice to perform a battery of tests for all additives that included a) a systematic review of published literature, b) a description of the physical and chemical properties of the additive, c) pyrolysis tests for the additive, d) in vitro tests and substantial in vivo tests. In the industry documents assessed, research on addictiveness and attractiveness was absent.

4.2.2 To assess the comprehensiveness and quality of evidence derived from the internal insert studies with regards to the priority additives.

Within Task 2.2 we proceeded to assess for each additive within the initial SCENIHR report[5], the scientific evidence available within the DIRECT database –of information submitted by the industry- that would warrant their potential inclusion as a priority additive, based on the evidence available in the DIRECT database.

Overall we evaluated the following additives and identified certain aspects outlined below:

1. **Titanium dioxide**: The industry files contained multiple references to publicly available documents, a number indicating that no effect exists. Other documents reference the International Agency for Research on Cancer (IARC) 2B classification. Since the IARC classification is the gold standard and has it noted

[4] Commission implementing decision (EU) 2016/787 of 18 May 2016 laying down a priority list of additives contained in cigarettes and roll-your-own tobacco subject to enhanced reporting obligations
[5] http://ec.europa.eu/health/scientific_committees/emerging/docs/scenihr_o_051.pdf

as a 2B substance, Titanium Dioxide is justified in the first priority list as there is evidence that it is carcinogenic in animals. Moreover evidence of its genotoxic effect also exist.

2. **Maltol**: The existence of indications of genotoxicity, cellular toxicity, oral toxicity and its potential effect on increasing the concentrations of other constituents, such as nicotine, arsenic and nitrosamines in test cigarettes, as noted in submitted industry studies warrant its position in the priority list.
3. **Diacetyl**: The information available indicate that this substance is of interest specifically due to occupational inhalation studies as also mutagenicity genotoxicity tests. The question is if these parameters are related to diacetyl per se or to related compounds (glyoxal), which is more toxic. There were no data on carcinogenicity.
4. **Geraniol**: It is important to note that other substances such as geranium oil (CAS: 8000-46-2) contain 10-33% geraniol, while geranium oil also contains citronellol at similar concentrations. Geraniol is also found in Palmarosa oil (CAS: 8014-19-5), in concentrations >80% and in petitgrain oil (2-3% in the oil), but is identified also after pyrolysis). Geranium absolute, and pelargonium oil is also mentioned. Toxicity, mutagenicity and cytotoxicity of geraniol has been noted. To what extent the identified findings are related specifically to geraniol itself is difficult to tell, a broader definition of this "family" may be of greater utility.
5. **Guaiacol**: The only genotoxicity test on mammalian cells gave positive results (SCE in human lymphocytes), while some industry studies indicate negative results. However the substance is an irritant in unburnt form and has reprotoxic and potentially cytotoxic properties. It is possible that other forms of guaiacol should also be noted in this family.
6. **Fenugreek**: Pyrolysis of the substance indicated that many carcinogenic or otherwise toxic compounds are produced. Possible benign and beneficial effects are negated when the product is burned.
7. **Fig**: Produces carcinogenic or toxic substances during combustion. The existence of indications of chromosome damage in Chinese hamster ovary cells is a matter of some concern. Of greater concern is the carcinogenic and otherwise toxic nature of many of the products of combustion of fig extract and fig juice.
8. **Guar gum**: Guar gum caused chromosomal aberrations in human embryonic lung cells. While most studies of mutagenesis were negative, there were a few studies that produced some evidence that guar gum is mutagenic. Feeding guar gum to chicks resulted in growth inhibition. A similar effect was also observed in rats, but not in other animals. Adding guar gum to cigarettes increased the levels of lead, arsenic, cadmium, isoprene, formaldehyde and hydrogen cyanide in tobacco smoke. Of greatest concern is that several pyrolysis studies consistently showed the product of combustion of guar gum to include carcinogens and other toxic agents.
9. **Carob bean and/or extract powder, gum**: Carob bean has showed reproductive and maternal toxicity. It has produced changes in hematology and serum biochemical parameters and also several toxic and irritating results in humans. Carob bean also promotes the increases of several chemical substances in cigarette smoke. Purge and trap tests for Carob bean identified Furan as an emission, which is a possible carcinogen to humans.
10. **Propylene Glycol:** Reproductive concerns at high level exposure were raised. The possible carcinogen Furan was identified during purge and trap tests.

