

TOX/2011/29

COMMITTEE ON TOXICITY OF CHEMICALS IN FOOD, CONSUMER PRODUCTS AND THE ENVIRONMENT (COT)

RESTRICTION REPORT*: PROPOSAL FOR A RESTRICTION Bis(2-ethylhexyl)phthalate (DEHP), Benzyl butyl phthalate (BBP), Dibutyl phthalate (DBP) and Diisobutyl phthalate (DiBP).

(Drafted by Danish CA)

Public Consultation

Referral

1. HSE have asked for advice from COT on the scientific basis used to propose restrictions on placing on the market of articles intended for use indoors in unsealed applications and articles that may come into direct contact with skin or mucous membranes containing one or more of the 4 phthalates (DEHP, BBP, DBP and DiBP) in a concentration greater than 0.1% by weight of any plasticized material.

Introduction

2. A brief introduction and background information is given below. A summary of the restriction report set out in the order adopted by the Danish CA for REACH (Danish EPA) is also provided. A copy of the report (excluding sections on alternative chemicals) is appended as Annex 1. An information paper was provided to members on the timeline for the publication of the Restriction report and UK input to EU-wide biomonitoring studies of phthalates (TOX/2011/27)

Danish EPA report on phthalates

3. The COT considered the report by the Danish Environmental Protection Agency (EPA) entitled '*Survey and Health Assessment of the Exposure of 2-year olds to Chemical Substances in Consumer Products*' at the February 2010 meeting.* The Committee did not consider that the information presented to the February 2010 meeting (summary and conclusion of the report) raised concerns which required urgent consideration. Members welcomed the approach to studying total exposures from a range of different scenarios. Members asked to see the full report and for further information on the exposure estimates and the basis for of the derived no effect level (DNEL). The COT considered the Danish EPA report at the June 2010 meeting. The risk assessments presented in the report focused on realistic worst-case exposure scenarios and were based on EU REACH guidance.

* Danish Ministry of Environment, EPA report No 102, 2009
<http://www.mst.dk/Publikationer/Publications/2009/10/978-87-92548-81-8.htm>

COT consideration of DBP in clogs

4 The COT considered a risk assessment of the use of di-n-butyl phthalate (DBP) in children's clogs at the December 2010 meeting. Members noted that the proposed worst-case risk characterisation ratio (RCR - exposure/DNEL) was likely to be an over-estimate, due to the conservative nature of the LOAEL (a dietary level of 20 mg/kg diet for effects on development of sperm in offspring (=1.5-3.0 mg/kg bw/day)), and the long duration (10 hours) that was assumed for wearing clogs. Members agreed that direct measurements of systemic uptake of DBP from clogs would be useful, together with information on the prevalence of DBP in the environment and how commonly it occurred in clogs. The Committee agreed that while small children were the critical population subgroup with regard to possible risks from DBP in rubber clogs, there was a need for biomonitoring studies in the UK with particular focus on women of childbearing age. This programme of work should explore the main sources of DBP exposure, and should investigate trends over time as well as patterns and determinants of exposure at baseline.

COT consideration of phthalates

5. The COT published a statement on dietary exposure to phthalates based on data from a Food Standards Agency (FSA) total diet study (TDS) in May 2011. A copy is appended for information as Annex 2. The COT did not attempt to review the entire toxicological literature on phthalates or to establish Tolerable Daily Intakes (TDIs) but noted the TDIs for a number of phthalates that had been set by the European Food Safety Authority (EFSA) in 2005. The COT concluded that the EFSA TDIs could be used in assessing possible risks from dietary exposure to phthalates since there had been no studies published since 2005 which might alter these TDIs. The EFSA TDIs for the phthalates which are considered in the Restriction Report, together with the relevant no observed adverse effect level (NOAEL) or lowest observed adverse effect level (LOAEL) and the uncertainty factor (UF) applied in setting the TDI are given in Table 1 below. These are also further considered in paragraph 7 below, and compared to the reference doses used in the Restriction report.

