

Comments by BASF SE on the „Review of Exposure and Toxicity Data for Phthalate Substitutes
Contract No. CPSC-D-06-006, Task Order 004
Document prepared by Versar Inc. and Syracuse Research Corp.
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Page i, Executive Summary

The statement “*recently developed, DINCH lacks extensive toxicological data*” is incorrect. DINCH was registered in the EU nearly 10 years ago under the European Unions New Chemicals Entity legislation and has a broad database regarding physico-chemical, ecotoxicological and toxicological data that were developed in accordance with EU regulatory requirements. Those data include systemic toxicity following single through life-time exposure, reproductive toxicity, and developmental toxicity (in 2 species: rats and rabbits). Furthermore, BASF conducted additional studies for toxicological effects typically associated with phthalate esters. All studies were conducted according to GLP and to most recent OECD guidelines. Based on these results DINCH was approved in the EU. Subsequent approvals have been obtained in Switzerland, Australia, Canada, Japan, China and Korea. In the US, DINCH is listed in NSF Standard 61.

page 3

Cyclohexane-1,2-dicarboxylates are missing from the list of alternatives, yet DINCH is discussed in the Executive Summary and later in the document. This is an oversight. Cyclohexane-1,2-dicarboxylates, of which DINCH is a member, should clearly be listed as another alternative.

page 6,7

The document naively attempts to rank available data based on the metric “Toxline hits”. Such naïveté is inappropriate for a comprehensive review and cannot be used to determine sufficiency of toxicity information available. There are legal reasons, e.g. Regulation (EC) No. 1907/2006, toxicological studies generated in the last 10 years for registration of substances in the EU are not published. Using this metric only means that the reviewers have identified studies conducted prior to 2000; in fact, many of the studies for ATBC are pre-GLP and pre-guideline, which calls into question their utility. Thus, the conclusion that a lack of Toxline “hits” means no data is wrong! This is especially true for new and innovative products in the EU and is related to protection of proprietary rights. However, the competent authorities have evaluated all the reports of the respective studies; thus, for these substances just the opposite is true, i.e., all study reports underwent an indepth study evaluation by the competent authority in the country where the substance was notified. Acceptance of the studies is the required condition to obtain the notification of use.

Especially for new chemical entities the results in the literature searches by the consultants seem not to be not representative and obviously important and

publicly available information was missed. For example, the independent full public evaluation report from the Australian competent authority is missing. The NICNAS report is dated August 2008 and can be downloaded from the internet pages of NICNAS by the attached link:

<http://www.nicnas.gov.au/publications/car/new/std/stdsummr/std1000sr/std1259.asp>

Page 9, Table 1-1

We disagree with the terse evaluation of the cancer “negative effect” for DINCH. In the rat, DINCH resulted in an increased incidence of thyroid adenomas, by a mode of action known to be secondary and that according to US EPA guidance is not to be relevant to humans. Therefore, the statement “negative effect” is a misrepresentation.

Page 12, Table 2-1 and in each of the repeats of that table i.e 3-1 to 7-1 on pages 23, 37, 51, 58 and 73

Regarding **Hexamoll® DINCH**, the Koc value is missing:

Koc > 398107 (log Koc > 5,6 at 23°C; OECD121)
(log Koc = 5,82; calculated using US EPA Episuite 4.0
(Kowwin 1.67))

HENRYs LAW CONSTANT at 25 deg C = 7.06E-005 atm-m3/mole (calculated using US EPA Epi suite 4.0)

These data were part of the NICNAS report which the reviewers overlooked.