Propylene Glycol was found to promote reproductive, cytotoxic, genotoxic, carcinogenic and mutagenic effects, as well as several adverse effects in humans and animals, when tested. When pyrolysed at 700 C, pyrolysis products include polycyclic aromatic hydrocarbons (PAHs), quinones, and aldehydes. However when pyrolysed at 900 C, the products formed include cyclopropane, acetone, benzene, toluene.

11. **D-Sorbitol:** showed mutagenic and reproductive toxicity. D-Sorbitol was shown to produce carcinogenicity in rats, reproductive, cytogenic and mutagenic effects. D-Sorbitol also promotes cataract formation in diabetic patients and in rats. D-Sorbitol showed humectant properties while when added in cigarette smoke, it increases the level of 3,4-benzpyrene in mainstream smoke and tar. Products of D-Sorbitol pyrolysis are PAHs, anthraquinone, m-cresol and formaldehyde.
12. **Glycerol:** The existence of indications of genotoxicity, cellular toxicity and tumorgenicity and its potential effect on increasing the concentrations of other constituents, such as particulate matter, tar, water, nicotine, phenol, acetaldehyde, acrolein, HCN, CO and CO_2 in test cigarettes has been noted.
13. **Cocoa:** Cocoa has shown tumorgenicity in high doses, several genotoxic and cardiovascular effects, while irritating effects have also been reported. Cocoa powder up to 5% has been associated with numerous toxic effects mainly due to theobromine which is a major constituent of cocoa. Finally, cocoa produces many chemical constituents during pyrolysis. More tests on cocoa and cocoa's constituents (e.g. theobromine) are necessary.
14. **Liquorice/licorice**: Liquorice was shown to promote reproductive, genotoxic, mutagenic and hypertensive effects. High intake is also associated with various metabolic health effects in humans while pyrolysis of the substance resulted several chemicals components.
15. **Menthol:** Menthol was found to lead to some carcinogenicity, genotoxicity and cytotoxicity outcomes.

Methodological findings/gaps identified within the DIRECT database:

Through the evaluation of the data incorporated within the database we identified a number of key methodological gaps in industry related studies.

- ✓ It was common practice to perform a comparison with a "reference cigarette" study. Within this type of studies the CMR properties of a test cigarette (that included the evaluated additive at a higher concentration than usual) was compared to a reference cigarette. A methodological issue that this study brings forward is the high baseline CMR properties of the reference cigarette which the test cigarette is being compared to.
- ✓ Exposures through unrelated routes (dermal exposures, intraperitoneal infusions, oral feeding studies) which while may be used as a gross index of the additive's CMR properties, they cannot be compared to inhalation studies.
- ✓ Documents marked as confidential might include additional information unavailable to the selected experts who had only the extracts from pdfs and not the whole pdf.
- ✓ Information based on animal studies was frequently cited however the methodological approaches may not be currently valid as they often noted outdated protocols and studies. Methodologies are based on early studies and previous detection limits and test types.

✓ Below is a summary of the types of protocols/techniques noted in the industry documents in the DIRECT database and more recent protocols available:

DIRECT Database Techniques	Current Techniques
Carcinogenicity Tests	
FDA 1997 guidance	FDA 2002 guidance
UDS assay methods	OECD 488 TGR (2013)
NTP 2 year study (1987)	NTP "2 year study protocol"
NTP 10-40 week studies (1982)	NTP "13 week toxicity study"
NTP 13 week studies (1981)	OECD TG 453 (2009)
NTP lifetime rodent bioassay (LRB)	OECD GD 116 Second edition (2011)
Skin painting	Oxidative stress tests
	Telomerase Activity
Mutagenicity Tests	
Ames test (salmonella test) , E. coli test	NTP "The Salmonella/E. coli Mutagenicity Test"
Mouse lymphoma assay	NTP "Mouse lymphoma" (see OECD 476)
Chinese hamster ovary (MN)	NTP "Chinese Hamster Ovary Cell
SCE tests	NTP "The SCE Test" (Sister chromatid exchanges)
Mouse bone marrow micronuclei (MN) test	NTP " The CA Test " (Chromosomal abbreviations)
Human lymphocytes (MN)	OECD 474 (Mammalian Erythrocyte Micronucleus Test)
Dominant lethal gene assay	OECD 475 (Mammalian Bone Marrow Chromosomal Aberration Test) 2014
	OECD 487 (In Vitro Mammalian Cell Micronucleus Test) 2014
	OECD 473 (In Vitro Mammalian Chromosome Aberration Test)
	OECD 489 (In Vivo Mammalian Alkaline Comet Assay)
	OECD 476 (In Vitro Mammalian Cell Gene Mutation Tests using the Hprt and xprt genes) 2015
	OECD 478 (Rodent Dominant Lethal Test) 2014
	NTP "Drosophila Melanogaster"(NTP "Sex-Linked Recessive Lethal Mutation Test"
	NTP "Drosophila Melanogaster"(NTP "Reciprocal Translocation Test")
	NTP "Micronucleus" (NTP "Bone marrow assays")
	NTP "Micronucleus" (NTP "Micronucleus analysis in NTP toxicity studies")
	NTP "Rodent Cytogenetics"(NTP "In Vivo Mouse1 Bone Marrow Chromosal Aberrations Test Protocol")
	NTP "Rodent Cytogenetics"(NTP "In Vivo Mouse1 Bone Marrow Sister Chromatid Exchange Test Protocol")
Reprotoxicity Tests	
FDA 1997 guidance	FDA 2011 guidance
3 generation studies	NTP "Reproductive Assessment by Continuous Breeding (RACB)"
Teratologic Evaluation of FDA 1973	OECD 422 Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity Screening Test
Chernoff-Kavlock teratology assay	OECD 443 (Extended One-Generation Reproductive Toxicity Study)
	OECD 421 (Reproduction/Developmental Toxicity Screening Test) 2015
	EPA Guidelines "Reproductive Toxicity Risk Assessment"

4.2.3 Synopsis of WP2 findings

To summarise, the DIRECT database was too extensive to perform a comprehensive evaluation of all tobacco product additives, within the timeframe of the current project. Further research is needed to evaluate the full capacity and evidence within the database, however the preliminary evaluation has indicated the following:

- ✓ Our overview indicated the existence of slightly over 900 additives, many of which belonged to individual "families".
- ✓ Our research indicated that 12 of 15 additives in the priority list of the implementing decision had a score of 9/10 or 10/10 (an indication of the existence of types of research studies and not an indicator of toxicity), while about half of the noted additives had a score <5/10, while 150 additives had a score of 0 – indicating that the industry has acknowledged their inclusion but may never have provided information on them to EU MS regulators.
- ✓ There is a broad range in the types of studies that have been performed to assess these additives, ranging from simple literature reviews of the evidence to detailed in-vitro tests.
- ✓ Within the DIRECT database a significant number of industry studies and conclusions were based on, and performed using, "reference cigarette" studies with a high CMR threshold.
- ✓ Pyrolysis studies have been performed and reported for all short listed additives. We were unable to evaluate the quality/methodology of these performed tests.
- ✓ There was an evident gap in the existence of studies reflecting the evaluation of addictiveness and/or attractiveness of additives, an area for future action.
- ✓ A large number of natural extracts were noted within the list of additives located within the DIRECT database. The role of each natural extract was not evaluated within the context of this tender, however an exploratory analysis did indicate that pyrolysis tests for these substances had been performed the results of which indicated the formulation of substances with CMR properties.
- ✓ It was noted that among the non-confidential documents evaluated, that in some cases, the submitted report for a specific additive would commence with a description of the physical and chemical properties of the additive, continue with an overview of the published evidence and in certain instances would also include additional studies performed.
- ✓ Further research is needed to evaluate the full capacity and content of the DIRECT database, however the existence of keywords, CAS numbers and the ability for a full text search using Boolean terms facilitate additional use of the dataset.
- ✓ DIRECT was able to provide input to the establishment of the priority additive list through the evaluation of the additives submitted and also as regards the types of studies performed, and their results for each of the shortlisted additives.

4.3 WP3- Detailed Methods and Results

The aim of this WP was to develop recommendations regarding the reporting format and methodology of studies to be carried out by the manufacturers in light of the enhanced reporting obligations foreseen for priority additives, in line with Article 6 of the TPD and on the basis of the results of WP2. Two primary tasks were performed under this WP:

Task 3.1: A proposition of the types and criteria of studies that should be requested (including methodologies and reporting templates) needed to be carried out by the manufacturers.

