Committee for Risk Assessment

RAC

Annex 1

Background document

to the Opinion proposing harmonised classification and labelling at Community level of

diisobutyl phthalate (DIBP)

EC number: 201-553-2
CAS number: 84-69-5

CLH-O-0000001412-86-24/F

The background document is a compilation of information considered relevant by the dossier submitter or by RAC for the proposed classification. It includes the proposal of the dossier submitter and the conclusion of RAC. It is based on the official CLH report submitted to public consultation. RAC has not changed the text of this CLH report but inserted text which is specifically marked as 'RAC evaluation'. Only the RAC text reflects the view of RAC.

Adopted

04 December 2014

CLH report

Proposal for Harmonised Classification and Labelling

**Based on Regulation (EC) No 1272/2008 (CLP Regulation),
Annex VI, Part 2**

Substance Name: Diisobutylphthalate (DIBP)

EC Number: 201-553-2

CAS Number: 84-69-5

Index Number: 607-623-00-2

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Part A.

Part B.

Part A.

1 PROPOSAL FOR HARMONISED CLASSIFICATION AND LABELLING

1.1 Substance

Table 1: Substance identity

Substance name:	***Diisobutyl phthalate (DIBP)***
EC number:	***201-553-2***
CAS number:	***84-69-5***
Annex VI Index number:	***607-623-00-2***
Degree of purity:	***>99.5<100% (w/w)***
Impurities:	***Confidential***

1.2 Harmonised classification and labelling proposal

Table 2: The current Annex VI entry and the proposed harmonised classification

	CLP Regulation
Current entry in Annex VI, CLP Regulation	Repr. 1B; H360Df: C ≥ 25% Repr. 2; H361f: 5% ≤ C < 25%
Current proposal for consideration by RAC	Removal of SCL
Resulting harmonised classification (future entry in Annex VI, CLP Regulation)	Repr. 1B; H360Df

1.3 Proposed harmonised classification and labelling based on CLP Regulation and/or DSD criteria

Table 3: Proposed classification according to the CLP Regulation

CLP Annex I ref	Hazard class	Proposed classification	Proposed SCLs and/or M-factors	Current classification [1)]	Reason for no classification [2)]
2.1.	Explosives				
2.2.	Flammable gases				
2.3.	Flammable aerosols				
2.4.	Oxidising gases				
2.5.	Gases under pressure				
2.6.	Flammable liquids				
2.7.	Flammable solids				
2.8.	Self-reactive substances and mixtures				
2.9.	Pyrophoric liquids				
2.10.	Pyrophoric solids				
2.11.	Self-heating substances and mixtures				
2.12.	Substances and mixtures which in contact with water emit flammable gases				
2.13.	Oxidising liquids				
2.14.	Oxidising solids				
2.15.	Organic peroxides				
2.16.	Substance and mixtures corrosive to metals				
3.1.	Acute toxicity - oral				
	Acute toxicity - dermal				
	Acute toxicity - inhalation				
3.2.	Skin corrosion / irritation				
3.3.	Serious eye damage / eye irritation				
3.4.	Respiratory sensitisation				
3.4.	Skin sensitisation				
3.5.	Germ cell mutagenicity				
3.6.	Carcinogenicity				
3.7.	Reproductive toxicity	Repr.1B; H360Df	No SCL	Repr.1B; H360Df Repr. 1B; H360Df: C ≥ 25% Repr. 2; H361f: 5% ≤ C < 25%	
3.8.	Specific target organ toxicity – single exposure				
3.9.	Specific target organ toxicity – repeated exposure				
3.10.	Aspiration hazard				
4.1.	Hazardous to the aquatic environment				
5.1.	Hazardous to the ozone layer				

[1)] Including specific concentration limits (SCLs) and M-factors
[2)] Data lacking, inconclusive, or conclusive but not sufficient for classification

Table 4: **Proposed labelling according to the CLP Regulation**

	Labelling	Wording
Pictograms	GHS08	
Signal Word	Danger	
Hazard statements	H360Df	May damage the unborn child. Suspected of damaging fertility.
Suppl. Hazard statements	-	-
Precautionary statements	P201 P202 P281 P308 + P313 P405 P501	Obtain special instructions before use Do not handle until all safety precautions have been read and understood Use personal protective equipment as required IF exposed or concerned: Get medical advice/ attention Store locked up. Dispose of contents/container to …

Proposed notes assigned to an entry:

-

Proposed notes assigned to an entry:

-

2 BACKGROUND TO THE CLH PROPOSAL

2.1 History of the previous classification and labelling

Diisobutylphthalate was discussed by the Technical Committee on Classification and Labelling between March 2005 and October 2006.

In March 2006 the TC C&L agreed to classify the substance in category 2 for developmental effects and in category 3 for effects on fertility based on available data. The proposal for specific concentration limits was submitted by IND in ECBI/116/04 Add. 10 and Member States had the possibility to react to this proposal in written. Due to split opinions from the Member States the issue was revisited at the October 2006 meeting.

In October 2006 the TC C&L agreed to set classification limits with 25% for developmental effects as follows: C ≥ 25%: Repr. 1B – H360Df and 5% ≤ C < 25%: Repr. 2 – H361f.

2.2 Short summary of the scientific justification for the CLH proposal

Since 2006 another relevant paper was published investigating the influence of an *in utero* exposure to diisobutylphthalate on male reproductive development (Saillenfait et al., 2008).

2.3 Current harmonised classification and labelling

2.3.1 Current classification and labelling in Annex VI, Table 3.1 in the CLP Regulation

Index number: 607-623-00-2	Classification	Wording	Specific concentration limits, M-factors
Hazard classes, Hazard categories	Repr. 1B		
Hazard statements	H360Df	May damage the unborn child. Suspected of damaging fertility	Repr. 1B; H360Df: C ≥ 25% Repr. 2; H361f: 5% ≤ C < 25%

Index number: 607-623-00-2	Labelling	Wording	Specific concentration limits, M-factors
Pictograms	GHS08		
Signal Word	Danger		
Hazard statements	H360Df	May damage the unborn child. Suspected of damaging fertility	Repr. 1B; H360Df: C ≥ 25% Repr. 2; H361f: 5% ≤ C < 25%
Suppl. Hazard statements	-	-	
Precautionary statements	None listed in Annex VI		

