Ms Joanne MAK

LEGCO

Hong Kong.

Dear Sir,

PROPOSED LEGISLATION ON PHTHALATES (TOYS AND CHILDREN'S PRODUCTS SAFETY (AMMENDMENT BILL) 2013

I writing to you in my personal capacity to express my concern regarding aspects of the proposed legislation. I am an academic scientist, who has been involved with the toxicology of phthalates for many years both as a researcher and as the Chair of two EU Scientific Advisory committees to DG SANCO, firstly the Committee on Toxicity, Ecotoxicity and the Environment (1996-2004) and the Committee on Emerging and Newly Identified Health Risks (2004-2013) – see attached short CV.

There are two issues in the proposed legislation that I would like to draw your attention to:

i) The proposed grouping of lower molecular weight and higher molecular weight phthalates together as a single category.

The toxicological data, which is extensive and for di-Isonylphthalate (DIDP) and di-Isodecylphthalate (DINP) is summarized in the appendices to this letter is very extensive. It is clearly different from that of the lower molecular weight phthalates, such as di-Butylphthalate(DBP), Bis(2-iethylhexyl) phthalate (DEHP) and, Butylbenzenephthalate (BBP). This is clear from the attached table (Table1). I note that one of the reasons for your proposed action is to bring your legislation in line with that of legislation elsewhere. The following is therefore relevant to your deliberations.

In 2005 the European Food Safety Authority (EFSA) was asked to consider whether a group tolerated daily intake (TDI) could be assigned to all the low and high molecular weight phthalates. Their conclusion was as follows: 'While

it may appear that DBP, DEHP and BBP act on the same target organ, 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 other two DINP and DIDP primarily affect the liver rather than the testis. But even in this the end points indicate that different mechanisms are involved. Consequently, a group TDI cannot be allocated for all these phthalates. This statement which is based on the toxicology data is supported by publications since 2005.

EU regulation by REACH of these chemicals also shows a quite separate treatment of lower and higher molecular weight phthalates. Di-Butylphthalate (DBP), Bis(2-ethylhexyl phthalate (DEHP) and Butylbenzenephthalate (BBP) are classified as hazardous (Category 1B for CMR's). di-Isononylphthalate (DINP) and di-Isodecylphthalate are not classified as hazardous due to the absence of CMR properties. I note that the Australian Authorities in 2012 (NICNAS) who have examined child exposure to DINP did not identify a health concern even at the highest (very conservative) exposure scenarios.

It should be concluded therefore that the risks to young children from mouthing toys and other objects are very low in the case of DINP and DIDP. For the lower MW phthalates the risk is clearly higher.

ii) <u>The availability of safer replacements if the ban is enacted</u>

A further consideration that needs to be addressed, prior to legislative action is what are the proposed replacements and what is the evidence that the replacement will produce advantages from a health view point over DINP and DIDP? The SCENIHR (which I chaired) reviewed phthalates in medical devices (where exposure of patients including very young children is order of magnitude higher than from chewing toys or other objects) concluded in it opinion SCENIHR, 2008) that at that time no suitable alternative to phthalates could be identified. This is currently under review by the SCENIHR.

I would be very happy to discuss these issues with you further or provide additional scientific data to assist you in your very important decision.

Yours sincerely

Professor Jim Bridges Emeritus Professor of Toxicology and Environmental Health, University of Surrey, UK.

APPENDICES

1. COMPARISON OF THE PROPERTIES OF VARIOUS PHTHALATES

All five of these phthalates has a very rich toxicological data base, far greater than the vast majority of chemicals to which children are exposed regularly. The toxicological profile for the five phthalates is summarized in the attached table. I am happy to provide details for dibutyl, diethyl hexyl and butylbenzene if this would be helpful. Since my concern is their grouping with DINP and DIDP I have set out a summary of DINP and DIDP toxicology in appendix 2.

