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MINUTES OF THE 12TH PLENARY MEETING OF THE SCIENTIFIC PANEL ON FOOD ADDITIVES, FLAVOURINGS, PROCESSING AIDS AND MATERIALS IN CONTACT WITH FOOD Held in Parma on 28-30 June 2005

(The minutes were adopted on 3 October 2005 at 13th Plenary meeting)

AGENDA:

Address :
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MINUTES OF THE 12TH PLENARY MEETING OF THE SCIENTIFIC PANEL ON FOOD ADDITIVES, FLAVOURINGS, PROCESSING AIDS AND MATERIALS IN CONTACT WITH FOOD (AFC) Held in Parma on 28-30 June 2005

PARTICIPANTS

Panel Members:
Susan Barlow (chair); Dimitrios Boskou; Riccardo Crebelli; Wolfgang Dekant; Karl-Heinz Engel (1st and 2nd day); Werner Grunow (2nd vice chair); Marina Heinonen; Maria Rosaria Milana, Iona Pratt; Ivonne Rietjens; Kettil Svensson; Paul Tobback; Fidel Toldrá.

Experts
Jean-Claude Lhuguenot (2nd and 3rd day); Jørn Gry (1st and 2nd day); Paul Brantom (3rd day);

Apologies
Robert Anton; Laurence Castle; Stephen Forsythe, John Christian Larsen (1st vice chair); Catherine Leclercq; Wim C. Mennes;

EFSA
Torben Hallas-Møller (scientific co-ordinator of AFC Panel), Dimitrios Spyropoulos (assistant scientific co-ordinator of AFC Panel); Anne Theobald (assistant scientific co-ordinator of AFC Panel); Lourdes Suarez Gonzalez (assistant scientific co-ordinator of AFC Panel); Maud Pâques (administrative secretary of AFC Panel); Ilse Koenig (administrative assistant of AFC Panel);

Commission
Almut Bitterhof, DG Health and Consumer Protection, Interface unit;

1. WELCOME, APOLOGIES FOR ABSENCE

The Chair welcomed the members and others attending from EFSA and the Commission.

Apologies were noted.

2. ADOPTION OF THE AGENDA

The agenda was adopted.

3. DECLARATIONS OF INTEREST

These are noted under the specific item on phthalates (item 10.1-3).

4. MATTERS ARISING FROM THE 11TH PLENARY MEETING ON 26-28 APRIL 2005

The members were informed that a press release on the opinion on semicarbazide was going to be published on 2 July at the same time as the publication of the opinion.

The minutes can be seen on:
http://www.efsa.eu.int/science/afc/afc_meetings/898/afc_minutes_meet113.pdf and the opinion on semicarbazide on http://www.efsa.eu.int/science/afc/afc_opinions/1005_en.html

5. GENERAL INFORMATION FROM EFSA AND THE COMMISSION

The Panel was informed about the official inauguration of EFSA in Parma. Further details can be seen on http://www.efsa.eu.int/press_room/efsa_journal_2004/special_edition_july_2005/catindex_en.html.

6. FEEDBACK FROM RECENT MEETINGS OF THE SCIENTIFIC COMMITTEE

The chair informed Members of the 13th meeting of the Scientific Committee (SC) held on 21-22 June. Main issues were the adoption on an opinion on exposure assessment, which can be seen on http://www.efsa.eu.int/science/sc_commitee/sc_opinions/1028_en.html and the evaluation of EFSA, which has begun and will consider, among other topics, the workload and configuration of the Panels.

Further details can be found in the minutes from the SC meeting:
http://www.efsa.eu.int/science/sc_commitee/sc_meetings/catindex_en.html

6.1. Appointment of participants to SC Animal Welfare WG.

Members were invited to participate in an SC Working Group on Animal Welfare.

7. FOOD ADDITIVES

7.1. Illegal dyes in food (Sudan red I, II, III and IV, Para Red, Rhodamine B, Orange II and other)

The rapporteur introduced the draft opinion which was thoroughly discussed and several changes were suggested. It was decided that the Additives Working Group should further refine the text and that the final draft should be adopted by written procedure.