2.4 Current self-classification and labelling

2.4.1 Current self-classification and labelling based on the CLP Regulation criteria

Table 5: Notified classification and labelling according to CLP criteria (excerpt of ECHA site, taken 10/14/2013)

Hazard Class and Category Codes	Hazard Statement Code(s)	Hazard Statement Code(s)	Pictograms, Signal Word Codes	Specific concentration limits, M-factors
Repr. 1B	H360	H360	GHS08 Dgr	Repr. 1B: C ≥ 25%, Repr. 2: 5% ≤ C < 25%
Repr. 1B	H360	H360	GHS08 Dgr	Repr. 2: 5% ≤ C < 25% Repr. 1B: C ≥ 25%
Repr. 1B Aquatic Chronic 3	H360 H412	H360 H412	GHS08 Dgr	Repr. 1B: C ≥ 25% Repr. 2: 5% ca. C < 25%
Repr. 1B	H360	H360	GHS08 Dgr	
Repr. 1B	H360	H360	GHS08 Dgr	Repr. 1B: C ≥ 25%
Repr. 1B Aquatic Acute 1 Aquatic Chronic 2	H360 H400 H411	H360	GHS08 Dgr	
Repr. 1B	H360	H360	GHS08 Dgr	
Repr. 1B	H360	H360	GHS08 Dgr	Repr. 2: 5% < C < 25% Repr. 1B: C > 25%
Repr. 1B Aquatic Chronic 1	H360 H410	H400 H360 H410	GHS09 GHS08 Dgr	
Aquatic Acute 1 Aquatic Chronic 1	H400	H400 H410	GHS09 Wng	M(Chronic)=0
		H360	GHS08 Dgr	
Repr. 1B Aquatic Acute 1	H360 H401	H412 H360	Dgr	Repr. 2: 5% ≤ C < 25% Repr. 1B: C ≥ 25%
Repr. 1B Aquatic Chronic 3	H360 H411	H401 H412 H360	GHS08 Dgr	Repr. 2: C ≥ 5% Repr. 1B: C ≥ 25% M(Chronic)=0
Not Classified				
Repr. 1B	H360	H360	GHS08 Dgr	Repr. 1B: C ≥ 25% Repr. 2: 5% ≤ C ≤ 25%
Repr. 1B	H360	H360	GHS08 Dgr	Repr. 1B: C ≥ 25% Repr. 2: 5% ≤ C < 25%
Repr. 1B	H360		GHS08 Dgr	Repr. 1B: C ≥ 25% Repr. 2: C ≥ 5%
Asp. Tox. 1 Repr. 1B Aquatic Acute 1	H304 H360 H400	H304 H360 H400	GHS09 GHS08 Dgr	
Repr. 1B Aquatic Acute 1 Aquatic Chronic 1	H360 H400 H410	H360 H400 H410	GHS09 GHS08 Dgr	Repr. 2: 5% ≤ C < 25% Repr. 1B: C ≥ 25%

3 JUSTIFICATION THAT ACTION IS NEEDED AT COMMUNITY LEVEL

Considering the generic concentration limit of ≥ 0.3% for category 1B reproductive toxicants as well as the new study results on reproductive toxicity of DIBP the SCL of 25% needed a re-evaluation. The new CLP criteria (4th ATP) have been applied and a new calculation of SCL values has been performed according to the Guidance on the application of the CLP criteria (Version 3.0, November 2012).

In January 2010, the substance was included in the candidate list as a substance of very high concern.

Part B.

SCIENTIFIC EVALUATION OF THE DATA

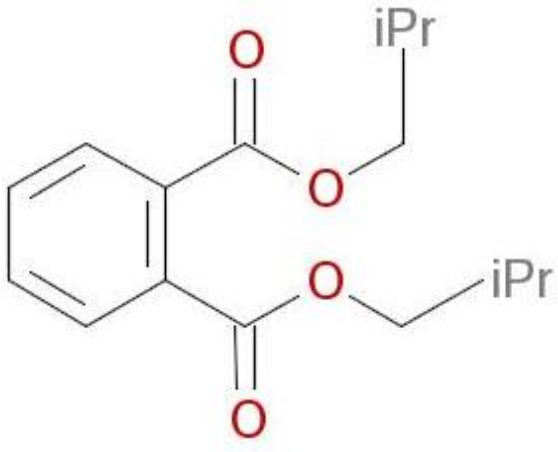
1 IDENTITY OF THE SUBSTANCE

1.1 Name and other identifiers of the substance

Table 6: Substance identity

EC number:	201-553-2
EC name:	diisobutyl phthalate
CAS number (EC inventory):	84-69-5
CAS number:	84-69-5
CAS name:	1,2-Benzenedicarboxylic acid, bis(2-methylpropyl) ester
IUPAC name:	diisobutyl phthalate
CLP Annex VI Index number:	607-623-00-2
Molecular formula:	$C_{16}H_{22}O_4$
Molecular weight range:	278.3435 g/mol

Structural formula:



1.2 Composition of the substance

Table 7: Constituents (non-confidential information)

Constituent	Typical concentration	Concentration range	Remarks
Diisobutylphthalate (DIBP)		> 99.5 < 100% (w/w)	

Current Annex VI entry:

Table 8: Impurities (non-confidential information)

Impurity	Typical concentration	Concentration range	Remarks

Current Annex VI entry:

Table 9: Additives (non-confidential information)