Task 3.2: To propose a structure/template of the reports on the results of the studies carried-out. These reports should facilitate subsequent subject to peer-review if required (in line with Art. 5(4) of the TPD).

To conclude and enhance the exchange of information between bodies working on the priority additives list, WP3 concluded with a joint meeting with the SCEER working group on priority additives.

4.3.1 Proposition on the types of studies to be requested

The evaluation and toxicological testing of additives has been previously discussed within the international literature and is based on the principals of preventive, regulatory toxicology. The procedure is aimed at characterizing and evaluating the hazard of the additives in **burned** and **unburned** form. One of the most discussed approach is the multi-step tier system, based on the DKFZ stepwise approach that takes into account an evaluation process rejecting/accepting each additive based on its process through the steps.

In light of the theoretical framework of the tier approach and taking however into account the regulatory needs as outlined in the TPD, we suggest the following approach:

- ✓ A complete dossier is developed and submitted by the industry to regulators. This dossier must meet the requirements of the TPD and allow for subsequent peer reviewers to provide evidence based advice on an additive.
- ✓ The evaluation of the additive (with or without the use of a tier approach) is done collectively at the peer review level, and not at the submission level and hence the industry must provide a complete battery of tests for each additive.
- ✓ In light of the above a chronological tier system would be inappropriate and may potentially not fit within the timeframe available to manufacturers and hence would pose a lost opportunity for regulatory action.

For each of the types of tests that could be performed the following aspects were noted as areas of importance:

- ✓ Comprehensive Reviews
    - o A review should include published literature but also grey literature and internal reports.
    - o Information submitted via DIRECT or the EU Common Entry Gate (EU-CEG) for the submission of information to EU MS, could also be taken into account.

- Information with regards to CLP regulation and REACH should also be requested[6]. International standards of CMR properties may also be taken into account.
- Read across studies and in silica studies could also provide further information at this level.
- Potential CMR properties and addictiveness in synergy with other additives must also be assessed.

✓ Pyrolysis Studies
- Identification and quantification of pyrolysis products should be performed using best practices in pyrolysis studies.
- Similar structure/function with substances with CMR properties and read across studies within pyrolysis products may be warranted for further evaluation
- Specific technical issues (temperature, oxygen, timeframe etc.) should be taken into account.

✓ In vitro studies
- For an adequate evaluation of the CMR potential, different endpoints (i.e. for genotixicity induction of gene mutations, structural and numerical chromosomal alterations) have to be assessed by the use of multiple test systems.
- Due to the plethora of types of studies, the studies best suited to the circumstance should be used. This may include a battery of in vitro tests for each CMR endpoint.

✓ In vivo studies
- The use of animal studies should not be ruled out but should be used to provide further evidence. Due to the physiology involved, animal studies may significantly contribute to the evidence, and with a higher weight.
- Emphasis should be on the reduction and replacement of animal studies, but not necessarily the elimination of such studies.
- The REACH Regulation aims at refinement, reduction and replacement of animal testing (3Rs strategy) as well as at promoting alternative testing methods (as per directive 86/609/EEC), while Council Directive 86/609/EEC, requires support of the development, validation and acceptance of methods which could reduce, refine or replace the use of laboratory animals.
- With regards to animal studies, many aspects of the industry submitted research is based on dated protocols and approaches. We suggest that the methodology of studies should adhere to current best practices which would allow for the use of fewer animals.

Additional considerations in study design

Methodological design: The methodological approach of studies should be based on the most recent existing protocols and regulations where applicable. The Council Regulation 440/2008 laying down test methods pursuant to Regulation (EC) 1907/2006 of the European Parliament and of the Council on the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH), is such a reference document which contains detailed

[6] European Chemicals Agency (ECHA) regulations. https://echa.europa.eu/regulations

information with regards to the methods for the determination of toxicity and other health effects (in vitro/in silica/in vivo studies).

Read across studies and in silico testing: Consideration can be given to the use of read-across from an analogue chemical or chemical category, within all steps of the regulatory process. Read-across is a technique for data-gap filling where endpoint information from one chemical is used to predict the same endpoint for another chemical which is considered to be similar in some important aspect relating to that endpoint. Similarly (Q)SAR studies can also be applied at all of the aforementioned levels in the decision making process. In silico studies may also be of added value and could be performed so as to aid the regulatory process.