Table 1 Comparison of NOEL/LOELs for different phthalates

Phthalate	**Lead effect**	**Threshold value for effect mg/kg/body weight/day**	**Reference**
Dibutyl	Reproduction-germ cell development	LOAEL 2mg	Lee 2004
Diethylhexyl	Reproduction-germ cell depletion -reduction in testes weight	NOEL 5mg	Wolfe and Leyton 2003
Butylbenzene	Reproduction: epididymal spermatozoa concentration -anogenital distance	NOAEL 20mg NOAEL 50mg	NTP 1997 Tyi *et al* 2004
Diisononyl	Liver and kidney: Spongiosis hepatis	NOAEL 88mg	ARISTECH/EXXON

	Reproduction: Transitory changes in testosterone and gonocytes		Clewell 2012
Diisodecyl	Liver: Spongiosis hepatis Reproduction: Offspring survival D 1-4	NOAEL 88 mg	ARISTECH/EXXON Huska *et a*l 2001

2. MORE DETAILS OF THE TOXICOLOGY OF DINP AND DIDP

Table. 2 Summary of the risk assessment issues for DINP and DIDP

Parameter	**Risk assessment conclusion**
2.Identification of a NOAEL for RA purposes based on spongiosis hepatis for DINP	Data for the two key studies should be combined *Relevant value 88mg/kg body weight per day*
3. Identification of a NOAEL for RA purposes DIDP based on possible SH as the lead effect	Data limited. Utilize same NOAEL for DIDP as for DINP
4. relevance of reproduction endpoints	Uncertain because of the relevance of rat data to

for man	man and the transitory nature of effects
5.Identification of a NOAEL based on reproduction endpoints DINP	Testosterone levels and gonocyte numbers . 50mg/kg body weight/day
6. Identification of a NOAEL based on reproduction for DIDP	Reduced viability for PND . 33mg/kg body weight/day

FINDINGS FROM LIFE TIME STUDIES

Overview of the chronic /lifetime toxicity data on DINP

Spongiosis hepatis

The observed spongiosis hepatis in male rats :

i) had a high incidence in control animals.

ii) showed an increased incidence but not an increased severity at higher doses and was not associated with any other serious lesions.

iii) Only occurred in ageing male rats and was not found in a life time study in mice nor in shorter term studies in dogs or monkeys.

These factors raise serious doubts regarding the relevance of spongiosis hepatis as a critical endpoint for the assessment of human health risks from DINP exposure. These doubts are greatly strengthened by the classical text book on human liver pathology (McSween *et al* 2002) that there is no comparable human liver lesion to spongiosis hepatis in the rat. The nearest comparable lesion in man is peliosis hepatis which has been found to occur in humans following chronic use of certain drugs. It can be concluded that there

is no equivalent ageing disease in human liver to spongiosis hepatis.

Nonetheless there is as yet an insufficient mechanistic basis to exclude the possibility that a spongiosis hepatis like lesion could be caused by chronic exposure to a chemical in humans.

The uncertainty in this evaluation lies in the possibility that a spongiosis like lesion could occur in humans following life time exposure despite the fact that the sole model for this is the ageing male rat. The degree of uncertainty based on all the available evidence is however small. If as a conservative approach Spongiosis hepatis is accepted as the lead effect then is to define a valid NOAEL. The Exxon and Aristech studies have different dose regimens. In the Exxon study the doses were : 300ppm (15 mg/kg body weight) , 3000 (152 mg /kg body weight per day) and 6000 ppm (307 mg /kg body weight per day). In the Aristech study the doses were 0, 500 (29mg/kg body weight per day), 1500 (88.3 mg/kg body weight per day), 6000 (359 mg/kg body weight per day) and 12000ppm (733 mg/kg body weight per day). At 152 mg/kg body weight per day in the Exxon study and at 359 mg/kg body weight per day in the Aristech study an increased incidence of spongiosis hepatis was observed, with corresponding NOAELs of 15 mg/kg/ body weight per day and 88.3 mg/kg body weight per day. Thus a likely reason for the differences in the NOAEL values for spongiosis hepatis is the different dose spacing in the two key studies.