Additive	Function	Typical concentration	Concentration range	Remarks

1.2.1 Composition of test material

1.3 Physico-chemical properties

Table 10: Summary of physico - chemical properties

Property	Value	Reference	Comment (e.g. measured or estimated)
State of the substance at 20°C and 101,3 kPa	The substance is a clear, oily colourless liquid with a characteristic ester odour. The test item DIBP was an organic and pale yellow liquid with faint odour.	Anon.; 2010; Notes on observation Renzi A.; 2008; 01 ISOBUTYL-PHTHALATE (OIBP) Appearance; POLYNT Spa Via E. Fermi, 51 I - 24020 Scanzorosciate – Bergamo; 201-553-2_001.EP	according to EPA OPPTS OPPTS 830.6303 (Physical State); EPA OPPTS 830.6302 (Color); EPA OPPTS 830.6304 (Odor)
Melting/freezing point	ca. –64 °C; ca. 1 atm –52 °C	Richard J. Lewis, Sr.; 1991; Hazardous Chemicals Desk Reference; Van Nostrand Reinhold, New York Renzi A.; 2008; 01 ISOBUTYL-PHTHALATE {DIBP} Melting Point (Method Pour Point); POLYNT Spa Via E. Fermi, 51 I - 24020 Scanzorosciate – Bergamo; 201-553-2_002.EP	equivalent or similar to OECD Guideline 102 (Melting point / Melting Range) according to other guideline: Method ASTM D 97-02
Boiling point	ca. 327 °C; ca. 1 atm	Richard J. Lewis, Sr.; 2007; Hawley's Condensed Chemical Dictionary; Wiley-Interscience, A John Wiley & Sons, Inc., Publication	equivalent or similar to OECD Guideline 103 (Boiling point/boiling range)
Relative density	1038.9 kg/m³; 20 °C	Renzi. A.; 2008; 01 ISOBUTYL-PHTHALATE (DIBP) Density by Digital Density Meter; POLYNT Spa Via E.Fermi, 51 24020 - Scanzorosciate – Bergamo; 201-553-2_004.EP	according to OECD Guideline 109 (Density of Liquids and Solids); EPA OPPTS 830.7300 (Density / Relative Density / Bulk Density); EU Method A.3 (Relative Density)
Vapour pressure	ca. 0.0185 hPa; 20 °C	M. Potin-Gautier, P. Grenier, and J. Bonastre; 1982;	Article published in established peer-reviewed journal; calculated value based on

	0.084 mm Hg; 100 °C equal to 11.2 Pa	Nouvelle application analytique de la methode de determination des pressions de vapeur par saturation d'un gas inerte; Analytical Letters 15(A17), 1431-1448; Faculte des Sciences	extrapolation of data measured at 60, 80, 100 degrees C. equivalent or similar to OECD Guideline 104 (Vapour Pressure Curve)
Surface tension			For this substance the study is scientifically unjustified as substance not designed or expected to have surface active properties.
Water solubility	ca. 20.3 mg/L; 20 °C	F. Leyder and P. Boulanger; 1983; Ultraviolet Absorption, Aquesou Solubility, and Octanol-Water Partition for Several Phthalates; Bulletin of Environmental Contamination and Toxicology, 30, 152-157; University of Liege	according to OECD Guideline 105 (Water Solubility)
Partition coefficient n-octanol/water	log P_{ow} ca. 4.11; 20 °C	F. Leyder and P. Boulanger; 1983; Ultraviolet Absorption, Aquesou Solubility, and Octanol-Water Partition for Several Phthalates; Bulletin of Environmental Contamination and Toxicology, 30, 152-157; University of Liege	according to OECD Guideline 107 (Partition Coefficient (n-octanol / water), Shake Flask Method)
Flash point			
Flammability			
Explosive properties			
Self-ignition temperature			
Oxidising properties			
Granulometry			This substance is a liquid; the study is technically not feasible.
Stability in organic solvents and identity of relevant degradation products			The stability of the substance is not considered to be critical.
Dissociation constant			The substance does not contain any functional groups that dissociate and therefore testing

			does not appear scientifically necessary.
Viscosity	40.95 mm2/s; 20 °C 13.96 mm2/s; 40 °C	Renzi A.; 2008; DIISOBUTYL-PHTHALATE (DIBP) Kinematic Viscosity of Liquids; POLYNT Spa Via E.Fermi, 51 24020 Scanzorosciate – Bergamo; 201-553-2_017.EP	according to other guideline: ASTM D 445-06; EPA OPPTS 830.7100 (Viscosity); OECD Test Guideline 114 (Viscosity of Liquids)

2 MANUFACTURE AND USES

Not relevant for this dossier.

3 CLASSIFICATION FOR PHYSICO-CHEMICAL PROPERTIES

Not relevant for this dossier.

4 HUMAN HEALTH HAZARD ASSESSMENT

4.1 Toxicokinetics (absorption, metabolism, distribution and elimination)

Not relevant for this dossier.

4.2 Acute toxicity

Not relevant for this dossier.

4.3 Specific target organ toxicity – single exposure (STOT SE)

Not relevant for this dossier.

4.4 Irritation

Not relevant for this dossier.

4.5 Corrosivity

Not relevant for this dossier.

4.6 Sensitisation

Not relevant for this dossier.

4.7 Repeated dose toxicity

Not relevant for this dossier.

4.8 Specific target organ toxicity (CLP Regulation) – repeated exposure (STOT RE)

Not relevant for this dossier.

4.9 Germ cell mutagenicity (Mutagenicity)

Not relevant for this dossier.

4.10 Carcinogenicity

Not relevant for this dossier.

4.11 Toxicity for reproduction

Several studies were available on the developmental toxicity of DIBP.[1] Furthermore, the studies used by the lead registrant (Basell Poliolefine Italia S.r.l) were evaluated. Since it was intended to calculate if the SCL could be adjusted to values above the generic concentration limit, only studies were included with more then three dosage levels and a sufficient number of animals investigated (≥ 10 animals/dose). The calculations were performed according to the new guidance on the application of the CLP criteria (Version 3.0, November 2012).

The two key studies of the lead registrant (Saillenfait et al., 2006 and Saillenfait et al., 2008) are the key studies of this dossier. The following studies were not considered for the calculatioin of the SCL: The Howdeshell-study (Howdeshell et al., 2008) was not considered since only five to eight animals per treatment group have been used. The Borch-study (Borch et al., 2006) was not considered since only eight animals have been used in only one treatment group. The Boberg study (Boberg et al., 2008) was not considered since only one treatment group was used.