Following the first report in 2003 of the illegal presence of the dye Sudan I in some foods in the European Union (EU), there have been many notifications by EU Member States of the presence of this and other illegal dyes in chilli powder, curry powder, processed products containing chilli or curry powder, sumac, curcuma and palm oil. The dyes concerned are Sudan I, Sudan II, Sudan III, Sudan IV, Para Red, Rhodamine B and Orange II. The available toxicity data on these seven dyes (see Annex 1 to the opinion) have been reviewed.

The Panel concluded that there are insufficient data on any of the illegal dyes, Sudans I-IV, Para Red, Rhodamine B, and Orange II, found so far in foods in the EU to perform a full risk assessment. However, there is experimental evidence that Sudan I is both genotoxic and carcinogenic and that Rhodamine B is potentially both genotoxic and carcinogenic. For the following dyes, conclusive evidence is lacking but, because of structural similarities to Sudan I, it would be prudent to assume that they are potentially genotoxic and possibly

carcinogenic: Sudan II, Sudan III, Sudan IV, Para Red. For Orange II genotoxicity cannot be ruled out and the existing data on carcinogenicity are inadequate for any conclusion.

In order to offer some guidance on structural features of dyes that may provide alerts for possible genotoxic and carcinogenic activity, the Panel reviewed information from the literature on other genotoxic and/or carcinogenic industrial dyes, not hitherto found in food, (see Annex 2 to the opinion). This information, together with consideration of structure-activity relationships indicates that dyes with azo, triphenylmethane and anthraquinone structures should initially be considered suspect. Among the azo dyes, the potential to be metabolised to lipidsoluble aromatic amines, in particular benzidine derivatives, is an alert for genotoxicity/carcinogenicity, while sulphonation of all ring components, as is the case in most of the azo dyes approved as food colours in the EU, eliminates genotoxic and carcinogenic activity.

Consideration of reports of dyes that have been used illegally in countries from which spices originate and dyes that have been used in the past as food colours in other countries but withdrawn from food use following discovery of toxicity, together with laboratory studies and structure activity considerations suggest that the following dyes should be viewed as genotoxic and/or carcinogenic:

Acid Red 73 (CAS-No. 5413-75-2), Sudan Red 7B (CAS-No 6368-72-5), Metanil Yellow (CASNo 587-98-4), Auramine (CAS-No 492-80-8), Congo Red (CAS-No 573-58-0), Butter Yellow (CAS-No 60-11-7), Solvent Red I (CAS-No 1229-55-6), Naphthol Yellow (CAS-No 483-84-1), Malachite Green (CAS-No 569-64-2), Leucomalachite Green (CAS-No 129-73-7), Ponceau 3R (CAS-No 3564-09-8), Ponceau MX (CAS-No 3761-53-3), Oil Orange SS (CAS-No 2646-17-5) A number of other withdrawn food dyes had inconclusive evidence of genotoxicity and this may be related to the poor specification of the dyes tested in early studies, since structure-activity analysis would not suggest these properties.

8. SUBSTANCES USED AS NUTRIENT SOURCES

8.1. Status of incoming dossiers to date

The Panel was informed that a considerable amount of new requests for evaluation of food supplements had already been received and that a several more could be expected. The Additives Working Group will in first instance have a look at the dossiers and suggest an evaluation strategy.

On the Commission website
http://europa.eu.int/comm/food/food/labellingnutrition/supplements/food_supplements.pdf
can be found a list of submitted requests.

9. FLAVOURINGS

9.1. Flavouring group evaluations

In relation to some of the Flavouring Group Evaluations, the Panel noted that genotoxicity data are not available for many flavouring substances in the EU Register

(http://europa.eu.int/eur-lex/pri/en/oj/dat/1999/l_084/l_08419990327en00010137.pdf). This fact does not preclude the possibility to apply the Procedure for the safety evaluation of chemically defined flavouring substances as referred to in Commission Regulation EC n. 1565/2000. However, the Panel will reconsider this situation in the light of the more extensive data requirements for the safety assessment of other substances occurring in food

The opinions on the following flavouring group evaluations were introduced by the Flavis Chair. There was extensive discussion of these drafts. A number of substantive changes to the text were agreed, together with a number of editorial changes. The Chair of the Flavourings Working Group, the Flavis Secretariat and the Panel Secretariat would revise the documents.

9.1.1. FGE10 Aliphatic primary and secondary saturated and unsaturated alcohols and esters containing an additional oxygenated functional group and lactones from chemical group 9, 13, and 30

The opinion was adopted in principle but subject to final adoption by written procedure.