Overview of the chronic /lifetime toxicity data on DIDP

Using a weight of evidence approach, the data on DIDP has to be regarded as providing a poor basis for a risk assessment as each of the studies conducted raises concerns regarding the adequacy of the methodology. The estimated NOAEL in the Cho *et al* (2008, corrected 2010) study relies on spongiosis hepatis as the critical effect which is not recognized by the authors as significant and as noted for DINP therefore spongiosis hepatis is unsound as a basis to extrapolated from rats to man. A valid approach is to use the DINP data as the basis for the selection of the NOAEL. Bearing in mind the very close structural similarity and the much stronger data base this is a more valid approach. As noted above on this basis a BMD 10 of 72.4 mg/kg body weight or a NOAEL of 88mg/kg body weight should be used.

REPRODUCTION STUDIES

DINP

Much more sensitive tests have been used for both DINP and DIDP than the conventional ones because of the evidence that some lower molecular weight phthalates do have effects on the reproductive organs.Though modifications of testosterone levels have been observed in several studies following exposure of pregnant rats to DINP, the changes appear to be transitory and there is even (at high doses) very limited indication of reproductive toxicity. A weight of evidence evaluation provides no evidence that DINP causes low incidences of the permanent effects observed with short chain phthalates that are associated with androgen deficiency. Consequently, DINP does not meet the criteria for an endocrine disrupter.

From a risk assessment perspective the following four issues need to be considered:

- The relevance of any effects on the developing foetus/ new born at dose levels that produce maternal toxicity;
- The validity of using read -across from lower chain length phthalates to fill any data gaps for DINP and DIDP;
-The relationship of changes in testosterone levels to endpoints of clear adverse effects. This includes whether they are permanent or of a transitory nature;
- The basis for the extrapolation of findings in rats to man and to the developing human foetus in particular.

The weight of evidence identifies that at doses of 750 mg/kg body weight per day and above maternal toxicity occurs. This is likely to result in changes in the physiological environment of the foetus. Effects observed at doses of this order and above need to be evaluated with great caution. Changes in testosterone levels and multinucleated gonocytes in the testes, if substantial and persistent are of concern. Transitory changes, in the absence of any prolonged adverse effects, should not necessarily be regarded as adverse rather as an indicator that there is a perturbation which the body is

able to adjust to. A barrier to further interpretation is that the variability of testes testosterone and multinucleated gonocyte levels between individual animals and at different times in control rats is not yet characterized sufficiently. It is not clear how such changes relate to the other transitory effects observed at higher exposure levels such as changes in anogenital distance, Leydig cell aggregates and multinucleated gonocyte numbers.

A critical consideration is the validity of the rat for the purposes of human risk assessment. Studies in mice, exposed to DINP, indicate a considerably lower sensitivity than in rats. Moreover, it was shown that mice and marmosets are less sensitive than rats to DBP. An important recent study using xenographs confirms that, in this model, mice are much less sensitive than rats. Importantly, the same study indicates that humans are more like mice in the responsiveness of the foetal testis to phthalates as far as steroidogenesis is concerned. The available data indicates that effects on gonocytes should be the favoured endpoint for risk assessment purposes, not changes in testosterone production or levels.

A conservative approach for risk assessment purposes would be to set an NOAEL of 50 mg/kg body weight per day. This is based on changes in multinucleated gonocytes at 250mg/kg body weight per day. It should be noted, however, that:

- The interpretation of such a short-lived change as adverse is questionable.
- It is a more sensitive endpoint than those traditionally used to examine for reproductive effects.

DIDP

The data base for DIDP is adequate for risk assessment purposes. Based on the Hushka *et al* study a NOAEL of 33 mg/kg body weight per day derived from the LOAEL value may be used for DIDP. It is noted that this is similar to that identified for DINP of 50mg/kg body weight per day using other parameters to estimate the NOAEL. Bearing in mind the structural similarity between the two phthalates the DINP and DIDP, findings might be regarded as mutually supportive. However, it is not clear why there are apparent differences in rats between DINP and DIDP in:

- Effects on testes testosterone levels
- Effects on F2 generation pup survival at PND 1-4.