[1] For review see: "Candidate List of Substances of Very High Concern for Authorization" http://echa.europa.eu/web/guest/candidate-list-table?search_criteria=201-553-2

Table 11: Summary table of relevant reproductive toxicity studies

Method	Results	Remarks	Reference
Developmental Toxicology, close to OECD 414. Sprague Dawley rats, 23-24 animals per group, Dosage: 0 (olive oil), 250, 500, 750 and 1000 mg/kg bw/day by gavage. GD 6-20	No maternal deaths. Signs of transient maternal toxicity were observed. **Resorptions** were statistically significantly increased to 28% at 750 mg/kg bw/d and to 59% at 1000 mg/kg bw/d. Mean **fetal body weight** (abs.) was statistically significantly reduced at 500 mg/kg bw/d and higher doses amounting to a decrease of 24% -26% at 1000 mg/kg bw/d in comparison to controls. Incidence of **total external malformations** (neural tube closure defects, anophthalmia) and of total visceral malformations (urinary tract and vascular defects) was statistically increased at 750 and 1000 mg/kg bw/d. **Skeletal evaluations** revealed malformations primarily of the axial column with the incidences of fused sternebrae statistically significantly increased at 750 and 1000 mg/kg bw/d and variations (delayed ossification and supernumerary ribs) at 750 and 1000 mg/kg bw/d with supernumerary ribs in 95% of the fetuses of the 1000 mg/kg group. **Visceral variations** involved mainly the urinary tract with statistically significantly increased incidences of ureter variations in the 1000 mg/kg group and the male reproductive system. Unilateral or bilateral **undescended testes** occurred at 500 mg/kg/d and was significantly increased at 750 mg/kg/d (in 30/55 male fetuses and in 16/20 litters) and at 1000 mg/kg bw/d (in 30/34 male fetuses and in 16/17 litters). In addition the degree of transabdominal descent was significantly impaired at 500 mg/kg/d with about two third of the testes located in the upper half of the abdominal cavity at	No evidence of embryo or fetal effects was found at the 250 mg/kg dose level. Therefore, a NOAEL/developmental toxicity of 250 mg/kg/d can be derived from the study.	Saillenfait et al., 2006

	the 1000 mg/kg dose group.		
Postnatal developmental toxicity study. Sprague Dawley rats, 11-13 animals per group, Dosage: 0 (olive oil), 125, 250, 500 and 650 mg/kg bw/day by gavage. GD 12-21 Pup body weights were recorded on PND 1, 4, 7, 14 and 21. AGD was measured on PND1 and litters culled to 10 pups on PND 4. All pups were examined for the presence of areola and/or nipples on the ventral surface of the thorax on PND 12-14. At weaning on PND 21 three to four male pups from each litter were randomly selected and retained and unselected pups sacrificed and submitted to internal examination. After weaning the dams were sacrificed and the number of implantations recorded from their uteri. All retained males were examined for preputial separation (PPS) and individual body weights recorded at acquisition. Adult males were necropsied on PND 76-86 (two males in each litter) or on PND 111-122 (the remaining males in each litter).	No differences in maternal body weight gain were observed between the controls and the treatment groups. All dams delivered live pups. Post-DIBP implantation loss, litter size, sex ratio, and pup survival to PND 4 and PND 21 were unaffected by treatment. **Anogenital distance (AGD)** measured on PND 1 was dose-dependently significantly reduced in male pups from 250 mg/kg bw/d to the higher doses with or without adjustment for body weight. The decrease amounted to 11% at 250 mg /kg bw/d and 22% at 625 mg/kg bw/d, compared to controls. **AGD** of females was not affected at any dose. **Pup body weight** at PND 1 of both sexes was statistically significantly decreased at 625 mg/kg bw/d, and remained lower in comparison to controls in the male pups at weaning. On PND 12-14 or at adult necropsy **retained areolas** and/or nipples were apparent in males at 250 mg/kg bw/d and their incidence increased with dose. No such effects were observed in animals from vehicle controls or the 125mg/ kg bw(d treated group. Acquisition of preputial separation (PPS) was delayed by approximately 4 days at 500 mg/ kg bw/d. Evaluation of PPS was precluded in half of the males at the high dose by presence of hypospadias. Mature males displayed **severe malformations** (hypospadias with exposed os penis in the more severely affected animals, and non-scrotal testis) at the two high doses. **Non-descended testes** were always located in the inguinal or supra-inguinal area; none were in the intra-abdominal position. Markedly underdeveloped (less than 10% of control weight) or absent testes and/or epididymes were seen in 2%, 16% (7 males	Based on these observations a NOAEL /developmental toxicity could not be determined. Therefore, a LOAEL /developmental toxicity of 125 mg DIBP/kg bw/day can be derived from this study.	Saillenfait et al., 2008

	from 5 litters), and 13% (5 males from 4 litters) of the animals in the 250, 500 and 625 mg/kg bw/d dose groups. At sacrifice (PND 76-86, resp. PND 111-122) **organ weights of the testes, epididymes, seminal vesicles and prostate** were significantly reduced (with or without body weight as covariate) at 500 and 625 mg/ kg bw/d. These reductions amounted to 39-59% for the testes and the epididymes, and 28-33% for the seminal vesicles and the prostate. **Histological examinations** revealed testicular damage in all DIBP treated groups with moderate or severe degeneration of seminiferous tubules (including Sertoli cell only tubules). The lesions were uni- or bilateral and associated with oligospermia or total azoospermia in the corresponding epididymides.		

4.11.1 Effects on fertility

Not relevant for this dossier.

4.11.2 Developmental toxicity

4.11.2.1 Non-human information

Saillenfait et al., 2006

In a guideline according prenatal toxicity study on Sprague-Dawley rats, DIBP was administered to pregnant animals (23-24 animals per treatment group) by gavage at doses of 0 (olive oil), 250, 500, 750 and 1000 mg/kg bw/d on GD 6-20 (Saillenfait et al., 2006). An endpoint included in addition to TG 414 was determination of the degree of transabdominal testicular migration (TTM). There were no maternal deaths. Signs of transient maternal toxicity were observed, as evidenced by significant reduction in body weight gain, at the beginning of treatment (GD 6-9) at 500 mg/kg bw/d and higher doses, however, overall weight gain corrected for gravid uterus was not different from controls at the end of gestation. No treatment related efffects were observed for maternal food consumption, pregnancy rate or number of implantations. The incidences of resorptions were statistically significantly increased to 28% at 750 mg/kg bw/d and to 59% at 1000 mg/kg bw/d. Mean fetal body weight was statistically significantly reduced at 500 mg/kg/d and higher doses amounting to a decrease of 24% -26% at 1000 mg/kg/d in comparison to controls. The incidence of total external malformations (neural tube closure defects, anophthalmia) and of total visceral malformations (urinary tract and vascular defects) was signifanctly increased at 750 and 1000 mg/kg bw/d. Skeletal evaluations revealed malformations primarily of the axial column with the incidences of fused sternebrae statistically significantly increased at 750 and 1000 mg/kg bw/d and

variations (delayed ossification and supernumerary ribs) at 750 and 1000 mg/kg bw/d with supernumerary ribs in 95% of the fetuses of the 1000 mg/kg group. Visceral variations involved mainly the urinary tract with statistically significantly increased incidences of ureter variations in the 1000 mg/kg group and the male reproductive system. Unilateral or bilateral undescended testes occurred at 500 mg/kg/d and was significantly increased at 750 mg/kg/d (in 30/55 male fetuses and in 16/20 litters) and at 1000 mg/kg bw/d (in 30/34 male fetuses and in 16/17 litters). In addition the degree of transabdominal descent was significantly impaired at 500 mg/kg/d with about two third of the testes located in the upper half of the abdominal cavity at the 1000 mg/kg dose group. Thus, it appeared that alterations of the male reproductive system occurred at lower doses than those producing structural malformations/variations and embryotoxicity. No evidence of embryo or fetal effects was found at the 250 mg/kg dose level. Therefore, a NOAEL/developmental toxicity of 250 mg/kg/d can be derived from the study.

