PHTHALATES STAKEHOLDER WORKSHOP

SUMMARY REPORT

March 26, 2014
Ottawa, Canada

Canada

Contents

Acronyms

ACC	American Chemistry Council
AGD	Anogenital distance
CAS RN	Chemical Abstracts Service Registry Number
CEPA1999	*Canadian Environmental Protection Act* 1999
CMP	Chemicals Management Plan
CRA	Cumulative risk assessment
DSL	Domestic Substances List
EC	Environment Canada
GoC	Government of Canada
HC	Health Canada
MNGs	Multinucleated gonocytes
MOA	Mode of action
RPS	Rat Phthalate Syndrome

INTRODUCTION

Given the complex scientific considerations pertaining to the assessment of certain phthalates, and the substantial activity by multiple international organizations, the Government of Canada (GoC) hosted an interactive multi-stakeholder technical workshop on March 26th, 2014 in Ottawa, Canada. The objective of the workshop was to obtain input from invited participants on key scientific considerations pertaining to assessment of phthalates, with a focus on human health. Participants included individuals from industry, non-governmental organizations and academia. Officials from Health Canada (HC) and Environment Canada (EC) provided oral presentations of workshop materials and acted as observers and note takers. The workshop consisted of a series of presentations surrounding two main themes: a proposed approach for addressing certain human health effect data gaps; and factors involved in considering a cumulative approach to risk assessment. Presentations were followed by breakout sessions with charge questions and plenary discussion periods.

This report is a summary of stakeholder input. Inputs are presented as they were understood and are not reported verbatim. The stakeholder comments summarized below are directly related to the information presented at the workshop.

Overview – Phthalate Substances Grouping and the Chemicals Management Plan

A presentation by officials of the GoC was provided on the principal aspects of the Phthalate Substances Grouping under the Chemicals Management Plan (CMP).

Stakeholder comments/questions included:

- **Scope of assessments:** Government officials indicated that there are 28 phthalates of interest under consideration, with 14 phthalates identified as a priority for assessment. The additional 14 phthalates may inform the planned cumulative risk assessment (CRA) of phthalates and as a result all phthalates may not be included in the assessment. The GoC published a mandatory survey to capture all uses in Canada of all 28 phthalates. Open literature will also be used to identify possible sources and uses. Exposure will be addressed in the published risk assessment documents. It was also noted that medical devices are not regulated under The *Canadian Environmental Protection Act, 1999* (CEPA 1999).
- **Alternative plasticizers:** Government officials indicated that there are no plans to address alternative plasticizers in the current phthalate assessment activities. If the alternative plasticizers are not currently on the Domestic Substance List (DSL), it is expected that they would be evaluated through a different assessment stream conducted for new substances under CEPA1999.
- **Phthalate use in children's toys and child care articles:** Government officials indicated that Canadian regulations are harmonized with those of the European Union (EU) and the United States (US)[1]. Stakeholders suggested these uses are decreasing and pointed to the decline of EU Rapid Information System (RAPEX) notifications for phthalates violations in children's toys in the EU.

The Proposed Category and Read-Across Approach

A detailed presentation was provided by officials of HC on the proposed approach for use of chemical categories and read-across to address data gaps for effects of certain phthalates on the developing male reproductive system in rats. A document entitled "Proposed Approach for Using Chemical Categories and Read-Across to Address Data Gaps for Effects on the Developing Male

[1] http://www.hc-sc.gc.ca/ahc-asc/media/nr-cp/_2011/2011_07-eng.php

Reproductive System" generated by HC was distributed three weeks in advance of the workshop with associated charge questions in preparation for table discussions.

