April 2009

Cumulative risk assessment should be required for phthalates with additive effects

Considerations for risk assessment and REACH authorisation

Recognising the international concern about the suggested adverse trends in male reproductive health[1,2], there is a need for new scientific data on combined effects to be considered in the risk assessment of certain phthalates. Three phthalates (namely dibutyl phthalate (DBP), bis (2-ethyl(hexyl)phthalate) (DEHP) and benzyl butyl phthalate (BBP), all of which have well-established adverse effects on the development of the male reproductive system in laboratory animals[3] have been put forward for the authorisation procedure under REACH. A substance by substance approach, that is, a 'single-substance risk assessment' will not secure adequate protection of wildlife and human health.

The following list of studies, many of which have been funded by the European Commission[4-9], or conducted by the US Environmental Protection Agency at their Reproductive Toxicology Division laboratory, at Research Triangle Park, North Carolina[10-19], need to be taken into account. Peer reviewed published studies have thus concluded that several phthalates can act additively to affect male developmental processes. Moreover, several studies have shown that phthalates with anti-androgenic properties can also act additively with other substances with anti-androgenic properties which are not phthalates, and that these substances can together cause effects even when each substance is individually present below its effect level.

The recent report by the US National Academies "Phthalates and Cumulative Risk Assessment", which has recommended that cumulative risk assessment should focus on common adverse outcomes, provides a comprehensive review of the issue. A brief synopsis of this report is enclosed and the 188 pages of the full report on "Phthalates and Cumulative Risk Assessment" can be read online at:
http://www.nap.edu/catalog.php?record_id=12528#toc

In conclusion, public health and wildlife will not be adequately protected from harm if the risk associated with exposure to each phthalate was assessed individually, with no consideration of potential combined effects. Therefore, CHEM Trust, HEAL and WWF suggest that it is imperative that the risks of phthalates should be assessed with consideration of the potential combined effects not only from current exposure to other

similarly acting phthalates, but also from current exposure to other substances *known* to cause similar effects on the development of the male reproductive system. Because people are exposed to multiple phthalates and other chemicals that affect male reproductive development, a cumulative risk assessment is needed that evaluates the combined effects of exposure to all these chemicals.

Moreover, it is crucial to recognise that the public and wildlife may be exposed to low levels of a variety of anti-androgenic substances, at a variety of concentrations, and that each person's exposure may be quite different. This highlights the need for a pragmatic and easily applicable approach by which cumulative risk assessment can be undertaken within the risk assessment procedures applied under REACH.

Implications for REACH authorisation and REACH guidance

We do not agree with the suggested route for authorisation, i.e. that the phthalates DBP, DEHP and BBP should be authorised via the adequate control of the risk route. There is now incontrovertible evidence that they can act additively, and moreover, can contribute to effects in animals even when each is below its 'effect' concentration (see 2008 report by the US National Academy of Sciences). In addition, there is known widespread exposure to phthalates and other substances that act as anti-androgens. Therefore, we believe that the best way forward would be to accept that due to the likely combination effects it is not possible to identify a DNEL or derive a PNEC with confidence, and thus it should be deemed under Annex 1, 1.4.2 and 3.3.2 of the REACH regulation that it is not possible to determine a threshold. In order to protect humans and wildlife, authorisation should therefore only be granted if the socio-economic benefits outweigh the risk and there are no suitable alternatives. Guidance on the derivation of DNEL and PNECs for chemicals with common adverse outcomes should be written to reflect this concern about combined effects.

If at this stage, the adequate control of the risk route to authorisation is not blocked for these 3 phthalates, then it is important to ensure that the risks from the likely combined effects from exposure to other phthalates and chemicals with common adverse outcomes are given consideration. Therefore, exposure to other similarly acting substances must be taken into account. The guidance of May 2008, E.3.5 allows that "in special cases, where exposure occurs to the substance as well as several closely related and similar acting substances,... the exposure evaluation and risk characterisation should reflect this aspect. If data do not allow for a quantitative assessment, an attempt should be made to address the issue in a qualitative way."

Here it is important to stress that such closely related chemicals should embrace not just those with the same mechanism of action, but rather, all chemicals that have common adverse outcomes. For example, in the case of the three phthalates, DBP, DEHP and BBP, this should include not only all anti-androgenic phthalates, but also all chemicals which adversely affect the same male developmental processes. The guidance may need some modification in order to make this clear.

One option for taking account of these combined effects might be to employ an additional assessment factor in the risk assessment to allow for additive effects when chemicals with common outcomes are considered. This builds on current methodologies. Risk assessment is not an exact science, but rather uses scientifically based assumptions. Risk assessment has long dealt with uncertainty by using assessment factors. A factor of 10 is used to take account of intra-species variation in, for example, metabolism, and another factor of 10 is used to allow for differences in extrapolating from rats to man. Having an additional assessment factor for cumulative

effects would follow that tradition.

Some modification to the guidance is clearly urgently needed also to ensure that industry undertakes risk assessments of chemicals with known additive effects (that are not currently prioritised for authorisation) which take into account the combination effects. More international discussion is needed to ensure that an agreed methodology for undertaking cumulative risk assessment of such substances is clearly outlined in the guidance.

Conclusion

Given that science has shown that substances such as DBP, DEHP and BBP can together cause effects even when each substance is individually present below its effect level, we do not consider that phthalates should follow the adequate control of the risk route to authorisation. Thus, the NGOs preferred way of dealing with the issue of combined effects for phthalates and other chemicals which act on male developmental pathways would be to take these through to authorisation via Article 60(4).

