DEHP - DECISIONS ON REQUESTS FOR VARIATIONS

Request 1.1: David Cadogan on behalf of the Vinyl Council

To amend Section 7.6 of the Report (page 70) paragraph "However, elements of the plausible mode of action for these effects, which includes perturbations of steroidogenesis and the expression of genes associated with the development of the male reproductive system, are common in rodents and humans. Therefore, the reproductive toxicity of DEHP is regarded as relevant for humans and is considered for risk characterization in this assessment." **with the following wording:**

"*It should be noted that the studies used in the hazard assessment of DEHP with regard to reproductive effects have been conducted on rodents. In similar studies on marmosets no adverse effects were seen and no risk would be identified.*
"Furthermore it has been demonstrated in recent studies on the marmoset that it is more appropriate than the rat as a model for the human especially with regard to male reproductive development.
"It follows that basing the hazard assessment on data from studies on the rodent rather than the marmoset will result in a risk assessment that is very much a worst case one."

The request was accompanied with a discussion regarding the comparison of the rodent and marmoset animal models for investigating DEHP toxicity and their comparative relevance for assessment of risks of DEHP-associated toxicity in humans. Some very recent results of toxicity investigations for a similar phthalate, DBP, in marmosets were also provided.

Decision 1: Variation partly approved.

NICNAS comments 1:
The rationale for the request for variation by Vinyl Council raised two issues, (i) assessment of the toxicity hazard for DEHP using marmoset model, including consideration of data from the related phthalate, DBP, and (ii) risk assessment considering lower sensitivity of the marmoset model compared to the rodent model.

The report discusses available studies of DEHP toxicity in the marmoset model (Section 6.2.4 page 36, Section: 6.2.7 and Section 7.5.2). These are limited in number with two major studies, Rhodes et al., (1986*), and the Mitsubishi Chemical Safety Institute (MCSI) - Kurata et al., (1998*), MCSI, (2003*), Tomonari et al., (2003*, 2006*). Results of the MCSI study were reported at different time points post treatment. The studies include significant methodology limitations, such as treatment of adult or juvenile animals during the 'quiescent' period for testicular function, thus not allowing an ample conclusion to be drawn for the lack of potential for reproductive developmental toxicity of DEHP in humans.

The data cited in the rationale for the request for variation relate to studies in the marmoset system using the related phthalate DBP and its metabolite MBP in neonatal and foetal marmosets (Hallmark et al., 2007 and McKinnel et al., 2009). The DBP studies in marmosets address a key life stage which is not addressed in the DEHP studies. These studies are also conflicting and the authors conclude that they require further investigation.

Therefore, considering the limitations of the investigations in this primate system, the possibility for reproductive toxicity of DEHP in primates, marmoset or human, can not be excluded in light of the robust and consistent evidence for DEHP reproductive and developmental toxicity in rodents and the plausible mode of action through alteration of steroidogenesis and expression of genes crucial for development of males in mammals. NICNAS acknowledges the apparent low sensitivity of marmosets to DEHP toxicity in the Risk Characterisation section (page 72 paragraph 8). The report also discusses

the differential sensitivity to DEHP reproductive toxicity within the rodent models where mice are less sensitive than the rats and the type and severity of the effects vary depending on the time and duration of dosing, and the age at which effects are monitored. Generally, younger animals are more sensitive than older animals.

The available studies in marmosets are not sufficient to quantitatively address the apparent lower sensitivity of the marmoset primate system compared with rodents. A chemical specific uncertainty factor to be applied in the risk assessment for humans cannot be derived. Therefore the standard uncertainty factors applied in the risk estimates in the report i.e. 10 for inter- and 10 for intra-species variations, are considered appropriate.. The NOAEL from the multi-generational study with rats is considered most adequate based on the adequate route of exposure and robustness of the endpoints monitored (fertility, pre and postnatal development).

NICNAS supports the view that future long term and multigenerational studies of DEHP toxicity in the marmoset model could significantly reduce the uncertainties (outlined in sections 8.3.1 and 8.3.2). To emphasise this point the discussion of uncertainties in Sections 8.3.1 and 8.3.2 will be strengthened. In addition, the limitations of these studies will be emphasised in the summary sections.