As noted in the conclusions for DINP the use of a NOAEL value of 33mg/kg body weight per day does not take into account the fact that the rat appears to be more sensitive to several reproductive effects than other species including man.

3 SHORT CV FOR PROFESSOR (EMERITUS) JIM BRIDGES BSc, PhD, DSc, Hon DSc (Hong Kong)

I spent most of his academic career at the University of Surrey where, at various times he held posts of:

* founding Director of the Robens Institute of Industrial and Environmental Health and Safety,

* founding Head of the European Institute of Health and Medical Sciences and Dean of Science.

* I have published nearly 400 scientific papers and reviews particularly in the areas of toxicology, environmental and environmental health risk assessment. These include a number of publications on phthalates. My current research is on risk assessment methodology.

I have also played a very active role in committees that advise governments on risks concerning chemicals. I have a very strong commitment to the use of good science as the basis for risk management decisions on chemicals and other stressors.

* In the UK I was the chair of the Veterinary Residues Committee from 2000-2004 which dealt with contaminants in Food.

* For the European Union from 1997-2004 I was the chair of the newly established EU Independent Scientific Advisory Committee on Toxicity, Ecotoxicity and the Environment (CSTEE)

*From 2004 April 2013 I served as the chair of the EU Independent Scientific Committee on Emerging and Newly Identified Health Issues (SCENHIR). Both these Committees reviewed the toxicity of phthalates on a number of occasions and the findings were published by DG-SANCO. I am also a recognised expert by EFSA and have been involved in a number of their opinions.

Throughout my career I have been very active in the development of education programmes in toxicology and environmental health. I played an active role in the establishment of the MSc in Environmental Health Management at Hong

Kong Baptist University. I also played a leading role in the establishment of both the British Toxicology Society and EUROTOX.

REFERENCES

Adamsson A, Salonen V, Paranko J and Toppari J(2009)'Effects of maternal exposure to di-isononylphthalate(DINP) and 1,1-dichloro-2,2-bis(p-chlorophenyl)ethylene (p,p-DDE) onsteroidogenesis in the fetal rat testis and adrenal gland' *Reproductive Toxicol*, **28**:66-74

Aristech Chemical Corporation (1994) '*2-year dietary oral toxicity study in rats with Diisononyl Phthalate'* TSCA 8(e) submission 8EHQ-0794-13083.CAS n 68515-48-0(as cited in EC 2003)

Babich M, Chen S, Greene M, Kiss CT, Porter W, Smith T, Wind M and Zamula W(2004)' Risk assessment of oral exposure to diisononyl phthalate from children's products' *Regul Toxicol Pharmacol*, **40**(2):151-167

Babich M and Osterhout A(2010) *Toxicity review of diisononyl phthalates (DINP)* US Consumer Product Safety Commission. hhtp://www.cpsc.gov/about/cpsia/toxicityDINP.pdf

Bannasch P(2003)'Comments on R Karbe and R Kerlin (2002) Cystic degeneration/spongiosis hepatis (Toxicol Pathol 30:216-227), *Toxicol Pathol* **31**:566-570

Boberg J, Christiansen S, Axelstad M, Kledal T, Vinggaard A, Dalgaard M, Nelleman C and Hass U(2011)'Reproductive and behavioural effects of diisononyl phthalate (DINP) in perinatally exposed rats' *Reproduc Toxicol*, **31**(2):200-209

Clewell R, Andersen M, and Schaski M(2011a) *Pharmacokinetics and fetal testes effects after diisononyl phthalate administration in rat gestation*. The Hammer Protocol#09016 Final Report DiNP Phase I Study. The Hammer Institutes for Health Sciences, Research Triangle Park, NC 27709-2137. Sponsored by ExxonMobil Biomedical Sciences Inc.