The following endpoints have been evaluated for ED10 values according to the guidance on the application of the CLP criteria (Version 3.0, November 2012): external malformations (per litter/per fetus), visceral malformations (per litter/per fetus), skeletal malformations (per litter/per fetus), post-implantation loss per litter and fetal weight. Calculation on all endpoints but skeletal malformations per litter yielded in ED10 values > 400 mg/kg. Data for skeletal malformations are presented in the following table:

Table 12: Malformations in Rats treated with DIBP (Saillenfait et al., 2006)

Dose (mg/kg bw/d)	**0**	**250**	**500**	**750**	**1000**
Total number of fetuses (%) with skeletal malformations	0	0	4 (3.4)	18(17.0)**	34(61.8)**
Total number of litters (%) with skeletal malformations	0	0	4 (19.0)	11(52.4)**	15(83,3)**

** Significant difference from the vehicle control, p<0.01, Fisher´s test.

Determination of ED10 value

Per fetus

Control malformation rate is 0%. ED10 rate would be 10%.

Calculation: Interpolation between 500 mg/kg bw/d (3.4%) and 750 mg/kg bw (17.0%) leads to an ED10 of 621 mg/kg bw/d.

(750 - 500) / (17 – 3.4) = 18.4 mg/kg per % (steepness). Going form 3.4% to 10% requires addition of 6.6%. This equals 6.6% * 18.4 mg/kg per% = 121 plus 500 as the starting point = **621 mg/kg** bw/d.

Per litter

Control malformation rate is 0%. ED10 rate would be 10%.

Calculation: Interpolation between 250 mg/kg bw/d (0%) and 500 mg/kg bw (19.0%) leads to an ED10 of 382 mg/kg bw/d.

(500 - 250) / (19 – 0) = 13.2 mg/kg per % (steepness). Going form 0% to 10% requires addition of 10%. This equals 10% * 13.2 mg/kg per% = 132 plus 250 as the starting point = **382 mg/kg bw/d**.

The results clearly show that the evaluation on litter base is more sensitive and therefore the value of 382 mg/kg bw/d was used for further calculations. Based on the evaluation per litter, the preliminary potency group is medium. Further evaluations take place at 4.11.5.

Saillenfait et al., 2008

In a study on Sprague-Dawley rats, which was performed to determine whether in utero exposure to DIBP would induce permanent and dose-responsive alterations of male reproductive development, DIBP was administered to pregnant animals (11-13 animals per treatment group) by gavage at doses of 0 (olive oil), 125, 250, 500, and 650 mg/kg bw/d on GD 12-21 (Saillenfait et al., 2008). Doses were based on an unpublished preliminary study in which 625 mg DIBP/(kg day) on GD 12-21 caused reproductive tract malformations in male offspring and had no effects on litter size or pup survival. Litters of the definite study were examined as soon as possible after birth to determine the number of viable and stillborn pups. Pup body weights were recorded on PND 1, 4, 7, 14 and 21. AGD was measured on PND1 and litters culled to 10 pups on PND 4. All pups were examined for the presence of areola and/or nipples on the ventral surface of the thorax on PND 12-14. At weaning on PND 21 three to four male pups from each litter were randomly selected and retained and unselected pups sacrificed and submitted to internal examination. After weaning the dams were sacrificed and the number of implantations recorded from their uteri. All retained males were examined for preputial separation (PPS) and individual body weights recorded at acquisition. Adult males were necropsied on PND 76-86 (two males in each litter) or on PND 111-122 (the remaining males in each litter). They were examined for the presence of areolas and/or nipples on the ventral surface of the thorax, for gross abnormalities of external and internal genitalia, and for position of testes. Testes, epididymides, seminal vesicles (with the coagulating glands and seminal fluid), and prostate were weighed. Histopathology was conducted on testes and epididymides of all DIBP animals necropsied on PND 76-88. No differences in maternal body weight gain were observed between the controls and the treatment groups. All dams delivered live pups. Post-DIBP implantation loss, litter size, sex ratio, and pup survival to PND 4 and PND 21 were unaffected by treatment. AGD measured on PND 1 was dose-dependently significantly reduced in male pups from 250 mg DIBP/(kg day) to the higher doses with or without adjustment for body weight. The decrease amounted to 11% at 250 mg DIBP/(kg day) and 22% at 625 mg DIBP/(kg day), compared to controls. AGD of females was not affected at any dose. Pup body weight at PND 1 of both sexes was statistically significantly decreased at 625 mg DIBP/(kg day), and remained lower in comparison to controls in the male pups at weaning. During the post weaning period mean body weights of the offspring were lower than controls at 500 and 625 mg DIBP/(kg day) (6-8% and 10-12%, respectively). On PND 12-14 or at adult necropsy retained areolas and/or nipples were apparent in males at 250 mg DIBP/(kg day) and their incidence increased with dose. No such effects were observed in animals from vehicle controls or the 125 mg DIBP/(kg day) treated group. Acquisition of PPS was delayed by approximately 4 days at 500 mg DIBP/(kg day). Evaluation of PPS was precluded in half of the males at the high dose by presence of hypospadias. Mature males displayed severe malformations (hypospadias with exposed os penis in the more severely affected animals, and non-scrotal testis) at the two high doses. Non-descended testes were always located in the inguinal or supra-inguinal area; none were in the intra-abdominal position. Markedly underdeveloped (less than 10% of control weight) or absent testes and/or epididymes were seen in 2%, 16% (7 males from 5 litters), and 13% (5 males from 4 litters) of the animals in the 250, 500 and 625 mg /(kg day) dose groups. At sacrifice (PND 76-86, resp. PND 111-122) absolute organ weights of the testes, epididymes, seminal vesicles and prostate were significantly reduced (with or

without body weight as covariate) at 500 and 625 mg DIBP/(kg day). These reductions amounted to 39-59% for the testes and the epididymes, and 28-33% for the seminal vesicles and the prostate. Histological examinations revealed testicular damage in all DIBP treated groups with moderate or severe degeneration of seminiferous tubules (including Sertoli cell only tubules). The lesions were uni- or bilateral and associated with oligospermia or total azoospermia in the corresponding epididymides. Based on these observations a NOAEL/developmental toxicity could not be determined. Therefore, a LOAEL/developmental toxicity of 125 mg DIBP/kg bw/day can be derived from this study.