Request 1.2: David Cadogan on behalf of the Vinyl Council

It is acknowledged that the report clearly states that the risk assessment on DEHP in cosmetics uses the assumption that all DEP is substituted by DEHP. However it is requested **to amend** the wording in **Section 5.3 to include**:

a) DEHP is not used in cosmetics because it does not meet the performance requirements whereas DEP does and its use is approved
b) The risk assessment is aimed at determining the hypothetical worst case exposure to DEHP if it could replace all DEP currently used in cosmetics.

Decision 1.2: Variation is partly approved.

NICNAS comments 1.2:

NICNAS recognizes that "there are likely to be limits on the extent to which dissimilar phthalates can be used." (Section 4.2.3. page 13 last paragraph). However, in the absence of information to characterise these limits on substitutability, it is necessary to assume complete substitutability. The assumption of complete substitutability is also supported by the listing of DEHP in the International Cosmetic Ingredients Dictionary and Handbook (Gottschalck & McEwen, 2006), as fragrance ingredient, plasticiser and solvent, the functions also listed for DMP, DEP and DBP.

Under the Australian cosmetics regulatory framework, there is no positive list of approved cosmetic ingredients, and to date no restrictions on use of DEHP in cosmetics in Australia have been imposed.

That DEHP is, or can potentially be, used in cosmetic products is further supported by the Australian data collected by NICNAS where importation of perfumery and cosmetic products containing DEHP with a typical concentration of approximately 0.05% was reported although the type of products was not specified. Therefore, it can not be concluded that DEHP is not used in cosmetics in Australia.

Based on the discussion above it is plausible that DEHP can be used as a cosmetic ingredient and that DEP can be substituted with DEHP in certain cosmetics products if regulatory and economic

circumstances allow and favour such substitution. However this point will be emphasized in section 5.3.2 page 22 by adding a modified version of the proposed **Variation 1.2.b.**

Request 1.3: David Cadogan on behalf of the Vinyl Council

A typographical error was pointed out on page ix

NICNAS comments 1.3:
NICNAS will correct the error.

Request 2: CHOICE

CHOICE supported recommendations 1 and 2 of the NICNAS PEC report on DEHP.

CHOICE recommended broadening the scope of the recommendations in the report to extend to FSANZ and ACCC for action in relation to use of DEHP in all food packaging and food contact materials including items such as plastic wrap, drink bottles and lid gaskets for jars.

Variation of the recommendation section in the report was proposed to include:

2.1 That Food Standards Australia and New Zealand (FSANZ) and ACCC enforce a ban on the use of DEHP in all food packaging and food contact materials including items such as plastic wrap, drink bottles and lid gaskets for jars.

2.2 That the ACCC consider labelling of all products containing DEHP, so that consumers can make an accurate choice for themselves.

It was advised that this proposal would be brought to the attention of Ministers Roxon and Emerson.

Decision 2.1: Variation is not approved

NICNAS comments 2.1

The scope of the PEC report was defined in the declaration notice (see: http://www.nicnas.gov.au/Publications/Chemical_Gazette/pdf/2006mar_whole.pdf#page=9).
Therefore the report focuses on assessment of the risks associated with use of DEHP in two consumer applications, children's toys and childcare articles and use in cosmetics, as industrial applications with potential for high and repeated exposure to DEHP. The use of DEHP in food packaging and food contact materials is outside of the scope of the assessment, as defined in the declaration notice, and were not addressed in the report. Consequently NICNAS can not make a recommendation related to uses of DEHP for which risks were not examined.

NICNAS will advise FSANZ and ACCC of the concerns raised by CHOICE and if requested will provide advice, as appropriate.

Decision 2.2: Variation is not approved.

NICNAS comments 2.2

The scope of the assessment, as defined in the declaration notice, did not include evaluation of exposure from all products that could contain DEHP. The recommendation from NICNAS to ACCC is based on assessment of potential risk associated with DEHP exposure through the use of children's toys and childcare articles. This was found to be highest for toys that can be mouthed for extensive amounts of time. Dermal exposure during other everyday handling of toys did not contribute significantly to the overall exposure in the toy use scenario.