Stakeholder comments/questions included:

- **The mode of action (MOA) and its relevance to humans will need to be addressed:** Government officials indicated that for forming categories of phthalates and applying read-across, it is considered that the MOA, based on considerations in Foster et al. 2005[2] and the 2008 National Academy of Science Report[3], is plausible in humans.
- **Recent data indicate that effects of phthalates on humans may occur through another MOA, potentially not linked to testosterone:** Government officials confirmed their awareness that this data exists and that other MOAs involved in rat phthalate syndrome (RPS) were reviewed and briefly described in the presentation.
- **Epidemiological studies indicate the presence of several health outcomes in human neonates consistent with effects described within the animal-based phthalate syndrome, regardless of which MOAs are in operation:** It was noted that human relevance considerations may need to start at the level of common adverse health outcomes, after which MOAs are brought in as an additional consideration. Also, recent epidemiology studies show the presence of multinucleated gonocytes (MNGs) in humans showing that the MOA is plausible for humans.
- Government officials indicated that the lines of evidence used in the proposed approach (e.g., gene expression variations, testosterone production and anogenital distance (AGD) are being used to support the read-across of apical effects for in vivo studies. All anti-androgenic effects will be considered for the potential CRA.
- **Few experimental studies on human testis (*in vitro*) investigating effects of phthalates are available and most do not demonstrate the anti-androgenic effects of phthalates**. These results raise the issue of the

[2] Foster, PMD. 2005. Mode of action: Impaired fetal leydig cell function - effects on male reproductive development produced by certain phthalate esters. Critical Reviews in Toxicology 35(8-9):713-719.

[3] [NAS] National Academy of Sciences. 2008. Phthalates and Cumulative Risk Assessment: The Tasks Ahead. Committee on Health Risks of Phthalates. Washington, D.C (US). The National Academies Press. Available from: http://www.nap.edu/openbook.php?record_id=12528

relevance of rodents as an appropriate model to evaluate the effects of phthalates on the human reproductive system. However, government officials indicated that they were aware of studies showing effects on testosterone production. The majority of the studies investigate adult male immortalized Leydig cell tumours.

- When asked about using TOXcast data, government officials indicated that its utility is limited without the inclusion of pharmacokinetic data. The GoC, in partnership with academia, is conducting research to further support read-across of apical effects where appropriate.
- Studies using routes of exposure other than oral routes will be addressed in upcoming risk assessments, as appropriate.
- The GoC will be transparent on how it addresses available information. Uncertainties in the risk assessment(s) will be documented.

Table Discussion #1: What do you like about the approach? Why?

Four groups were created to discuss the charge question. One reporter was selected for each table.

Stakeholder general comments were:

- The category approach document was successful in condensing large amounts of information on data rich sources into a clear summary.
- The approach and the three categories, including their names (i.e., short, medium and long chain phthalates) are appropriate. Selection of the closest analogue as opposed to the most harmful within a category is appropriate.
- The approach to focus on one endpoint and MOA based on several mechanisms was well-received.
- Stakeholders supported the acknowledgement in the approach of different anti-androgenic potencies for different phthalates.

Table Discussion #2: Are there aspects of the approach that could be strengthened? Why? How?

Three groups were created to discuss the charge questions. One reporter per table was selected.

Question 1 *- Are the proposed category boundaries appropriate as presented? Justify.*

- It was noted that there was some divergence from the American Chemistry Council (ACC) categorization approach. Government officials highlighted that although the ACC approach was done well, MOA data was limited at the time the approach was developed.
- Concerns were raised regarding the categorization selection for data-poor phthalates. Uncertainties and limitations of the approach should be clearly outlined in the assessments.
- Flexibility should be kept in the approach so that categorization endpoints can be different than risk assessment endpoints. Assessments should capture all MOAs and mechanisms.
- AGD is an endpoint that is suitable for use in the category approach, but the science does not support its use in risk assessment. AGD has been shown to be reversible in some cases therefore it is not necessarily adverse. The three different endpoints selected for the approach are appropriate, but slopes and thresholds are remarkably similar between endpoints. The question was raised as to whether a different endpoint selection (i.e., systemic effects vs developmental reproductive effects) would have led to the formation of different phthalate categories.
- It was noted that the endpoints that constitute the RPS may be independent, and that RPS should not be considered relevant to all 28 phthalates.
- Concerns were raised with inclusion of diisononyl phthalate (DINP) in the medium chain category:
    - Examining three lines of evidence, there were effects on testosterone levels and gene expression, but apical effects were not seen at the same level as other medium chain substances; and
    - There was no impetus to make DINP an outlier or create a fourth category. The issue could be addressed through communication.