Table 1: EFSA TDIs previously applied by COT

Phthalate	EFSA TDI (mg/kg bw/day)	Critical study NOAEL/LOAEL and UF
DBP	0.01	Lee <i>et al</i> ,(2004) LOAEL 2 mg/kg bw/day. UF 200
DiBP	Not set	Not considered
DEHP	0.05	Wolfe and Layton (2003), NOAEL 5 mg/kg bw/day. UF 100
BBP	0.50	Tyl <i>et al</i> . (2001, 2004), NOAEL 50 mg kg bw/day. UF 100

This is a background paper for discussion. It does not reflect the views of the Committee and should not be cited.

6. The Restriction report presents a risk characterisation for all potential sources of exposure to phthalates including dietary exposure. The estimated high level dietary exposure (97.5th percentile to phthalates from the whole diet ($\mu\text{g}/\text{kg bw}/\text{day}$) from the FSA TDS is provided in table 2 below for the age groups considered in the Restriction Report (2 years, 6/7 years, adult). These data are compared in the appropriate section of this cover paper (paragraph 12) to the dietary exposure estimates used in the Restriction Report.

Table 2: Dietary intakes reported in the FSA Total Diet Study (TDS) ($\mu\text{g}/\text{kg bw}/\text{day}$)

Age group	DBP	DIBP	DEHP	BBP
>1.5-2.5 years	0.4-1.0*	1.4-2.7	6.9-9.9	0.07-1.3
>2.5-3.5 years	0.4-0.8	1.3-2.1	6.3-7.9	0.07-1.1
4-6 years	0.4-0.7	1.0-1.8	5.5-6.7	0.06-0.9
7-10 years	0.3-0.6	0.9-1.5	4.6-5.2	0.05-0.7
Adults	0.2-0.3	0.6-0.9	3.4-4	0.04-0.5

*Ranges represent lower bound (undetectable concentrations were assumed to be zero) to upper bound (undetectable concentrations assumed to be at the limit of detection)

6. Overall the Committee concluded that levels of phthalates that were found in samples from the 2007 TDS do not indicate a risk to human health from dietary exposure alone, either when the compounds are considered individually, or when they are assessed in combination. The Committee considered information on combined effects of phthalate esters, and agreed that, in view of their similar structure and toxicological effects (the Committee noted that reproductive effects were seen with most, if not all, of the phthalates for which information was available), as a first tier approach, a cumulative risk characterisation was appropriate, based on an assumption of dose-additivity. Due to the lack of established TDIs and limited toxicological information for many of the phthalates a hazard index or relative potency factor approach was not possible.

Restriction Report

Reference Dose Levels for phthalates

7. The reference dose level derived in the Restriction Report for use in risk characterisation is the internal Derived No Effect Level. (i.e. critical (NOAEL/LOAEL)/UF x Absorption factor). A review of the critical studies used for reference dose setting is provided in section B5.9 pages 61-72 (see tables 16 and 17 of Restriction Report). A summary is provided in table 3 below.

Table 3: Reference Doses used in the Restriction Report

Phthalate	Internal DNEL (mg/kg bw/day)	Critical study NOAEL/LOAEL UF, Absorption factor	Comment
DBP	0.0067	Lee <i>et al.</i> (2004) 2 mg/kg bw/day, UF 300, Abs 1.0	Same critical study as used by EFSA, but larger UF used (300 v 200)
DiBP	1.25	Sallenfait <i>et al.</i> (2008), 125 mg/kg bw/day UF 100, Abs 1.0	Based on reduced AGD, and nipple retention. Study not previously seen by COT (see Annex 3)
DEHP	0.025	Wolfe and Layton (2003), 4.8 mg/kg bw/day, UF 100, Abs 0.5	Same critical study as used by EFSA, but using absorption of 50%. Further study by Christiansen <i>et al.</i> (2010) with NOAEL of 3 mg/kg bw/day also cited (See Annex 3)
BBP	0.5	Tyle <i>et al.</i> (2004), 50 mg/kg bw/day, UF 100, Abs 1.0	Same critical study and UF as used by EFSA.

Exposure Assessment

8. A literature search for the best available exposure estimates on human exposure to DBP, DiBP, DEHP, BBP via articles, food, indoor environment and from biomonitoring studies (urine samples) was undertaken and the data converted to internal dose estimates ($\mu\text{g}/\text{kg}$ bw/day) when absorption is less than 100%. Exposure estimates were calculated for 2 year olds (15.2 kg), 6/7 year old (23.1 kg) and for adults (60 kg). The authors estimated the lowest median and highest median exposures (considered to represent a realistic scenarios) and the 95th percentile exposure (considered to represent a realistic worst case scenario).