Feasibility of the proposed studies: It is important to take into account the timeframe for the provision of these proposed studies to regulators. The first three pillars in the proposed regulatory process (Pillar 1: Review of the literature, Pillar 2: Pyrolysis studies and Pillar 3: In vitro/silica studies) are applicable within the context of the timeframe between the notification of the industry and the reporting deadline. It is possible that Pillar 4: In vivo research, may be potentially feasible to be performed in this timeframe, however this is dependent on the outcome evaluated.

Human studies: While these studies should not (and cannot) ethically be performed, epidemiological and historical data and other experience of human exposure, such as accidental poisoning or occupational exposure, may be useful to include in a weight of evidence approach. On the contrary, with regards to evaluating addictiveness, human panel studies may be of interest and could be explored.

The types of studies identified in the DIRECT database to have been performed for each additive is presented in **Annex 1**, as an indicator of the types of tests used by the industry in their testing for these specific additives to date.

4.3.2 Development of a structure/template of the reports

With respect to the reporting of ingredients used by tobacco companies, TPD Article 5 provides for implementing acts laying down the format for the submission and dissemination of the information on ingredients and their dissemination to the general public. It requires manufacturers and importers to submit relevant toxicological data regarding the ingredients within their products, and this reporting be facilitated through a uniform format. These reports should further facilitate peer-review if required in line with Art. 6(4) of the TPD.

According to Article 6(2) of the TPD, MS shall require manufacturers and importers to carry out comprehensive studies for additives in the priority list as published on the 20th May 2016 The studies that are to be carried out in the context of these increased reporting obligations are to be formulated as a report that apriori should include "*an executive summary, and a comprehensive overview compiling the available scientific literature on that additive and summarising internal data on the effects of the additive*" as outlined by Art. 6(4) of the TPD, which further states that these reports may be peer reviewed by an independent scientific body, in particular as regards their comprehensiveness, methodology and conclusions."

In line with the above and the overall consensus that checklists and reporting templates are needed to aid the scientific peer review process, the purpose of this task was to outline

the minimum contents that should be provided in the reporting of individual studies that would be incorporated within the complete report that would be submitted.. The information given in the Annex to this WP hence does not describe the requirements to pass the peer review process or the content of the report that is to be submitted, but should be seen as guide for preparation of the reporting of individual studies within the report, which would allow thorough evaluation and derivation of conclusions by the independent scientific body.

It is important primarily that this template should allow for the easy understanding of the data submitted, should be clear and concise, mainly though for experts and hence these templates must be structured in a way to aid the regulatory review process. It is important to stress that our focus was the creation of checklists at the study level without prejudice to how these should be collated in the overall report summarising all studies done within 18 months.

Overall there a number of reporting checklists and guides in public domain that are designed to support the reporting of relevant research studies, which were evaluated within the context of WP3 for their relevance to the requirements of the TPD. These include, but are not limited to, the following documents:

- ✓ Council Regulation (EC) No 440/2008 of 30 May 2008 laying down test methods pursuant to Regulation (EC) No 1907/2006 of the European Parliament and of the Council on the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH).
- ✓ The European Chemical Agency (ECHA) report "Practical Guide 1: How to report in vitro data".
- ✓ The ECHA report on "Practical Guide 3-How to report robust study summaries"
- ✓ The Good Cell Culture Practice advices on in vitro experimentation and provides standards for any work involving cell and tissue cultures, including the preparation of cells and tissues derived from humans and animals, characterization and maintenance of important characteristics, quality assurance, recording and reporting, safety, education and training, and ethics.
- ✓ Gold Standard Publication Checklist offers consultation on the accurate design and conduct of animal studies
- ✓ STROBE: which is an initiative to strengthening the reporting of observational studies in epidemiology. STROBE does not make quality assessments, but provides a checklist with items that are important to include in reports of observational studies. Multiple extensions of the STROBE statement have now been developed for specific fields of study.
- ✓ PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses.
- ✓ The ARRIVE Guidelines Checklist (Animal Research: Reporting In Vivo Experiments) ARRIVE Guidelines were designed to improve the design, analysis and reporting of research using animals.
- ✓ Other guidelines – reporting checklists developed by the EQUATOR network, have been developed so as to standardise the reporting requirements of research within peer reviewed journals. While not all fields are pertinent to the reporting requirements in this specific situation, these too were evaluated for their point by point relevance.