NICNAS commends the prompt action by ACCC (http://www.accc.gov.au/content/index.phtml/itemId/916813) as a response to the NICNAS report and the consultation process undertaken to discuss the scope of products, testing and labelling requirements. Since the time of the submission by CHOICE, this resulted in the Guidance Note for Suppliers regarding the temporary ban on certain children's/infant's products containing more than 1% DEHP (http://www.accc.gov.au/content/index.phtml/itemId/919489).

NICNAS will advise ACCC of the concerns raised by CHOICE and if requested will provide advice, as appropriate.

Request 3.1: National Toxics Network (NTN)

NTN supports Recommendations 1 & 2 and welcomes the announcement already made by the ACCC in relation to Recommendation 1.

NTN considers that another Recommendation must also be made in relation to how the problem of imported products arriving into Australia from countries with no restrictions on DEHP will be regulated.

NTN also considers that a biomonitoring program would provide useful data to ensure the Recommendations result in reduced exposures to DEHP.

Proposed Variation: That the existing Recommendations should be strengthened by inclusion of a statement: DEHP should be banned from all products such as adhesives, packaging, food wrapping, building and furnishing products, PVC flooring/ moulding, food containers.

In support of this variation request, study reports were discussed which examine possible association between environmental exposure to mixtures of phthalates mainly in indoor environments and occurrence of bronchial obstruction, asthma and allergic rhinitis.

Decision 3.1: Variation is partly approved.

NICNAS comments 3.1

The use of DEHP in building materials, food packaging and food contact materials is outside of the scope of the assessment, as defined in the declaration notice (see: http://www.nicnas.gov.au/Publications/Chemical_Gazette/pdf/2006mar_whole.pdf#page=9).
Therefore the exposure scenarios related to the use of DEHP in building, furnishing and flooring materials or food and food contact materials were not considered. Consequently NICNAS can not make a recommendation related to uses of DEHP for which risks were not examined.

The report discusses a review by the EU Scientific Committee on Health and Environmental Risks (SCHER) of the findings and limitations of the studies cited in the submission by National Toxics Network (NTN) and other similar studies in the hazard assessment Section 6.3.2. SCHER concluded that the studies do not provide a consistent scientific evidence to establish a specific respiratory health hazard associated with exposure to various phthalates in indoor air.

ACCC has declared certain toys and childcare articles containing more than 1% of DEHP to be unsafe goods (http://www.accc.gov.au/content/index.phtml/itemId/916813). The ACCC enforces bans on unsafe goods. The ban applies to manufacturers, importers, distributors, retailers and hire companies. Complying with the ban requires appropriate labelling and testing of the goods within the scope of the ban as specified in the Guidance Note for Suppliers regarding the temporary ban on certain children's/infant's products containing more than 1% DEHP (http://www.accc.gov.au/content/index.phtml/itemId/919489).

The absence of biomonitoring information for the Australian population, general or subpopulations specifically affected by the recommendations, is recognized in the report and international data are used (Section 5.4). However, NICNAS will modify the report overview to emphasize the importance of biomonitoring information for assessing exposure.

Request 3.2: National Toxics Network

NTN commented that in assessing the impacts on humans, particularly children, the standard assessment factors, and the related MOE approach may not be appropriate.

The uncertainty of the assessment approach that does not take into account simultaneous exposure to groups of 'like' chemicals (e.g., all phthalates, all reproductive toxins) was also discussed.

No specific variation for the report is proposed.

NICNAS comments 3.2

In the current report NICNAS discusses extensively the uncertainties in the characterisation of risk for DEHP which arise from the limitations of the available data sources (sections 8.3.1 and 8.3.2). In addition the report specifically highlights the uncertainties related to the risk estimates for newborn and/or children.

The report further discusses the variability and the related uncertainty regarding the sensitivity of individuals and subpopulations to the critical health effects associated with exposure to DEHP (pages 77-79) in the context of the cosmetic exposure scenario. The report concludes "This raises concerns that the high exposure scenarios with MOE extremely close to or below 100 may be applicable to the subpopulation which is most at risk for reproductive developmental effects in their progeny i.e. pregnant and breastfeeding women." (page 79).