Page 36, 4.2, second line above Figure 4-1

The statement reads “isononyl **radicals**”. There are no “radicals” it should read “**isononyl residues**”. Also in Figure 4-1 it should read Diisononyl Cyclohexane-1,2-**Dicarboxylate** and not “*--Dicarbonylate*”

Page 37, Table 4-1 please refer to comment regarding page 12, Table 2-1

Page 37, last line of chapter 4.2

Partition coefficient and Henry’s Law constant were available (see e.g. NICNAS evaluation report)

Page 37, section 4.3, 1st paragraph

The statement “*Results showed that DINCH migrates quantitatively into foods with high fat content*” is a property generic to all plasticizers (see discussion of DEHA, ATBC, and DEHT). It is unclear why such a statement is made as though it is associated with DINCH alone.

page 38, 4.4 Toxicology

2nd paragraph, 3rd line:

It is clear that the reviewers are unfamiliar with the process within the EU. For example, reports were submitted by BASF SE (BASF AG at the time of submission), and not BASF Corporation. Further, reports submitted to the EU (not the EC) were confidential and such reports would **never** be publicly available on the internet (just as confidential data submitted to the US EPA OPPTS for a PMN are not publicly available). Finally, it is not clear to whom in BASF Corporation letters requesting access were directed. In any event, no access would be granted if the confidentiality of the reports could not be guaranteed. The phrasing in this section is totally misleading in that it portrays BASF SE and BASF Corporation as attempting to withhold information that:

- a) is summarized on public governmental websites, and
- b) is solely owned by BASF SE. BASF SE through its subsidiary, BASF Corporation, has offered on several occasions to provide the public Robust Summaries that are provided to the European Chemicals Authority, or to provide – under rules of confidentiality – the reports themselves.

Page 38, Section 4.4.1

“Elimination of DINP” should read “**Elimination of DINCH is rapid**”.

Same page two last lines should read:

(Primarily as **1,2-cyclohexane dicarboxylic acid**).

Page 40, last sentence regarding statistical significance

The statement “*The study did not report statistical significance*” is incorrect. The study report does include statistical evaluations, a fact which could have been confirmed simply by requesting clarification from BASF SE or BASF Corporation. The statistical analyses determined that a statistical significant increase of thyroid gland adenomas was observed in males from the mid- and the high dose groups and in females only the high dose group. (see excerpt from report below)

<i>Dose Group (24 months)</i>	<i>Males</i>				<i>Females</i>			
	<i>Control</i>	<i>Low</i>	<i>Mid</i>	<i>High</i>	<i>Control</i>	<i>Low</i>	<i>Mid</i>	<i>High</i>
Thyroid gland adenoma	3	5	11*	14**	1	3	3	9**
Hyperplasia, follicular cell	8	6	9	15	3	4	5	14

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Again, we challenge the statement of the second paragraph of the conclusions concerning the lack of data for DINCH. This substance has a very solid and extensive phys-chem., ecotoxicological and toxicological database. Clearly, there were basic errors in the data mining strategy of the consultants in that they

completely missed the full public evaluation report by NICNAS. NICNAS based its evaluation on the full study reports.

TOTM

Page 12, Table 2-1 and in each of the repeats of that table i.e 3-1 to 7-1

The water solubility listed for TOTM (100 mg/l @ 25°C) is physically impossible. If this value is derived from experimental data, it must be a method used previous to the Slow-Stir method recommended by EPA because the calculated value is much lower.

Calculation using EPIsuite 4.0 (WSKOW 1,67) results in a water solubility of **4.51 10⁻⁸ mg/l @ 25 °C**

Log Kow 5.94, based on the structure can't be right. Either > 5.94 or calculated value by EPIsuite 4.0 (Kowwin 1.67) **log Kow = 11.59**

Page 75

The study reports cited from secondary references can be obtained from MITI via the internet. It is not clear why the consultant did not download the reports?

Page 76

The statement that TOTM has the lowest migration potential is appropriate, but it ignores the fact that a major impurity is DEHP. Please see the publication by Welle et al. (2005) listed in the References that showed that in enteral nutrition fluids TOTM migration is low; however, the impurity DEHP migrated to such an extent that the tolerable daily intake was exceeded.

DINP

Page 12, Table 2-1 and in each of the repeats of that table i.e 3-1 to 7-1

Log Kow missing => in the EU Risk assessment report a value of 8.8 has been used for risk assessment purposes.