Clewell R, Andersen M, and Schaski M(2011b) *P A dose response study of the effects on male rat sexual development after administration of diisononyl phthalate to the pregnant and lactating dam.* The Hammer Protocol#10003 Final Report DINP Phase II Study. The Hammer Institutes for Health Sciences, Research Triangle Park, NC 27709-2137, Sponsored by ExxonMobil Biomedical Sciences Inc.

EFSA (2005) 'Statement of the Scientific Panel on Food Additives, Flavourings, Processing Aids and Materials in Contact with Food on 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)' EFSA, Parma

Exxon Biomedical Sciences (1986) *Chronic toxicity/oncogenicity study in F-344 rats.* Test Material:MRD-83-260 Project N326075 performed at Exxon Biomedical Sciences, Inc. Unpublished laboratory report (as cited in EC 2003)

Exxon Biomedical Sciences (1996a) *Reproduction toxicity study in rats with Diisononyl Phthalate (DINP;MRD-92-455)* Project N145535 from Exxon Biochemical Sciences Inc submitted to Exxon Chemical Company and Exxon Chemical Europe, unpublished laboratory report(as cited in EC 2003)

Exxon Biomedical Sciences (1996b) *Two generations reproduction toxicity study in rats with Diisononyl Phthalate (DINP;MRD-92-455)* Project from Exxon Biochemical Sciences Inc submitted to Exxon Chemical Company and Exxon Chemical Europe, unpublished laboratory report(as cited in EC 2003)

Exxon Biomedical Sciences (1997) *Two generations reproduction toxicity study in rats with Di-isodecyl Phthalate (DIDP;MRD-94-775)* Project N177535 for Exxon Chemical Company and Exxon Chemical Europe(as cited in EC 2003)

Johnson KJ, McDowell ER, Viereck MP and Xia JO (2011) species-specific dibutyl phthalate fetal testis endocrine disruption correlates with inhibition of SREBP-2 dependent gene expression pathways Toxicol Sci **120**, 460-474

Hannas BR, Lambright CS, Furr J, Howdeshell KL, Wilson VS, Gray LE(2011)'Dose-response assessment of fetal testosterone production and gene expression levels in rat testes following in utero exposure to diethylhexyl phthalate, disobutyl phthalate, disoheptyl phthalate, and diisononyl phthalate' *Toxicol Sci,* **123**:206-216

Heger N, Hall S, Sandrof M, Hensley J, Johnson K, Houseman E, Gaido K, and Boekelheide K(2011)'Interspecies approach to the assessment of human susceptibility to phthalate –induced endocrine disruption' *The Toxicologist*, **120**:2191

Hushka L, Waterman S, Keller L, Trimmer G, freeman J, Ambroso J, Nicolich M and McKee R(2001)' Two-generation reproduction studies in rats fed di-isodecyl phthalate' *Reprod Toxicol*, **15**:153-169

Johnson KJ, McDowell EN, Viereck MP and Xia JQ (2011) Species-specific dibutyl phthalate fetal testis endocrine disruption correlates with inhibition SREBP-2 dependent gene expression pathways. Toxicol Sci **120**, 460-474

Johnson KJ, Heger NE and Koekelheide K (2012) Of mice and men (and rats) induced fetal testis endocrine disruption is species specific. Toxicol Sci **129**, 235-248

Karbe E and Kerlin R(2002)'Cystic degeneration/spongiosis hepatis in rats' *Toxicol Pathol*, **30**:216-227

Kwack S, Kim K, Kim H and Lee B(2009)'Comparative toxicological evaluation of phthalates diesters and metabolites in Sprague-Dawley male rats for risk assessment' *J Toxicol Environ Health A*, **72**(21-22):1446-1454

Lambrot R, Muczynski V, Lecureuil C, Angenard G, Coffi H, Pairault C, Moison D, Frydman R, Habert R and Rouiller-Fabre V(2009)'Phthalates impair germ cell development in the human fetal testis in vitro without change in testosterone production' *Environ Health Perspect*, **117**(1):32-37

Lee B and Koo H(2007)' Hershberger assay for antiandrogenic effects of phthalates' *J Toxicol Environ Health A*, **70**(15-16):1365-1370

Lee KY, Shibutani M, Takagi H et al (2004) Diverse developmental toxicity of Di-n-butyl phthalate in both sexes of rat offspring after maternal exposure during the period from late gestation through lactation Toxicol 203, 221-238.