The following endpoints have been evaluated for ED10 values according to the guidance on the application of the CLP criteria: hypogenesis or agenesis of testes, reduced organ weights of reproductive organs, anogenital distance at PND 1, age at preputial separation and dose-related retention of nipples at PND 12-14.
Due to the low numbers of moderately affected testes (according to the new criteria) and sufficient endpoints for ED10 calculations no evaluations of histopathology were performed. Hypgenesis or agenesis of testes and reduced organ weights, except for prostate (PNW 11-12), yielded in ED10 values close to 400 mg/kg bw/d and above. Calculations on preputial separation did not yield an ED10 value. All other data are presented in the following table:

Table 13: Effects of prenatal DIBP treatment in rats (Saillenfait et al., 2008)

Dose (mg/kg bw/d)	**0**	**125**	**250**	**500**	**625**
Male anogenital distance PND 1 (mm)	2.55±0.17	2.44±0.15	2.28±0.30*	2.02±0.13**	1.98±0.16**
Incidence of males with thoracic areolas and/or nipples at PND 12-14.	0%	0%	8.3%	59.5%	73.7%
Prostate weight PNW 11-12 (g)	0.80±0.14	0.72±0.14	0.71±0.10*	0.67±0.11**	0.56±0.13**

* and **, significantly different from control group, $p<0.05$ and $p<0.01$, respectively (Mann-Whitney test)

Calculation male anogential distance (AGD) at PND 1

Control AGD is 2.55 mm. A 10% reduction of the control value of 2.55 gives 2.30 mm.

Calculation: Interpolation between 125 mg/kg bw/d (2.44 mm) and 250 mg/kg bw (2.28 mm) leads to an ED10 of 234 mg/kg bw/d.

(250 - 125) / (2.44 – 2.28) = 781 mg/kg per mm (steepness).
Difference of 2.44 mm and 2.3 mm yields 0.14 mm. This equals 0.14 * 781 mg/kg per mm = 109 plus 125 as the starting point = **234 mg/kg** bw/d.

Calculation incidence of males with thoracic areolas and/or nipples at PND 12-14

Control incidence of males with thoracic areolas and/or nipples at PND 12-14 is 0%. ED10 rate would be 10%.

Calculation: Interpolation between 250 mg/kg bw/d (8.3%) and 500 mg/kg bw (59.5%) leads to an ED10 of 258 mg/kg bw/d.

(500 - 250) / (59.5 – 8.3) = 4.9 mg/kg per % (steepness).
Going form 8.3% to 10% requires addition of 1.7%. This equals 1.7% * 4.9 mg/kg per % = 8,1 plus 250 as the starting point = **258 mg/kg** bw/d.

Calculation of prostate weight at PNW 11-12

Control prostate at PNW 11-12 is 0.80 g. A 10% reduction of the control value of 0.8 gives 0.72 g.

At **125 mg/kg** bw/d the prostate weight amounts precisely to 0.72 g and therefore the dose represents the ED10.

4.11.2.2 Human information

In the attempt to explore whether prenatal exposure to phthalates would be reflected in postnatal performance of genital parameters concentrations of 11 maternal urinary phthalate monoesters were determined in spot urine samples taken prenatally during pregnancy and associated to parameters such as anogenital index (AGI) – a biomarker suspected to be indicative of androgen action also in humans - and testicular descent in the male infants in a cohort of 85 mother-son pairs (Swan et al., 2005). In this investigation maternal urinary MIBP concentration was found to be inversely related to AGI, and that in general the boys classified as having a short AGI (AGI below 25th percentile for age) also had a higher prevalence of concomitant cryptorchidism. Although of limited value, due to the small number of subjects (n=85) and to other shortcomings (e.g., concentrations of phthalate metabolites in spot urine samples may not be representative for and adequately reflect maternal exposure during pregnancy), data of this study may support the hypothesis that prenatal phthalate exposure at environmental levels may affect male reproductive development also in humans. It should be noted, in addition, that little is known on the normal variation of AGD in human infants to adequately interpret the findings on AGI values lower than expected and that any long-term clinical implications of a shorter than expected AGD in humans has not yet been revealed.

4.11.3 Other relevant information

4.11.4 Summary and discussion of reproductive toxicity

The toxicity of diisobutyl phthalate on reproduction is well described and led to the classification as Repr. 1B in 2006 and to the identification as a substance of very high concern in 2010.

4.11.5 Comparison with criteria

The results of the ED10 calculations above are compiled in the following table. The medium potency group ranges from 4 mg/kg bw/d to <400 mg/kg bw/d according to the guidance on the application of the CLP criteria (Version 3.0, November 2012).

Table 14: Compilation of sensitive endpoints for preliminary potency evaluation.

Endpoint	ED10 in mg/kg bw/d	Reference
Total number of litters with skeletal malformations	382	Saillenfait et al., 2006
Male anogenital distance PND 1 (mm)	234	Saillenfait et al., 2008
Incidence of males with thoracic areolas and/or nipples at PND 12-14	258	Saillenfait et al., 2008
Prostate weight at PNW 11-12	125	Saillenfait et al., 2008

One of the endpoints (skeletal malformations on litter base) is close to the boundary of the medium potency group. However, the three remaining endpoints are more or less in the middle of the medium potency group.

The guidance on the application of the CLP criteria recommends the consideration of several elements that may modify the preliminary potency evaluation:

Dose-response relationship

Not relevant as ED10 is not borderline.

Type of effect / severity

Skeletal malformations can be judged as severe effects. Additionally, the effects on male animals such as reduced anogenital distance and incidence of thoracic areolas and/or nipples can be judged as severe effects.