Articles (section B.9.3.2.2)

9. Dermal exposure to articles was based on a number of surveys undertaken by the Danish EPA and is summarised on pages 80-85 of the Restriction report (see summary table 20 on page 84). A broad range of articles was investigated and considered to be representative for articles found indoors or in direct contact with skin. From the analysis presented the major determinants were sandals for children (see table below) and sex toys for adults. In adults the intake of DEHP was 0.02 $\mu\text{g}/\text{kg}$ bw/day (based on migration to simulated saliva) and 18.3 $\mu\text{g}/\text{kg}$ bw/day worst case migration into simulated saliva and oil based lubricant.. Oral exposure was based on the approach recommended by ECHA (page 85-87). The major determinant of oral exposure was mouthing/eating rubber erasers by children DEHP intake

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of 15.8 µg/kg bw/day for mouthing and 176 µg/kg bw/day for eating eraser. The authors note uncertainties in the estimates of exposure but considered that only a range of all the potential articles had been included in the report.

A summary tabulation of estimated dermal exposure from sandals is given in table 4 below. Further details are in table 20, page 84 of the Restriction report.

Table 4: Estimated dermal doses of phthalates from sandals

Phthalate	Age group	Median exposure µg/kg bw/day	Worst case µg/kg bw/day
DEHP	2 years	0.8986	3.6179
	6/7 years	1.8700	ND
	Adult	1.1664	1.4332
DiBP	2 years	ND	3.5578
	6/7 years	ND	ND
	Adult	4.9212	2.6122
DBP	2 years	ND	ND
	6/7 years	ND	3.9076
	Adult	0.8629	5.4971

ND= No data

Indoor environment (section B.9.3.2.3)

10. Estimated intake of phthalates in dust is presented below in table 5 and also in table 23, page 90 of the Restriction Report. Dust intake was considered to be 50 mg/day in adults and 100 mg/day in children. From the survey of published data on phthalate levels in dust, the study by Bornehag *et al.* (2005) was chosen for the calculation of realistic worst case intakes.

Table 5: Phthalate intakes from dust

Phthalate	2y median (95 th percentile) µg/kg bw/day	6/7 y median (95 th percentile) µg/kg bw/day	Adult median (95 th percentile) µg/kg bw/day
DBP	0.99 (3.74)	0.65 (2.46)	0.13 (0.47)
DiBP	0.3 (2.0)	0.19 (1.3)	0.04 (0.26)
DEHP	5.07 (26.77)	3.33 (17.61)	0.32 (1.70)
BBP	0.89 (3.94)	0.58 (2.59)	0.11 (0.50)

11. Exposure to phthalates from indoor air was determined by simulation and calculation based on the method used in the EU Risk Assessment report on DEHP and from data found in the literature (for DEHP). Estimated steady state levels in air are presented in table 24 (page 93 of report). Exposure to DEHP predominates and thus only potential exposure to DEHP for indoor air was taken forward to risk characterisation. For DEHP there was good agreement between simulated and literature estimations. The authors used simulated data for use in risk assessment 0.81 µg/m³ for realistic worst case and 0.16 µg/m³ for realistic exposure. An example calculation of inhalation exposure for DEHP is given on page 96.

Exposure from food (Section B.9.3.2.4)

12. Exposure from food in the Restriction Report was based on literature data where the highest published values were selected (pages 97-104 of the Restriction report). Internal dose estimates were reported assuming 100% absorption for DBP, DiBP, and BBP and 50% absorption for DEHP. The data are presented in table 27 (pages 101-102). Table 6 below reports the estimates used in the Restriction Report and the ratio of this estimate compare to estimated intakes reported to the COT when the Total Diet Survey for phthalates was considered. These data show that the published dietary exposure data overestimate actual intakes from around two-fold for DiBP and DEHP to possibly several orders of magnitude for DBP and BBP.