The checklist/templates presented in **Annex 2** are based on the above documents, appropriately adapted to the current regulatory context. Overall four template checklists were created:

1. Template for the reporting of literature reviews (11 subdomains)
2. Template for the reporting of pyrolysis studies (15 subdomains)
3. Template for the reporting of in vitro studies (22 subdomains)
4. Template for the reporting of in vivo studies (24 subdomains)

These templates have the following characteristics:

- ✓ For all types of studies five internal modules are to be provided, each with a number of internal subdomains that have to be addressed according to the different type of study.
- ✓ The four main modules include the Summary, the Introduction, the Methods and the Results/Discussion module.
- ✓ Each of the modules differ according to the type of study to be reported but in general include aspects related to the background, rational and objective; a very detailed methods reporting section that would allow for replication of the study; structured results reporting and a discussion including limitations, adequacy and comparability of the results.
- ✓ Specifically for in vitro testing, and in line with the 3Rs approach, detailed information is requested with regards to the ethical aspects, the experimental procedures, animals involved, housing and husbandry, sample size and allocation as also detailed reporting of outcomes and adverse events.

Other issues related to peer review and the reporting format/template

- ✓ The language of the reports should always be in English as peer review is routinely facilitated in English, but the overall abstract of the report should be provided to each EU MS also in their national language. This would limit the amount of translation but still allow MS regulators to receive also a summary in their national language.
- ✓ Other issues could be taken into account including the provision of raw data by the industry, declarations of truthful submission and the provision of definitions (glossary) in the report based on existing Commission terminology.
- ✓ Potential members of a peer review panel must have an absence of perceived or potential conflicts of interest that may impede or effect in any capacity the performance of an independent peer review from the tobacco industry.

4.3.3 Organisation of a joint meeting

In order to critically discuss the proposed methodologies suggested through the above tasks of WP3, DIRECT organised a working group meeting in Brussels with representatives of DG SANTE and SCEER. During this meeting the performed work to date and the different approaches were presented by discussed by both participating parties. Within the meeting the aspects related to the role of SCEER and the added value of DIRECT were discussed. Both parties agreed that the work performed was complimentary to each other and agreed to share information as necessary so as to aid the regulatory process.

4.3.4 Synopsis of WP3 findings

To summarise, WP3 had two main outcomes, the identification of the types of studies that have been previously reported by the industry in response to previous regulatory requirements and secondly to format a uniform reporting template and individual checklists for the facilitation of homogenous reporting of performed studies.

- ✓ A complete dossier would be needed for the peer reviewers and regulators to be able to make an informed decision on an additive. It is important to stress that our focus was the creation of checklists at the study level without prejudice to how these should be collated in the overall report summarising all studies done within 18 months.
- ✓ In light of the above a chronological tier system would be inappropriate and can be used within the decision making process but should not be used during the provision of evidence as it would lead to unnecessary delays in the provision and request for evidence.
- ✓ An outline of the different key issues that should be included in the battery of suggested tests (review, pyrolysis, in vivo, in vitro) was created and such a complete array of tests should be requested.
- ✓ In vitro (animal) testing should not be eliminated however all effort should be made to ensure the reduction in the use of animals and adherence to current best practices which may allow for the use of fewer animals.
- ✓ Checklists are routinely used in research methods to aid reporting and to increase comparability and decrease chance of missing information.
- ✓ As the reporting requirements of the TPD note the need of "an executive summary, and a comprehensive overview compiling the available scientific literature on that additive and summarising internal data on the effects of the additive" a comprehensive battery of studies would be needed so as to prove the inexistence of a CMR property.
- ✓ For all types of study checklists, five internal modules are provided, each with a number of internal subdomains that have to be addressed according to the different type of study performed.
- ✓ Issues such as language requirements, raw data requests and issues of independence and lack of conflict of interest must be taken into account for both peer reviewers and regulators.

5. ANNEXES

Annex 1. Types of tests used for priority additives as noted within the DIRECT database

Annex 2. Reporting template and checklist of studies to be requested

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