Data availability

Not relevant. Two studies are available with sufficient doses and animals per dose.

Mode of action

The mechanism (antiandrogen activity) is considered relevant to humans.

Toxicokinetics

Not relevant.

Bio-accumulation

There is no evidence for bioaccumulation of diisobutylphthalate and therefore no reason for modification of the potency group.

The evaluation of the modifying elements gives neither reason for a change to the low potency nor to the high potency group. According to the new guidance on the application of the CLP criteria, diisobutylphthalate qualifies for the medium potency group with three ED10 values in the range of 125 to 382 mg/kg bw/d.

4.11.6 Conclusions on classification and labelling

Diisobutylphthalate has been classified Repr. 1B in 2006. The evaluation of the potency yielded a classification of medium potency group as explained in this dossier.

According to the new guidance on the application of the CLP criteria, these results lead to a SCL for diisobutylphthalate of ≥ 0.3%, which corresponds to the generic concentration limit. The current SCL of ≥ 25% is not valid anymore.

RAC evaluation of reproductive toxicity

Summary of the Dossier submitter's proposal

Diisobutyl phthalate (DIBP) has an existing entry in Annex VI to the CLP Regulation, as Repr. 1B; H360Df: C ≥ 25 % and Repr. 2; H361f: 5 % ≤ C < 25 %. However, the specific concentration limit (SCL) which is currently on Annex VI is based on an outdated method, whereas a new method has meanwhile been agreed in ECHA's Guidance on the Application of the CLP Criteria, (Version 4, November 2013). The dossier submitter's proposal is for removal of the SCL from Annex VI.

The dossier submitter (DS) referred to two studies in rats, one prenatal development and one post natal development study. The grounds for classification were not challenged by the DS. Adverse effects on development were seen in both studies, which were not deemed to be caused by secondary, non-specific toxic effects.

The DS calculated an ED_{10} value for the most sensitive adverse effects observed and found them to range from 125 mg/kg/day to 382 mg/kg/day. Thus the calculated ED_{10} values were between 4 and 400 mg/kg/day, i.e. in the range of medium potency substances.

The DS also evaluated possible modifying factors and concluded that there were no relevant modifying factors to be taken into account.

The DS concluded that an SCL for this substance is not warranted, but that instead the Generic concentration limit (GCL) of 0.3% should apply.

Comments received during public consultation

Four MSCAs were in support of the proposal, while some others raised specific comments.
Two MSCA requested consideration and justification of the removal of the SCL for fertility.
One MSCA questioned whether the presence of an increased number of thoracic areolae and nipples itself should be considered a sufficiently severe effect for ED_{10} calculation, but recognised that it is considered an important indicator of hormone disruption which results in adverse effects.
Another MSCA proposed also considering the testicular findings, to which the DS agreed. The response and additional data provided by the DS in response to the comment can be found in the Background Document (BD).

The ED_{10} value calculated based on the additional data was also within the range of those presented in the CLH report.

Assessment and comparison with the classification criteria

Considerations about an SCL for developmental effects

Two key developmental toxicity studies performed in rats by the oral route were included by the DS in the analyses to support the removal of SCL (Saillenfait, 2006; Saillenfait, 2008). RAC agrees with the justification of the DS for the exclusion of three other developmental toxicity studies based on an insufficient number of animals (5-8 by treatment group) and/or use of a

single treatment group that does not allow a robust calculation of the ED_{10}.
For each of the two key studies, the DS calculated the ED_{10} values for the most sensitive parameters by linear interpolation, in accordance with the ECHA guidance for setting SCL.
According to CLP Guidance, the ED_{10} value is the lowest dose which induces reproductive toxic effects fulfilling the criteria for classification for reproductive toxicity with an incidence or magnitude of 10% after correction for the spontaneous incidence.

In the study by Saillenfait (2006), DIBP induced a decrease in fetal body weight and increased incidences of resorptions as well as external, visceral and skeletal malformations. ED_{10} values were not calculated in the CLH report for each effect. However, the analysis of the dose-response relationship (see table 1 below) for the different adverse effects as well as for the visceral variation undescended testes (consistent with impairment of the male reproductive development) confirms the conclusion of the DS that the most sensitive effect in this study for ED_{10} calculation is induction of skeletal malformations on a litter basis.
The ED_{10} for skeletal malformations is **382 mg/kg** on a litter basis while ED_{10} values for other effects exceed the upper boundary of 400 mg/kg for medium potency.

Table 1 – dose response of developmental effects in Saillenfait (2006)

Dose (mg/kg)	0	250	500	750	1000	ED_{10}[a]
% post-implant. loss per litter	6.7±7.6%	11.0±23.6%	13.9±20.9%	28.2±18.9%*	59.6±21.5%*	$500<ED_{10}<750$
Fetal body weight (g)	5.71±0.28	5.69±0.33	5.31±0.40*	4.72±0.33*	4.32±0.35*	$500<ED_{10}<750$
% fetuses with external malf.	0	0	0	2.4%	5.4%	> 1000
% litters with external malf.	0	0	0	19%	22.2%	$500<ED_{10}<750$
% fetuses with visceral malf.	0	1.4%	1.7%	12.3%	17.9%	$500<ED_{10}<750$
% litters with visceral malf.	0	4.8%	9.5%	38.1%	44.4%	$500<ED_{10}<750$
% male fetuses with testis, ectopic	0	0	5.5%	54%	88%	$500<ED_{10}<750$
% litters with testis, ectopic	0	0	9%	76%	88%	$500<ED_{10}<750$
% fetuses with skeletal malf.	0	0	3.4%	17.0%	61.8%	621
% litters with skeletal malf.	0	0	19.0%	52.4%	83.3%	**382**

*statistically significant

[a] calculated by DS or estimated by RAC

In the study by Saillenfait (2008), in male pups DIBP induced a decrease in body weight, a decrease in absolute and relative anogenital distance (AGD) at PND 1, retention of thoracic areolae and/or nipples and a delay of the onset of puberty (preputial separation (PPS)). At postnatal week 11-12 or 16-17, mature males displayed severe malformations of the reproductive tract and underdeveloped reproductive organs, with hypospadias, unilateral undescended testes and decrease in prostate weight (post-natal week 11-12) being the most sensitive effets. Histological examination revealed oligo/azoospermia in the epididymides and tubular degeneration and necrosis in the testes.
The analysis of the dose-response (see table 2 below) for the most sensitive effects confirms the conclusion of the DS that the lowest ED_{10} in this study is **125 mg/kg** based on decreased prostate weights in mature males and corresponds to medium potency (i.e. boundaries: 4 mg/kg bw/day < ED_{10} value < 400 mg/kg bw/day).
This is further supported by ED_{10} values for decreased AGD, retention of areolas, azoospermia

in epidydimides and tubular degeneration/atrophy, which are also in the range 4-400 mg/kg and therefore considered as medium potency.
For the decrease in AGD, RAC notes that a more appropriate assessment of potency should be based on a percentage of feminisation relative to an AGD in control females, representing 100% feminisation. This is however not considered to impact on the overall assessment of the developmental potency of DIBP.