Table 6: Estimates of dietary intake used in Restriction report and comparison to intake estimates reported in the FSA TDS. Median intake (95th percentile intake)

Phthalate	2 years µg/kg bw/day (95 th)	6/7 years µg/kg bw/day (95 th)	Adult µg/kg bw/day (95 th)	Ratio Danish EPA (2 years)/ FSA (1.5-2.5 years)*	Ratio Danish EPA (6/7 years)/FSA (4-6 years)*	Ratio Danish EPA/FSA (Adult)*
DBP	8.0 (20)	3.5 (10)	1.6 (10.2)	20-50	14.3-25	34-51
DiBP	0.48 (2.4)	0.2 (1.0)	0.5 (1.5)	0.9-1.7	0.6-1.0	1.7-2.5
DEHP	26 (31)	11 (16)	2.3 (7.8)	3.1-4.5	2.4-2.9	2.3-2
BBP	5.9 (9)	2.4 (0.8)	1.0(4.5)	6.9-128.6	0.9-13.3	9-112.5

*Ratio of Danish EPA 95th percentile estimate compared to 97.5th percentile estimate in Total Diet Study.

Exposure based on biomonitoring data (Section B.9.3.2.7)

13. The Danish EPA undertook a comparison of estimated exposure data with biomonitoring data to see if exposure levels estimated by calculation and simulation are in agreement with biomonitoring data. Tabulated exposure estimates based on biomonitoring studies are presented in table 28 (pages 107-109). Estimates based on volume of urine or urinary creatinine are presented when available. From page 105 of the Restriction Report only studies reporting exposure estimates based on measured urinary concentrations were included. Urinary volume estimates were used to generate realistic worst case exposure data. The estimates are generally higher in children than adults, most likely due to children's higher intake of food and dust in combination with lower body weight, and behaviour such as a tendency to mouth articles. A summary of the selected exposure estimates used for risk characterisation is given in table 7 below. The authors discussed whether these values reflect usage prior to restrictions on phthalates but overall concluded that overestimation is unlikely to be high.

Table 7: Estimated exposure derived from biomonitoring studies ($\mu\text{g}/\text{kg bw}/\text{day}$).

Phthalate	Age group	Median	95 th percentile	Basis of exposure estimate
DBP/DiBP	4-11years	7.6 (4.1)	30.5 (14.9)	Urinary volume (creatinine)
DBP	Adult	2.2	7.3	Urinary volume
DIBP	Adult	1.5	4.2	Urinary volume
DEHP	2-4years	10.7 (5.7)	45.0 (23.4)	Urinary volume (creatinine)
	5-6 years	10.0 (6.1)	19.4 (14.7)	Urinary volume (creatinine)
	Adult	2.7	6.4	Urinary volume
BBP	4-11 years	0.77 (0.42)	4.5 (2.6)	Urinary volume (creatinine)
	adult	0.88	4.0	Urinary Volume

Risk Characterisation

14. A cumulative risk characterisation was undertaken using dose addition to summarize the risk of cumulative phthalate exposure. RCRs were calculated for 2 year-old children, 6/7 year-old children and adults. The rationale for this was that 2 year-olds will often mouth articles, whereas 6/7 year-olds are not expected to mouth many articles, but will have greater dermal contact with articles compared to adults.

RCRs for exposure to phthalates from articles

15. RCRs for total phthalate exposure from articles are given in table 8 below. The order in which phthalate esters contributed to RCR calculations was DEHP>DBP>DIBP. It was also noted that DBP contributed significantly to the overall RCR for adults (specifically in relation to DBP in sandals). With regard to 6/7 year-old children, the predominant contributor was DEHP from mouthing erasers. RCRs exceeded 1 for the 95th percentile exposure to articles for 6/7 year-old children and for adults. The authors noted that the exposure particularly for the 'worst case scenario' (95th percentile exposure) is likely to be an overestimate.

Table 8: RCRs from articles (taken from table 29, pages 111-112 of Restriction Report) (combined DEHP, DBP, DIBP, BBP)

Age group	RCR based on lowest median	RCR based on high median	RCR based on 95 th percentile
2 years	0.07	0.07	0.18
6/7 years	0.74	0.74	7.65
Adult	0.19	0.19	1.62

RCRs for the Indoor environment

16. RCRs for total phthalate exposure from dust and total DEHP exposure from indoor environment (dust + indoor air) are given in tables 9 and 10 below. The order in which phthalate esters contributed to RCR calculations was DEHP>DBP>BBP>DIBP. RCRs for dust exceeded 1 for the 95th percentile exposure to articles for 2 year-old and 6/7 year-old children. RCRs for indoor air exposure to DEHP were all well below 1.