References discussing the MOE approach and the application of safety factors in particular circumstances, including assessment of risks for specific populations, are also referenced in the report, (IPCS, 1994*; ECETOC, 2003*; ECB, 2006*). This risk assessment approach is consistent with usual international practice.

In this context the report also emphasises the uncertainties of the risk estimates associated with possible cumulative toxic effects from co-exposure to other phthalates with similar modes of action (page 75).

Request 3.3: National Toxics Network

NTN commented that action needs to be taken on other phthalates where toxicity and exposure have been demonstrated in various published studies and international assessments. Regulatory actions on different phthalates in the international context were also highlighted.

No specific variation for the report is proposed.

NICNAS comments 3.3

The draft PEC report on DEHP discusses in detail the frame of international regulatory environment (Section 2).

NICNAS is currently conducting public health risk assessments for 8 other phthalates declared as Priority Existing Chemicals (PECs) for their use in children's toys, childcare articles and cosmetics. The phthalates are diisonyl phthalate (DINP), diisodecyl phthalate (DIDP), dioctyl phthalate (DnOP), diethyl phthalate (DEP), dibutyl phthalate (DBP), dimethoxyethyl phthalate (DMEP), dimethyl phthalate (DMP), and butyl benzyl phthalate (BBP).

It is expected that draft reports for DINP, DBP and DEP will be released successively shortly following the completion of the consultation process regarding the DEHP report.

COMMENTS

In addition to the formal requests for variation of the report, NICNAS received comments from the New Zealand Ministry of Consumer Affairs (MCA).

Comments by New Zealand Ministry of Consumer Affairs (MCA):

MCA has advised that in reaching a view on the content and recommendations of the PEC report on DEHP, it drew on toxicological expertise in other New Zealand ministries and agencies. The advice that MCA has received indicated no issues or concerns with the toxicological elements of the NICNAS report. MCA indicated that the submission is aimed at highlighting some concerns around the estimates of the potential exposures. MCA would be pleased to be involved in any future discussions around the issues of risk to humans from exposure to DEHP from consumer products.

The main points of the submission by MCA can be summarized as follows:

1. The exposure assessment for children from the use of toys containing DEHP requires further work to establish more realistic exposure scenarios based on the following:

- MCA states that marketplace surveillance work carried out in New Zealand last year showed that the level of DEHP in toys was very low. As part of a wider consumer product sampling and testing 58 toys and articles for children using EN 71 methodology DEHP has not been found at any significant level.
- The assumption of complete substitutability of DEHP for DINP in toys and childcare articles is noted in light of the apparent limited use of DEHP in toys (page ix) and the recognized limits in phthalate substitutability (page 13).
- The exposures for the typical and worst case scenario of toys use are significantly overestimated compared with population biomonitoring data and further research on appropriate exposure scenarios is needed.

2. The epidemiological evidence and science on the potential harm to humans from phthalates has not established causal links to DEHP in consumer products and is not yet clearly indicative of a significant risk. As one of the main arguments for this view it is emphasized that (i) the scientific analysis to date is done and based around tests on laboratory animals, (ii) the suggested potential harmful effects on the human population have been based on assumptions and worst case exposure scenarios, (iii) such exposure assessments may grossly overestimate the risk.

3. MCA favours a risk based approach which takes into account the severity of the hazard and the likelihood of that hazard occurring. MCA feels that to focus on the regulation of chemicals such as DEHP on a precautionary basis sets a precedent for the future that could in turn bring with it significant opportunity costs issues. It could deflect regulatory attention and resource away from other consumer product risks and issues where there is greater certainty of risk.

NICNAS response:

NICNAS welcomes the submission by MCA on the PEC assessment for DEHP and the interest in future discussions on this or any future issues regarding the safety of consumers. In the Australian context, NICNAS is continuing to work with the Australian Competition and Consumers Commission (ACCC).

NICNAS notes that MCA has not commented on the exposure scenario for cosmetic use and recommendation made to the NDPSC.

NICNAS comments focus on the points made by MCA relevant to the NICNAS PEC report risk assessment, based on which a recommendation was made to ACCC.