Lington A, Bird M, Plutnick R, Stubblefield W and Scala R(1997)'Chronic toxicity and carcinogenic evaluation of diisononyl phthalate in rats' *Fund Appl Toxicol*, **36**:79-89

MacLeod D, Sharpe R, welsh M, Fisken M, Scott H, Hutchison G, Drake A and van den Driesche S(2010)'Androgen action in the masculinization programming window and development of male reproductive organs' *Int J Androl*, **33**:279-287

McKee R, Pavkov K, Trimmer G, Keller L and Stump D(2006)'An assessment of the potential development and reproductive toxicity of Di-isoheptyl phthalate in rodents' *Reproduc Toxicol,* **21**:241-252

McKinnell C, Mitchell RT, Walker M et al (2009) Effect of fetal or neonatal exposure to monobutylphthalate on testicular development in the marmoset Human Reprod. 2**4**, 2214-2254

McSween RNM et al (2002) Pathology of the liver 4th Edition Elsevier, London

NTP (1997) Report no 458 Butyl benzyl phthalate in F344/N rats (feed study)

SCENIHR (2008) The safety of medical devices containing DEHP plasticised PVC or other plasticisers on neonates and other groups potentially at risk. DG SANCO Brussels.

Thoolen B, Maronpot RR, Harada T, Nyska A, Rousseaux C, Nolte T, Malarkey D, Kaufmann W, Kuttler K, Deschl U, Nakae D, Gregson R, Vinlove M, Brix A, Sing B, Belpoggi F and Ward J (2010) 'Proliferative and non- proliferative lesions of the rat and mouse hepatobiliary system' *Toxicol Pathol* 38:S81S

Thomas J, Haseman JK, Goodman JI, Ward JM, Loughran Jr and Spencer PJ (2007)' A review of large granular lymphocytic leukaemia in Fischer 344 rats as an initial step toward evaluating the implications of the endpoint to human cancer risk assessment' *Toxicol Sci* 99: 3-19

Tyl RW, Myers CB and Marr MC (2001) Reproductive toxicity evaluation of butyl benzene phthalate in rats Reproductive Toxicology 18, 241-264

US CPSC (2010a) Toxicity review of Diisononyl Phthalate (DINP) Memorandum: United States Consumer Product Safety Commission (USCPSC) staff assessemtn of the potential toxicity associated with Diisononyl Phthalate (DINP), http://www.cpsc.gov/about cpsia/toxicityDINP.pdf

US CPSC (2010b) Toxicity review of Di(isodecyl) Phthalate. Memorandum: United States Consumer Product Safety Commission (USCPSC) staff assessment of the potential toxicity associated with Di(isodecyl) Phthalate , http://www.cpsc.gov/about cpsia/toxicityDIDP.pdf

Waterman S, Ambroso J, Keller L, Trimmer G, Nikiforov A and Harris S(1999)' Developmental toxicity of di-isodecyl and di-isononyl phthalates in rats' *Reproduc Toxicol*, **13**(2):131-136

Waterman S, Keller L, Trimmer G,Freeman J, Nikiforov A Harris S, Nicolich M and McKee R(2000)' Two generation reproduction studyin rats given di-isononyl phthalate in the diet' *Reproduc Toxicol*, **14**(1):21-36

Wolfe GW and Layton KA (2001) Multigeneration reproduction toxicity study in rats: diethylhexyl phthalate:Therlmune Research Corporation (Gaithersburg, Maryland) TRC study no 7244-200