When adopted the full opinion will be published at
http://www.efsa.eu.int/science/afc/afc_opinions/catindex_en.html

9.1.2. FGE.15 Aryl-substituted saturated and unsaturated primary alcohol/aldehyde/acid/ester derivatives from chemical group 22

The opinion was adopted.

The Panel was asked to evaluate eight flavouring substances in the Flavouring Group Evaluation FGE.15, using the procedure as referred to in the Commission Regulation EC No 1565/2000. These eight flavouring substances belong to chemical group 22, Annex I of the Commission Regulation 1565/2000.
The available genotoxicity data are not sufficient to evaluate the genotoxicity adequately, however, the data available on mutagenic and clastogenic activity of both candidate and supporting substances as well as the chemical structures of the candidate substances do not give reason for concern with respect to genotoxicity of the eight candidate substances in this flavouring group evaluation.
It is noted that where toxicity data were available they were consistent with the conclusions in the present flavouring group evaluation using the Procedure.
It was considered that on the basis of the default Maximised Survey-derived Daily Intakes (MSDI) approach to estimate the per capita intakes of the flavouring substances in Europe these eight flavouring substances would not give rise to safety concerns at the estimated levels of intake arising from their use as flavouring substances.
When the estimated intakes were based on the modified Theoretical Added Maximum Daily Intake (mTAMDI) based on the normal use levels reported by industry, they ranged from 1600 to 3700 microgram/person/day for the eight flavouring substances from structural class I. Thus, the intakes were all above the threshold of concern for structural class I of 1800 microgram/person/day, except for one flavouring substance [FL-no: 05.156]. This substance is also expected to be metabolised to innocuous products.
Thus for seven of the eight flavouring substances considered in this opinion the intakes, estimated on the basis of the mTAMDI, exceed the relevant threshold for their structural class, to which the flavouring substance has been assigned. Therefore, for these seven substances more reliable exposure data are required. On the basis of such additional data,

these flavouring substances should be reconsidered along the steps of the Procedure. Following this procedure additional toxicological data might become necessary.

The full opinion can be found at
http://www.efsa.eu.int/science/afc/afc_opinions/catindex_en.html

9.2. **Smoke flavourings. Status of incoming dossiers**

The secretariat informed the Panel that EFSA had received 16 dossiers before the deadline of 16 June. It has been decided to form a new Working Group to deal with smoke flavourings. One of its first tasks will be to check the validity of the dossiers within the meaning of the Regulation on smoke flavourings.
The Working group will report back on next meeting.

10. FOOD CONTACT MATERIALS

10.1 – 10.3 Phthalates

The Chair indicated that she had an indirect interest in phthalates and would therefore vacate the Chair in favour of the 2nd Vice Chair. Following consultation with the Deputy Executive Director, it was decided that although this was not a conflict of interest the Chair should not participate in the discussion. Interests (advising national authorities or conducting studies on phthalates) were also declared by the following Members; Maria Rosaria Milana, Iona Pratt and Kettil Svensson. None of these were considered conflicts of interest by the 2nd Vice Chair and all were invited to participate in the discussion.

10.1. **Di-isononyl phthalate (Phthalic acid, diesters with primary, saturated C8-C10 branched alcohols, more than 60% C9). REF No 75100**

The rapporteur introduced the changes to the draft opinion and there was extensive discussion of the draft. A number of changes to the text were requested, together with a number of editorial changes. The opinion was adopted in principle, subject to formal adoption by written procedure.

The opinion can be found at:
http://www.efsa.eu.int/science/afc/afc_opinions/1144_en.html

10.2. **Di-isodecyl phthalate (Phthalic acid, diesters with primary, saturated C9-C11 branched alcohols more than 90% C10) Ref No 75105**

The rapporteur introduced the changes to the draft opinion and there was extensive discussion of the draft. A number of changes to the text were requested, together with a number of editorial changes. The opinion was adopted in principle, subject to formal adoption by written procedure.