Question 2 - *Are you aware of additional data for the 28 CMP phthalates that should be considered to strengthen the category boundaries?*

- Stakeholders agreed to check for additional relevant data.
- Government officials pointed out the need for information on chemical identification to characterize Chemical Abstract Service Registry Numbers (CAS RNs) correctly, particularly for mixtures (e.g., range of constituents in substances of unknown or variable composition, complex reaction products or biological materials (UVCBs)).

Stakeholders suggested reviewing the composition data presented and forwarding to HC partners any corrections or additional data if available. Data on composition is generally limited, and information on the starting alcohols is key.

- There are a number of UVCBs amongst mid- and long-chain phthalates and fitting UVCBs into a category and using UVCBs or mixtures for read-across can be problematic and requires more thought.
- Some inconsistencies in GoC nomenclature were noted, particularly the use of 'UVCB,' 'multiconstituent substance' and 'mixture' (including such terms as 'UVCB mixture'). Government officials agreed that terminology should be addressed.
- The proposed surrogate for B84P (CAS RN 16883-83-3) (i.e., diisobutyl phthalate (DIBP), CAS RN 84-69-5) was not considered the best analogue and benzyl butyl phthalate (BBP) (CAS RN 85-68-7) was suggested as the typical substance used for read-across of B84P. Benzyl 7-9 was also put forward as a potential analogue. Government officials indicated that they would look into BBP further as a potential candidate.
- It was also noted that DINP may not be the best analogue since it is not a single chemical but a mixture of compounds of different chain lengths.

Question 4 - *Are you aware of phthalate substances outside the 28 listed in the approach that should be considered in the analysis? Please provide supporting rationale.*

- The GoC should be including phthalate substitutes (e.g., trimelatate ester (TOTM), CAS RN 3319-31-1) in its assessments. Government officials indicated that there are no plans to address alternative plasticizers in the current Phthalate Grouping assessment activity.

Early Thinking on Approaches for a Potential Cumulative Risk Assessment for the Human Health Assessment

The presentation was an overview of the early thinking with respect to cumulative risk assessment approaches and considerations from a human health hazard and exposure perspective, in the context of the CMP. The presentation was followed by open discussion.

Stakeholder comments/questions included:

- Stakeholders were supportive of the government moving forward with a CRA of phthalates based on animal data.

- **Stakeholders asked if other anti-androgens could be considered in the CRA**. Government officials indicated that the CRA is expected to be limited to those substances currently in the Grouping (14 priority phthalates) and the additional 14 phthalates under consideration.
- **The GoC will look at both biomonitoring and modeling to characterize risk.** If there is a need, other methods can be used to indicate source attribution and will be considered if risk management is needed. Uncertainties associated with biomonitoring data will be included in the assessment.
- **Stakeholders inquired about effects outside the scope of phthalate syndrome** (e.g., a liver effect), since the HC approach typically entails use of a reference value (such as an oral reference dose), which is typically based on the most sensitive effect across all studied toxicity outcomes, to calculate a hazard quotient. The GoC stated that substances that are expected to be included into the CRA are those that act through a common MOA leading to effects of the RPS. For those substances in the substance grouping for which there are effects outside of the RPS, they will be assessed as part of the individual substance assessment.

NEXT STEPS AND CLOSING REMARKS

Overall, the Phthalates Stakeholder Workshop was well received. Two key observations were:

- Overall support exists for the categorization and the read-across approach, with constructive technical input on specific elements; and
- There is strong interest in staying engaged on scientific considerations as the GoC progresses in its assessment of the Phthalate Substance Grouping, in particular as the approach for a cumulative risk assessment is elaborated.

Officials of the government thanked participants, and indicated that input received throughout the workshop would strengthen the GoC's approach and future work on phthalates.