Table 2 – dose response of developmental effects in Saillenfait (2008)

Dose (mg/kg)	0	125	250	500	625	ED_{10} [a]
Male pup body weight PND1 (g)	7.19±0.71	7.10±0.70	7.04±0.43	7.03±0.53	6.45±0.60*	500<ED_{10}<625
Male AGD at PND 1 (mm)	2.55±0.17	2.44±0.15	2.28±0.30*	2.02±0.13**	1.98±0.16**	**234**
Incidence of males with thoracic areolae and/or nipples at PNW 12-14.	0%	0%	8.3%	59.5%	73.7%	**258**
Mean litter age at PPS (days)	46.9±1.5	45.1±1.6*	46.3±1.8	51.5±3.1*	49.8±3.2*	Not appropriate
Incidence of hypospadias in adult males	0%	0%	0%	11%	56%	Approx. 500 mg/kg

*statistically significant

[a] calculated by DS or estimated by RAC
[b] Calculated by RAC by interpolation between 250 mg/kg (3.6%) and 500 mg/kg (13.7%):
(500-250) / (13.7-3.6) = 25 mg/kg / % (steepness)
Note: the difference between 3.6 and 10% is +6.4%. This equals to 6.4*25= 160 plus 250 as the starting point = 410 mg/kg.

Overall, the most sensitive ED_{10} values derived by the DS and agreed by RAC correspond to the medium potency group (i.e. boundaries: 4 mg/kg bw/day < ED_{10} value < 400 mg/kg bw/day) for DIBP.

Modifying Factors

According to the CLP Guidance (section 3.7.2.5.5), modifying factors should also be considered when deriving an SCL. The modifying factors include type and severity of the effect observed, data availability (e.g. limitations in the database), dose-response relationship, mode or mechanism of action, toxicokinetics and bioaccumulation of substances. These modifying factors are used to account for case-specific data situations which indicate that the potency group for a substance, as obtained by the preliminary assessment, should be changed. The modifying factors were assessed for DIBP as follows:

Dose-response relationship:
No adaptations of the potency group are considered necessary on this basis, as most calculated ED_{10} values were not borderline.

Type and severity of the effect:
The type of effects observed in reproductive toxicity studies following exposure to DIBP included malformations. These are considered as severe and do not change the potency group.

Data availability:
The available data for DIBP were considered as adequate and do not justify adaptation of the potency group.

Mode or mechanism of action:

The mechanism of action of DIBP (antiandrogen activity) is considered relevant for humans. Therefore adaptation of the potency group is not necessary.

Toxicokinetics:
No toxicokinetic data are presented in the CLH report. It is noted that RAC concluded in its opinion on a proposal to restrict four phthalates including DIBP[2] that the available data do not allow a conclusion to be drawn on whether humans are less, equally or more sensitive than rats. No adaption to the potency group is therefore justified.

Bio-accumulation of substance:
No evidence for bioaccumulation is presented in the dossier and adaptation of the potency group is not necessary.

Conclusion on modifying factors:
Based on the available data, RAC considers that the consideration of possible modifying factors does not affect the potency of DIBP.

Therefore, DIBP is considered to be a medium potency reproductive toxicant for developmental toxicity and RAC agrees that according to CLP Guidance table 3.7.2-e, the GCL of 0.3% should be applied for DIBP developmental toxicity and the current SCL of 25% should be removed.

Considerations about an SCL for fertility effects

No specific justification for the removal of the SCL for fertility was given in the CLH report. The DS concludes that the application of a GCL for developmental toxicity (Repr. 1B at concentration > 0.3%) would be inconsistent with an SCL of 5% for fertility. However, the CLP guidance states in section 3.7.2.5.6.1 that "*The potency and resulting concentration limits have to be determined separately for the two main types of reproductive toxic effects. [...] These concentration limits will in all cases trigger different specifications of the hazard statements for the two main types of effects, to be applied to mixtures containing the substance.*"

RAC therefore concludes that although classification as Repr. 1B will apply from 0.3%, as a consequence of the removal of the SCL for development, the existing SCL for fertility has implications for the labelling specifications and its removal needs to be justified.

RAC notes that only SCLs for developmental toxicity were agreed by TC C&L during the last discussions on DIBP and no SCL for fertility was introduced in the Dangerous Substance Directive (DSD). The current SCL for fertility corresponds to the previous GCL under the DSD. Their introduction in the 1st ATP of CLP most probably results from a translation mistake from DSD to CLP and therefore their removal is justified.

As a supportive element, RAC notes that although fertility has not been thoroughly evaluated in the present CLH report, the data presented demonstrate that the male reproductive tract is a target for DIBP, with medium potency, during its development. Several of the most sensitive calculated developmental ED_{10} values involve effects on the developing male reproductive tract. In particular, the ED_{10} for decreased prostate weight, azoospermia in epidydimides and tubular degeneration/atrophy (Saillenfait, 2008) are in the range of 4-400 mg/kg defining medium potency and do not support the existing SCL of 5% for fertility.

[2] Opinion of the Committee for Risk Assessment (RAC) on an Annex XV dossier proposing restrictions on four phthalates. Adopted on 15 June 2012. ECHA/RAC/RES-O-0000001412-86-07/F

Therefore, RAC considers that the GCL of 3% should be applied for fertility classification of DIBP and the current SCL of 5% should be removed.

4.12 Other effects

Not relevant for this dossier.

5 ENVIRONMENTAL HAZARD ASSESSMENT

Not relevant for this dossier.

6 OTHER INFORMATION

No other information available.

7 REFERENCES

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8 ANNEXES

Confidential Annex