The opinion can be found at:
http://www.efsa.eu.int/science/afc/afc_opinions/1143_en.html

10.3. **Statement on the need for peroxisome proliferation studies**

There is a general consensus that rodents are highly sensitive to the phenomenon of peroxisome proliferation in the liver and that this particular effect should not be used for human risk assessment.
The Panel therefore concluded that the data requirement for peroxisome proliferation studies on alkyl esters, requested in the past by the SCF, be withdrawn.
Substances classified in List 6B, solely on the basis of suspicion for peroxisome proliferation activity in the liver, will be re-classified. If they have not in the meantime been fully evaluated and reclassified in one of SCF Lists 0-4 they will be reclassified from List 6B into List 7, 8 or 9 - depending on the data still needed - with no restriction, with the exception of those alkyl esters also suspect for neurotoxicity. These esters would remain in List 6B with a restriction of 0.05 mg/kg food and the request for neurotoxicity is maintained.

The statement is attached in Annex 2 of the minutes and can furthermore be found on http://www.efsa.eu.int/science/afc/afc_documents/1154_en.html.

10.4. **Statement on the need for establishing a group-TDI for Phthalates**

A statement explaining the reasons for which a group-TDI is not deemed appropriate for the 5 phthalates is attached in Annex 1 of the minutes.

The statement can also be found at:
http://www.efsa.eu.int/science/afc/afc_documents/1147_en.html

10.5. **Epoxy Phenolic Novolac Resins (NOGE), REF No 25552**

This item was deferred until the next meeting.

10.6. **9th list of substances for food contact materials**

The draft opinions on the following substances were modified and adopted:

Ref. No.:	15267
Name of the substance:	4,4'-Diaminodiphenyl sulphone
CAS number:	80-08-0
Classified in list:	3
Restriction:	5 mg/kg food

Ref. No.:	42080
Name of the substance:	Carbon black
CAS number:	1333-86-4
Classified in list:	3

Restriction:	specifications for CB: - Toluene extractables : maximum 0.1%, determined according to ISO method 6209; - UV absorption of cyclohexane extract at 386 nm: <0.02 AU for a 1 cm cell or <0.1 AU for a 5 cm cell, determined according to German BfR, BIII, Reinheitsprufung von Russen,Stand 1.7.1972 - Benzo(a)pyrene content: max 0.25 mg/kg Carbon Black - Maximum use level of Carbon Black in the polymer: 2.5% w/w

Ref. No.:	71960
Name of the substance:	Perfluorooctanoic acid, ammonium salt
CAS number:	3825-26-1
Classified in list:	3
Restriction:	Only to be used in repeated use articles, sintered at high temperatures

Ref. No.:	72081/10
Name of the substance:	Petroleum hydrocarbon resins (hydrogenated)
CAS number:	088526-47-0
Classified in list:	3
Restriction:	5 mg/kg food

Regarding the substance petroleum hydrocarbon resins (72081/10), the Panel was informed that industry is in discussions with the lab that performed the ADME study to see if kinetic modelling can be undertaken in order to better understand the situation.
The Panel has suggested that some further work-up could also be done on archived samples from the study to better assess where the tritiated label has gone, so that any confounding of the interpretation by contamination of samples with tritriated water is reduced.

The full opinion can be found at http://www.efsa.eu.int/science/afc/afc_opinions/1056_en.html

The following substances were deferred until the next plenary:

Ref. No.:	13618
Name of the substance:	1,2-Bis(triethoxysilyl)ethane
CAS number:	016068-37-4

Ref. No.:	16450
Name of the substance:	1,3-Dioxolane
CAS number:	00646-06-0

Ref. No.:	19112
Name of the substance:	1-Isocyanato-3-isocyanatomethyl-3,5,5-trimethylcyclohexane homopolymer, methyl ethyl ketone oxime-blocked
CAS number:	103170-26-9

Ref. No.:	38885

Name of the substance:	2,4-Bis(2,4-dimethylphenyl)-6-(2-hydroxy-4-n-octyloxyphenyl)-1,3,5-triazine
CAS number:	002725-22-6
Ref. No.:	93970
Name of the substance:	Tricyclodecane dimethanol-bis(hexahydrophthalate)
CAS number:	none

11. OTHER ISSUES WITHIN THE REMIT OF THE AFC PANEL

11.1. Treatment of poultry carcasses with antimicrobials

The Panel was informed that the BIOHAZ Panel will look at the question on efficacy while the Additive Working Group of the AFC Panel would continue to evaluate the chemical safety of the process.

12. WORKING PROGRAMME

12.1. New questions

The updated register of questions can be seen on the EFSA website at http://www.efsa.eu.int/register/qr_panels_en.html.