NICNAS's approach in assessing risks from chemicals is based on:

a) **Exposure Assessment:** Assessment of potential or actual exposure levels for relevant population;
b) **Hazard Characterization:** Assessment of nature of health hazards associated with the chemical and dose-response relationships i.e. toxicological assessment of critical endpoints and where possible establishing a No Adverse Effect Level (NOAEL); and
c) **Risk Characterization:** Interpretation and integration of the information from the previous steps to provide a practical estimate of risk and to identify any limitations and uncertainties of this estimate.

Comments regarding Exposure assessment:

ISSUE: Low DEHP concentrations from marketplace surveillance by MCA

The reporting of the results from the phthalate content tests performed by MCA is in terms of water extractability of DEHP, undertaken according to an EN 71 migration test in water, showing a maximum level of 21 μg/g water. This test does not measure the actual concentrations of phthalates found in the toys. The Standard, EN 71, notes that the scope of the Standard includes plasticisers, but specifically excludes phthalate plasticisers. The current European legislation limits the phthalate content in toys rather than phthalate migration. This followed an EU Scientific Committee on Toxicity, Ecotoxicity and the Environment (CSTEE) opinion in 1998 that no validated method of measuring phthalate migration existed (http://ec.europa.eu/health/ph_risk/committees/sct/docshtml/sct_out15_en.htm). An appropriate method of organic solvent extraction for estimating total phthalate content validated by the US Consumer Product Safety Commission (US CSPC) is found in http://www.toyassociation.org/AM/PDFs/Safety/PhthalatesRules0209.pdf.

The results of a validation study undertaken in Austria show the difference between the water extractability measurements and organic solvent extraction. In this study, a water extractability of 135 μg/g from 10 cm^2 toy in 100 mL water (using EN 71 Part 10) corresponded to an actual phthalate content in the toy, as measured by an organic solvent extraction method, of 34.0 % DEHP by weight of toy (Fiala and Steiner, 2005).

While numerous investigations on the DEHP content in PVC plastic toys (reported in Section 5.2.1 of the report) have established that toys can contain >40% DEHP (Bouma and Schael, 2002), the use of DINP at high levels is more common than use of DEHP. The studies undertaken on 58 toys and childcare articles in New Zealand do not define what proportion of the test articles were composed of PVC. It is therefore not clear whether the set of toys tested would be sufficiently large to give a representative sample of plasticiser content in PVC toys. Anecdotal information from the Australian vinyl industry indicates that it is likely that overseas production facilities still use DEHP in production lines not intended for export to countries which have banned DEHP use in toys. The available overseas data remain the most suitable basis to determine children's exposure to DEHP from toys and child care articles.

ISSUE: Complete substitutability

The assumption of complete phthalate substitutability in the manufacture of toys is valid as reported in the Intergovernmental Forum on Chemical Safety (IFCS, 2006*). The IFCS stated that DEHP was

used extensively in toys and manufacturers started using DINP as a substitute for DEHP in the 1980s. Information from the Australian vinyl industry indicates that DEHP is more cost effective than DINP.

ISSUE: Use of worst case exposure scenarios and overestimation of risk

The exposure assessment scenarios used are dependent on the level of DEHP found in typical toys. The validity of the assumption that a typical level of DEHP in a toy predominantly plasticised with DEHP is 43% is discussed in the report, and above. The methodology for estimating oral exposure for a toy of this type is derived from the EU SCCP. Targeted measurements of mouthing times and extractability of phthalates into saliva by chewing were undertaken to derive this methodology specifically for phthalate plasticisers. The NICNAS assessment uses these and the results from a variety of similar human studies. These studies are not conservative, particularly as the extractability test was conducted on DINP, which is less water soluble than DEHP.

The EU risk assessment (conducted according to the original SCCP methodology) exposure assessment is directly comparable with the NICNAS worst case exposure scenario. The NICNAS exposure assessment also includes a less conservative typical scenario. The typical scenario also shows reason for concern. Individual infants chewing on toys containing DEHP at such concentrations are likely to have exposures ranging between the typical and worst case estimates, and exposures of these individuals will be much higher than for individuals not having such exposures.