Dust

Table 9: RCRs from dust (taken from table 30 page 113) (combined DEHP, DBP, DIBP, BBP)

Age Group	RCR based on lowest median	RCR based on high median	RCR based on 95 th percentile
2 years	0.11	0.36	1.63
6/7 years	0.072	0.24	1.08
Adult	0.009	0.032	0.14

Indoor environment DEHP

Table 10: RCRs for DEHP from the indoor environment (taken from table 30 page 113 of Restriction Report)

Source	Age group	RCR based on lowest median	RCR based on highest median	RCR based on 95 th percentile
Indoor air	2 years	0.01	0.01	0.05
	6/7 years	0.012	0.012	0.06
	adult	0.0023	0.0023	0.01
Indoor environment total (dust+indoor air)	2 years	0.12	0.37	1.68
	6/7 years	0.084	0.252	1.14
	adult	0.0113	0.0343	0.15

RCRs from food

16. RCRs reported in the Restriction Report for total exposure to phthalates from food are presented in table 11 below. The order in which phthalate esters contributed to RCR calculations was DBP>DEHP>BBP>DIBP. The RCRs were >1 for high median exposure (2-year-olds) and for the 95th percentile exposure for all age groups. The authors noted that exposure to phthalates in foods was likely to be overestimated in the Restriction Report as no current data were available.

Table 11: RCRs from food (taken from table 31, page 114 of Restriction Report) (combined DEHP, DBP, DIBP, BBP)

Age group	RCR lowest median	RCR high median	RCR 95 th percentile
2 years	0.24	2.2	4.24
6/7 years	0.17	0.97	2.13
Adult	0.078	0.33	1.82

17. RCRs can also be calculated using the 97.5th percentile intake of DBP, DIBP, DEHP and BBP reported in the FSA TDS (see table 3 of COT Statement on dietary exposure to phthalates Annex 2). Using the total upper bound estimates of phthalate exposure (i.e. DEHP + DBP + DIBP + BBP; thus for 1.5-2.5 year old child = 14.9 µg/kg bw/day, 4-6 year old child = 9.3 µg/kg bw/day and adult = 5.7µg/kg bw/day) the following RCRs in tables 12 and 13 are calculated

Table 12: Calculated RCRs based on dietary exposure data from FSA TDS and using reference dose levels proposed in the Restriction Report

Age	DEHP RCR	DBP RCR	DIBP RCR	BBP RCR
1.5-2.5 years	0.396	0.149	0.002	0.003
4-6 years	0.268	0.104	0.001	0.002
Adult	0.16	0.045	0.0002	0.001

Table 13: RCRs for total phthalates (DEHP+ DBP + DIBP +BBP) and 97.5th percentile dietary intake (using TDS for phthalates) and reference doses set in the Restriction Report.

Age group	Total phthalate RCR 97.5 th percentile
1.5-2.5 years	0.55
4-6 years	0.375
Adult	0.206

RCRs based on biomonitoring data

18. RCRs were calculated for a child (aged 4-11 years) and for adults, as reported in table 14 below. The authors noted that these data may have also estimated current exposures to phthalates as many of the studies predated regulatory restriction on phthalates. However it was also noted that there were some restrictions in place on phthalates before the biomonitoring studies were undertaken.

This is a background paper for discussion. It does not reflect the views of the Committee and should not be cited.

Table 14: RCRs from biomonitoring data (table 32 page 115 of Restriction Report) (combined DEHP, DBP, DIBP, BBP)

Age	RCR lowest median	RCR highest median	RCR 95 th percentile
Child (4-11 years)	0.6	1.5	5.4
Adult	0.2	0.4	1.4

Overall RCRs (articles+ indoor environment + food)

19. Summed RCRs were calculated for all routes of exposure. A table summarising the evaluation presented in the Restriction Report is given in table 15 below along with a separate table using RCRs calculated using dietary intake data from the FSA TDS of phthalates (table 16).

Table 15: RCRs combining phthalate exposures from dust, food, consumer products.