12.2. Status of open questions

Because of lack of time this item was not addressed.

12.3. Dates for plenary meetings in 2006

Following dates were agreed:
24-26 January
28 February – 2 March
2-4 May

13. ANY OTHER BUSINESS

14. ANNEX 1 TO MINUTES OF THE 12TH MEETING OF THE AFC PANEL

Minutes' Statement of the Scientific Panel on Food Additives, Flavourings, Processing Aids and Materials in Contact with Food

on the withdrawal of the requirement for peroxisome proliferation studies for alkyl esters used in food contact materials

(expressed on 28 June 2005 at its 12th Plenary meeting, corresponding to item 10 of the agenda)

10.Food contact materials

10.3 Peroxisome proliferation studies

During the early 1990s, the Scientific Committee for Food (SCF) evaluated a number of alkyl esters that were being used, or were requested for use, as monomers or additives in plastics. These included a few extensively investigated substances, such as di-ethylhexyladipate (DEHA) and di-ethylhexylphthalate (DEHP), as well as a large number of esters for which there was little or no toxicity information.

For DEHP, the most sensitive change observed in rodents at that time was peroxisome proliferation in the liver. It was unclear then whether the peroxisome proliferation seen at relatively low doses was mechanistically linked to the development of liver tumours seen in rodents after chronic treatment with much higher doses of DEHP. Although limited evidence at that time indicated that liver cells from humans and from some other non-rodent species were relatively non-responsive to induction of peroxisome proliferation by DEHP or similar agents, the possibility that such agents might pose a carcinogenic risk to humans could not be ruled out.

In 1994, faced with these uncertainties, the SCF pursued a prudent approach and set a Tolerable Daily Intake for DEHP, based on the NOEL for peroxisome proliferation in rat liver. Since it was also known that some other structurally-related alkyl esters also induced peroxisome proliferation, the SCF issued an opinion in 1995 covering all the alkyl esters requested for use in food contact materials. In this opinion, a requirement was set for peroxisome proliferation studies to be submitted on those alkyl esters for which migration exceeded 0.05 mg/kg of food, unless there was evidence from structure-activity considerations that peroxisome proliferation would not be expected to occur.

In the decade since that SCF report, a large number of laboratory research studies have investigated the possible mechanisms underlying the formation of liver tumours in rats treated with peroxisome proliferators, but without any clear conclusion. Similarly, commentaries and reviews of the literature (e.g. IARC, 1995, 2000; Melnick, 2001; Huff, 2002; Bosgra, Mennes and Seinen, 2005) have continued to discuss the various possible mechanisms of toxicity and whether humans exposed to these agents are at any increased risk of cancer, again without any clear consensus emerging. There is, however, a general consensus that rodents are highly sensitive to the phenomenon of peroxisome proliferation and that this particular effect should not be used for human risk assessment.

The Panel therefore concluded that the data requirement for peroxisome proliferation studies on alkyl esters be withdrawn.

Since a number of the alkyl esters were classified by the SCF in List 6B, with a group restriction of 0.05 mg/kg of food, solely on the basis of suspicion for peroxisome proliferation activity, the consequence of withdrawing the requirement for special studies on peroxisome proliferation is that these esters (if they have not in the meantime been fully evaluated and reclassified in one of SCF Lists 0-4) will be reclassified from List 6B into List 7, 8 or 9 - depending on the data still needed - with no restriction, with the exception of those alkyl esters also suspect for neurotoxicity. These esters would remain in List 6B with a restriction of 0.05 mg/kg food and the request for neurotoxicity is maintained.

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IARC (1995). Peroxisome proliferation and its role in carcinogenesis. Views and expert opinions of an IARC working group. IARC Technical Report 24. International Agency for Research on Cancer, Lyon.

IARC (2000). IARC Monographs on the Evaluation of Carcinogenic Risks to Humans. Vol 77. Some Industrial Chemicals. DEHP, pp41-148. International Agency for Research on Cancer, Lyon.

Melnick RL (2001). Is peroxisome proliferation an obligatory precursor step in the carcinogenicity of di(2-ethylhexyl)phthalate (DEHP)? Environmental Health Perspectives 109, 437-442.