Finally, the typical case exposure scenarios reflect doses which are consistent with adult biomonitoring results, and recent literature (Becker et al., 2009) has demonstrated that exposure of young children to DEHP can be at levels three to five times adult levels, indicating that the worst case exposure scenario is also relevant for some individuals..

Comments regarding Hazard Characterization:

ISSUE: The epidemiological evidence and science on the potential harm to humans from phthalates has not established causal links to DEHP in consumer products, and the scientific analysis to date is done and based around tests on laboratory animals

Overall, the limited studies in humans do not identify significant and consistent associations between estimated DEHP exposures and reproductive parameters either in adults or children, as discussed in Section 6.3.4 of the report. However, in light of the robust and consistent evidence for reproductive toxicity of DEHP in rodents and the relevance of the postulated mode of action (MOA) for reproductive toxicity in rodents to humans, reproductive toxicity of DEHP in humans cannot be excluded. This is discussed in detail in Section 7 of the report and the NICNAS comments on Variation Request 1.1.

Long term human studies will assist in clarifying the effects in humans. Cohorts of children, for whom the pre- and neonatal DEHP exposure are known, are underway. When these children reach adulthood, at which time potential reproductive effects may be more evident, more consistent human data are expected to become available.

Comments regarding Risk Characterization:

ISSUE: Potential harm to humans from phthalates is not yet clearly indicative of a significant risk

The hazard assessment in the report establishes the relevance of the effects seen in rodents to humans under the Mode of Action (MOA) framework (IPCS, 2007). A No Observed Adverse Effect Level (NOAEL), below which adverse effects are not expected to be seen, was established from the rodent studies. Separately, estimates of potential exposure of infants in the absence of regulatory restrictions on DEHP use in toys and childcare articles were made using the best available experimentally derived data. The estimated exposure was compared with the NOAEL to determine a Margin of Exposure (MOE), which is a quantitative estimate of risk.

The MOE for the worst case scenario (Table 8.3) is significantly less than 100, indicating concern for individual children for whom exposure to DEHP from toys are higher than for the general population, due to use of toys containing DEHP as a major plasticiser. Considering the uncertainties within the risk estimates in this assessment, the type of the toxicity and the specific sensitivity of developing reproductive organs during the first few months after birth, there is a risk of reproductive toxicity in young children even for the typical exposure scenario with a MOE marginally above 100.

Comments regarding Risk versus Hazard based approaches for regulation of chemicals:

ISSUE: MCA favours a risk based approach which takes into account the severity of the hazard and the likelihood of that hazard occurring. MCA feels that to focus on the regulation of chemicals such as DEHP on a precautionary basis sets a precedent for the future

The estimates of risk for the likelihood of hazard of reproductive developmental toxicity occurring in infants and young children under exposure scenarios that are plausible in the absence of regulatory restrictions are undertaken on a quantitative basis. As Recommendation 1 to ACCC was made on the basis of a quantitative and plausible risk assessment, for the subpopulation using DEHP-containing toys, this recommendation is not considered by NICNAS to be precautionary.

While NICNAS recognises that there are a number of uncertainties in the hazard and exposure assessments, the approach taken by NICNAS has been conservative rather than precautionary. A conservative approach is justified in view of the potential adverse consequences of developmental and reproductive effect from exposure of infants. The conservatism of the assessment arises mainly from it examining the exposure of individuals for whom an exposure route is relevant (on an individual basis) rather than a population level mean or median exposure. Use of a mean exposure would lead to a population based conclusion that current exposures may be safe and this would be insufficiently protective of the smaller exposed population.

Additional Comments received during the Public Comment Phase

In addition to the formal comments addressed above, NICNAS received review comments from Health Canada during the Public Comment Phase. These comments are largely technical in nature. Some comments will result in minor changes, not affecting the key conclusions, in the assessment report. The changes will increase the clarity of the report.

REFERENCES:

*References marked by asterisks are included in the bibliography of the PEC Report on DEHP and are not listed here.

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McKinnell C, Mitchell RT, Walker M, Morris K, Kelnar CGH, Wallace WH, and Sharpe RM (2009) Effect of fetal or neonatal exposure to monobutyl phthalate (MBP) on testicular development and function in the marmoset Hum Reprod. 2009 September; 24(9): 2244–2254.