Phthalate source	Age	RCR lowest median	RCR highest median	RCR 95 th percentile
Articles and indoor environment	2 years	0.12	0.426	1.86
	6/7 years	0.824	0.982	8.79
	Adult	0.201	0.224	1.77
Food	2 years	0.24	2.2	4.24
	6/7 years	0.17	0.97	2.13
	Adult	0.078	0.33	1.82
Total (articles indoor environment and food)	2 years	0.43	2.7	6.10
	6/7 years	1.0	1.9	10.9
	Adult	0.28	0.55	3.59

Table 16: Calculated RCRs for phthalates from food (using FSA TDS estimates of phthalate intake)

Age	RCR total
2 years	2.41
6 years	9.17
Adult	1.77

20. The calculated RCR (total exposure) for adults in Table 16 is in close agreement with the biomonitoring derived RCR (1.77 cf 1.4 for biomonitoring). There is less agreement for the RCR (total exposure) given in Table 16 for children compared to the biomonitoring RCR (cf 2.41 for child aged approximately 2years and 9.17 for a child aged approximately 6 years compared to 5.4 for child based on biomonitoring data).

Epidemiology studies considered in Restriction Report

21. A brief review of epidemiology studies which possibly contribute to evidence for congenital effects and malformations of the male genitalia, semen quality, pubertal timing and testicular cancer is provided in the Restriction report on pages 72-75. Overall it was considered that it was '...difficult to draw exact conclusions from these studies but they could be seen as contributing to the overall picture.' The COT reviewed a number of epidemiology studies when considering the toxicological data on DBP. COT agreed there was some evidence for an effect of phthalates on anogenital distance (AGD). A summary of the papers reviewed by COT can be found as Annex 6 to TOX/2010/36. There were a number of studies considered by COT which have not been cited in the Restriction Report. Copies of relevant papers were appended to TOX/2010/36 and can be provided again on request.

COT Discussion and questions

22. The COT have been asked to advise on the science underpinning the proposal to restrict phthalate esters in articles including those likely to come into contact with skin.

- i. Are members content with the reference doses adopted in the Restriction Report? The critical studies selected are the same as those used by COT for DEHP, DBP and BBP, although a higher uncertainty factor has been used for DBP. In addition a reference dose was not used for DIBP in the COT evaluation.
- ii. Are members content with the exposure estimations presented in the Restriction Report? Thus with regard to the Restriction Report, overall major inputs to exposure arise from certain uses of articles and food. Are members content with these estimations? Do members agree that exposure from food has been significantly over estimated in the Restriction Report?
- iii. Are members content with the exposure estimated from biomonitoring studies?
- iv. Are members content with the calculated RCRs for total exposure to the 4 phthalates under consideration? Do the RCRs suggest the need for risk management measures, even when food intake as reported in the FSA Total Diet Study are included?
- v. Do the RCRs based on biomonitoring studies suggest the need for risk management measures?
- vi. What weight of evidence can be attached to the information from epidemiological studies included in the Restriction Report?

This is a background paper for discussion. It does not reflect the views of the Committee and should not be cited.

References

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This annex contains pages 1-127 and 216-343 of the Restriction Report, version number 2, 12 August 2011,

For copyright reasons the report is not included in the paper on the COT website. The full report can be accessed via

http://echa.europa.eu/reach/restriction/restrictions_under_consideration_en.asp

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COT STATEMENT ON DIETARY EXPOSURE TO PHTHALATES – DATA FROM THE TOTAL DIET STUDY (TDS) - COT statement 2011/04

available to download at:

<http://cot.food.gov.uk/cotstatements/cotstatementsyrs/cotstatements2011/cot201104>

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This annex contains 2 published papers:

Saillenfait AM, Sabaté JP, Gallissot F. Diisobutyl phthalate impairs the androgen-dependent reproductive development of the male rat. *Reprod Toxicol.* 2008 Oct;26(2):107-15.

Christiansen S, Boberg J, Axelstad M, Dalgaard M, Vinggaard AM, Metzdorff SB, Hass U. Low-dose perinatal exposure to di(2-ethylhexyl) phthalate induces anti-androgenic effects in male rats. *Reprod Toxicol.* 2010 Sep;30(2):313-21.

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