15. ANNEX 2 TO MINUTES OF THE 12TH MEETING OF THE AFC PANEL

Statement of the Scientific Panel on Food Additives, Flavourings, Processing Aids and Materials in Contact with Food on a request from the Commission

on the possibility of allocating a group-TDI for Butylbenzylphthalate (BBP), di-Butylphthalate (DBP), Bis(2-ethylhexyl) phthalate (DEHP), di-Isononylphthalate (DINP) and di-Isodecylphthalate (DIDP)

(Minutes' statement expressed on 28 June 2005 at its 12th Plenary meeting, corresponding to the item 10 of the agenda)

10.Food contact materials

10.4 g-TDI for phthalates

During the 1990s, the Scientific Committee for Food (SCF) evaluated a number of phthalates that were being used, or were requested for use, as additives in plastics. These included a few extensively investigated substances, BBP, DBP, DEHP, DINP and DIDP, as well as a large number of phthalates for which there was little or no toxicity information.

For the studied phthalates, the most sensitive change observed in rodents at that time was peroxisome proliferation in the liver. It was unclear then whether the peroxisome proliferation seen at relatively low doses was mechanistically linked to the development of liver tumours seen in rodents after chronic treatment with much higher doses. Although limited evidence at that time indicated that liver cells from humans and from some other non-rodent species were relatively non-responsive to induction of peroxisome proliferation by phthalates, the possibility that such agents might pose a carcinogenic risk to humans could not be ruled out.

In 1994, faced with these uncertainties, the SCF pursued a prudent approach and set a Tolerable Daily Intake (TDI) for many phthalic esters, based on the NOEL for peroxisome proliferation in rat liver. The five phthalates under current consideration, i.e. BBP, DBP, DEHP, DINP and DIDP were classified in SCF List 2 and the values for their TDIs were based on their peroxisome proliferation potencies. Since it was also known that some other structurally-related alkyl esters also induced peroxisome proliferation, the SCF issued an opinion in 1995 covering all the alkyl esters requested for use in food contact materials. In this opinion, a requirement was set for peroxisome proliferation studies to be submitted on those alkyl esters for which migration exceeded 0.05 mg/kg of food, unless there was evidence from structure-activity considerations that peroxisome proliferation would not be expected to occur. Since that SCF report, a general consensus has been agreed that rodents are

highly sensitive to the phenomenon of peroxisome proliferation and that this particular effect should not be used for human risk assessment.

As a consequence the Panel was asked to perform a new evaluation of phthalates on the basis of existing data and no longer considering the use of peroxisome proliferation studies as pivotal studies.

AVAILABLE TOXICOLOGICAL DATA ON PHTHALATES

The Panel reviewed the recent literature on toxicological studies and noted the pivotal studies, summarised in the Table below, that are relevant for the toxicological evaluation.

Main pivotal studies for phthalates (details and explanations can be found in the respective opinions)

Phthalate	***Pivotal study***	***End-point***	***NOAEL /LOAEL***	***Value***	***Ref.***
DBP	Developmental Toxicity in rats	Germ cell development	LOAEL	2 mg/kg b.w./day	Lee, 2004
DEHP	Developmental and testicular toxicity in rats	Germ cell depletion ↓ testis weight	NOAEL NOAEL	5 mg/kg b.w./day 5 mg/kg b.w./day	Wolfe and Leyton, 2003
BBP	Testicular toxicity in rats Developmental toxicity in rats	↓ epididymal spermatozoa concentration ↓ AGD (F1, F2)	NOAEL NOAEL	20 mg/kg b.w./day 50 mg/kg b.w./day	NTP, 1997 Tyl, 2001 and 2004
DINP	Liver and kidney toxicity (non related to PP) in	Spongiosis hepatis	NOAEL	15 mg/kg b.w./day	Aristech, 1994 Exxon, 1996

	rats				a,b
DIDP	Liver toxicity in dogs (non related to PP)	Microscopic lesions	NOAEL	15 mg/kg b.w./day	Hazleton, 1968
	Developmental toxicity in rats	↓ F2 offspring survival	NOAEL	30 mg/kg b.w./day	Exxon, 2000

ALLOCATION OF A GROUP TDI

The Panel considered that a group TDI for health protection should be employed if:

i) exposure to several members of a structurally related series of chemicals is likely to occur frequently, and

ii) several members of the series have been demonstrated to have a common target organ(s) cellular target(s) and the same mode of action.