However, if it is decided that the adequate control of the risk route to authorisation is to be taken, then significant modification to the current risk assessment procedure is needed – as cumulative risk assessment must be performed - or humans and wildlife will not be adequately protected because the normally striven for margins of safety will be eroded.

References:

[1] Bray F, Richiardi L, Ekbom A, Pukkala E, Cuninkova M, Møller H 2006b. Trends in testicular cancer incidence and mortality in 22 European countries: continuing increases in incidence and declines in mortality. Int J Cancer 118: 3099-3111.

[2] Andersson AM, Jørgensen N, Main KM, Toppari J, Rajpert-De Meyts E, Leffers H, Juul A, Jensen TK, Skakkebaek NE 2008. Adverse trends in male reproductive health: we may have reached a crucial 'tipping point'. Int J Androl 31: 74-80.

[3] See EU risk assessment reports conducted under the Existing Substances Regulation 793/93 available at http://ecb.jrc.it/esis/index.php?PGM=ora .

[4] Christiansen S, Scholze M, Axelstad M, Boberg J, Kortenkamp A, Hass U 2008. Combined exposure to anti-androgens causes markedly increased frequencies of hypospadias in the rat. Int J Androl 31: 241-248.

[5] Hass U, Scholze M, Christiansen S, Dalgaard M, Vinggaard AM, Axelstad M, Metzdorff SB, Kortenkamp A 2007. Combined exposure to anti-androgens exacerbates disruption of sexual differentiation in the rat. Environ Health Perspect 115: 122-128.

[6] Fisher JS, Macpherson S, Marchetti N, Sharpe RM 2003. Human 'testicular dysgenesis syndrome': a possible model based on in utero exposure of the rat to dibutyl phthalate. Hum Reprod 18: 1383-1394.

[7] Kortenkamp A, Faust M, Scholze M, Backhaus T 2007. Low-level exposure to multiple chemicals: reason for human health concerns? Environ Health Perspect 115: 106-114.

[8] Metzdorff SB, Dalgaard M, Christiansen S, Axelstad M, Hass U, Kiersgaard MK, Scholze M, Kortenkamp A, Vinggaard AM 2007. Dysgenesis and histological changes of genitals and perturbations of gene expression in male rats after *in utero* exposure to antiandrogen mixtures. Toxicol Sci 98: 87-98.

[9] Sharpe RM 2008. 'Additional' effects of phthalates on fetal testosterone production. Toxicol Sci 105: 1-4.

[10] Foster PM 2006. Disruption of reproductive development in male rat offspring following in utero exposure to phthalate esters. Int J Androl 29: 140-147.

[11] Gray LE Jr, Ostby J, Furr J, Price M, Veeramachaneni DN, Parks L 2000. Perinatal exposure to the phthalates DEHP, BBP, and DINP, but not DEP, DMP, or DOTP, alters sexual differentiation of the male rat. Toxicol Sci 58: 350-365.

[12] Gray LE Jr, Wolf C, Lambright C, Mann P, Price M, Cooper RL, Ostby J 1999. Administration of potentially antiandrogenic pesticides (procymidone, linuron, iprodione, chlozolinate p,p'DDE, and ketoconazole) and toxic substances (dibutyl- and diethylhexyl phthalate, PCB 169, and ethane dimethane sulphonate) during sexual differentiation produces diverse profiles of reproductive malformations in the male rat. Toxicol Ind Health 15: 94-118.

[13] Hotchkiss AK, Parks-Saldutti LG, Ostby JS, Lambright C, Furr J, Vandenbergh JG 2004. A mixture of the "antiandrogens" linuron and butyl benzyl phthalate alters sexual differentiation of the male rat in a cumulative fashion. Biol Reprod 71: 1852-1861.

[14] Gray LE Jr, Ostby J, Furr J, Wolf CJ, Lambright C, Parks L, Veeramachaneni DN, Wilson V, Price M, Hotchkiss A, Orlando E, Guillette L 2001. Effects of environmental antiandrogens on reproductive development in experimental animals. Hum Reprod Update 7: 248-264.

[15] Wilson VS, Blystone CR, Hotchkiss, AK, Rider CV, Gray LE Jr 2008. Diverse mechanisms of anti-androgen action: impact on male rat reproductive tract development. Int J Androl 31: 178-187.

[16] Howdeshell KL, Furr J, Lambright CR, Rider CV, Wilson VS, Gray LE Jr 2007. Cumulative effects of dibutyl phthalate and diethylhexyl phthalate on male rat reproductive tract development: altered fetal steroid hormones and genes. Toxicol Sci 99: 190-202.

[17] Howdeshell KL, Wilson VS, Furr J, Lambright CR, Rider CV, Blystone CR, Hotchkiss AK, Gray LE Jr 2008. A mixture of five phthalate esters inhibits fetal testicular testosterone production in the Sprague-Dawley rat in a cumulative, dose-additive manner. Toxicol Sci 105: 153-165.

[18] Rider CV, Furr J, Wilson VS, Earl Gray Jr L 2008. A mixture of seven antiandrogens induces reproductive malformations in rats. Int J Androl 31: 249-262.

[19] Rider CV, Wilson VS, Howdeshell KL, Hotchkiss AK, Furr JR, Lambright CR, Gray LE Jr. (2009). Cumulatve Effects of In Utero Administration of Mixtures of Antiandrogens on Male Rat Reproductive Development. Toxicol Pathol. Jan 15.

Contact details:
Gwynne Lyons, CHEM Trust, Gwynne.lyons@chemtrust.org.uk
tel: 0044-1603 507363
Lisette van Vliet, Health and Environment Alliance (HEAL), lisette@env-health.org
tel: 0032-22343645
Ninja Reineke, WWF European Policy Office, nreineke@wwfepo.org
tel: 0032-27400926