If the above mentioned criteria are met, individual members of the series should be assumed to have an additive effect. Even in cases where there are only limited toxicological data on one or more of the members it is assumed that these compounds contribute to the same effect on the target organ. Toxicological equivalence factors (TEF) can be introduced where there are adequate data and the potencies span 3-5 fold or more. If this is not possible, the most potent member of the series is assumed to be representative for the purposes of standard setting.

According to the above mentioned pivotal studies,

i) DBP and DEHP have pivotal effects on germ cell development/depletion,

ii) BBP has pivotal effects on epididymal spermatozoa concentration,

iii) DINP and DIDP have pivotal effects on the liver.

While it may appear that three phthalates (DBP, DEHP and BBP) act on the same target organ (the testis), their profile of effects at the hormonal and cellular level are not identical and their individual modes of action have not yet been demonstrated. Moreover, the two others, DIDP and DINP, primarily affect the liver rather than the testis. But even in this case, the end-points indicate that different mechanisms are involved.

Consequently a group-TDI cannot be allocated for butylbenzylphthalate (BBP), di-butylphthalate (DBP), bis(2-ethylhexyl) phthalate (DEHP), di-isononylphthalate (DINP) and di-isodecylphthalate (DIDP).

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Minutes' Statement of the Scientific Panel on Food Additives, Flavourings, Processing Aids and Materials in Contact with Food

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10.3 Peroxisome proliferation studies

During the early 1990s, the Scientific Committee for Food (SCF) evaluated a number of alkyl esters that were being used, or were requested for use, as monomers or additives in plastics. These included a few extensively investigated substances, such as di-ethylhexyladipate (DEHA) and di-ethylhexylphthalate (DEHP), as well as a large number of esters for which there was little or no toxicity information.

For DEHP, the most sensitive change observed in rodents at that time was peroxisome proliferation in the liver. It was unclear then whether the peroxisome proliferation seen at relatively low doses was mechanistically linked to the development of liver tumours seen in rodents after chronic treatment with much higher doses of DEHP. Although limited evidence at that time indicated that liver cells from humans and from some other non-rodent species were relatively non-responsive to induction of peroxisome proliferation by DEHP or similar agents, the possibility that such agents might pose a carcinogenic risk to humans could not be ruled out.

In 1994, faced with these uncertainties, the SCF pursued a prudent approach and set a Tolerable Daily Intake for DEHP, based on the NOEL for peroxisome proliferation in rat liver. Since it was also known that some other structurally-related alkyl esters also induced peroxisome proliferation, the SCF issued an opinion in 1995 covering all the alkyl esters requested for use in food contact materials. In this opinion, a requirement was set for peroxisome proliferation studies to be submitted on those alkyl esters for which migration exceeded 0.05 mg/kg of food, unless there was evidence from structure-activity considerations that peroxisome proliferation would not be expected to occur.

In the decade since that SCF report, a large number of laboratory research studies have investigated the possible mechanisms underlying the formation of liver tumours in rats treated with peroxisome proliferators, but without any clear conclusion. Similarly, commentaries and reviews of the literature (e.g. IARC, 1995, 2000; Melnick, 2001; Huff, 2002; Bosgra, Mennes and Seinen, 2005) have continued to discuss the various possible mechanisms of toxicity and whether humans exposed to these agents are at any increased risk of cancer, again without any clear consensus emerging. There is, however, a general consensus that rodents are highly sensitive to the phenomenon of peroxisome proliferation and that this particular effect should not be used for human risk assessment.

The Panel therefore concluded that the data requirement for peroxisome proliferation studies on alkyl esters be withdrawn [and that an amendment is made to the SCF guidelines currently used by the AFC Panel for evaluation of substances used in food contact materials].

Since a number of the alkyl esters were classified by the SCF in List 6B, with a group restriction of 0.05 mg/kg of food, solely on the basis of suspicion for peroxisome proliferation activity, the consequence of withdrawing the requirement for special studies on peroxisome

proliferation is that these esters (if they have not in the meantime been fully evaluated and reclassified in one of SCF Lists 0-4) will be reclassified from List 6B into List 7, 8 or 9 - depending on the data still needed - with no restriction, with the exception of those alkyl esters also suspect for neurotoxicity. These esters would remain in List 6B with a restriction of 0.05 mg/kg food and the request for neurotoxicity is maintained.

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