


Occupational exposure to phthalates. Urinary biomonitoring.

Alain ROBERT, INRS (France)

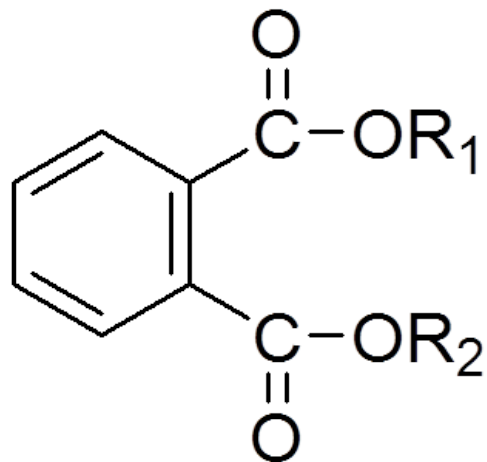
Symposium organized by the French National Research and Safety Institute (INRS) and the Chemistry section of the International Social Security Association (ISSA)

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Les phthalates

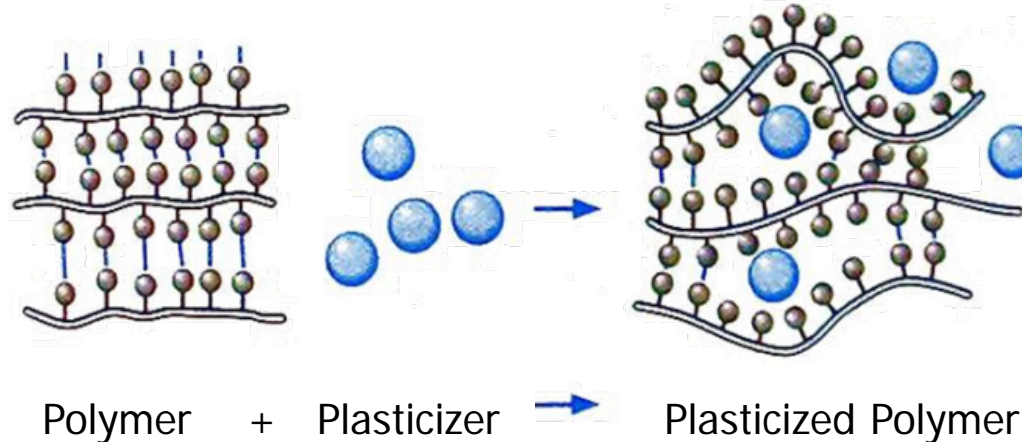
DEHP, DINP, DBP, BBP, DEP, DIDP...



- Chemicals derived from phthalic acid, consisting of a benzene ring and two carboxylate groups with linear or branched alkyl chains R1 and R2 in different sizes
- 3 million tons per year worldwide
- Phthalates are used as plasticizers to make plastics flexible
- They are not chemically bound

An emblematic phthalate: di(2-ethylhexyl) phthalate (DEHP)

- Plasticizer of PVC, 100,000 tons used in the EU (500,000 in 2005)
- 20 to 50% by weight of DEHP are contained in flexible PVC
- DEHP present in many objects of daily life, cosmetics, medical devices...



The effects on health?

(European and American risk assessments)

- Carcinogenic effect (controversial) : - IARC* downgraded from group 2B to group 3 (2000),
- US EPA° group 2B (possible human carcinogen)
- Toxic for reproduction (category 1B of the EU classification) -
suspected endocrine disruptor (decreased anogenital distance, feminization, decreased fertility, hypospadias, cryptorchidism)
- Carcinogenic, Mutagenic and toxic for Reproduction (CMR decree of February 1, 2001)
- Banned by EU in toys (1999), childcare articles (2005), tubes in pediatric, neonatal and maternity (2012)
- Irritating to the respiratory tract (asthma?)

Mentioned in the literature: obesogenic and neurotoxic effects

*International Agency for Research on Cancer

° Environmental Protection Agency (EPA)

DEHP is ubiquitous

(like all phthalates)

Blount (National Center for Environmental Health, USA) in 1999 and **Koch** (Institute and Outpatient Clinic of Occupational, Social and Environmental Medicine, University of Erlangen-Nuremberg, Germany) in 2002 showed the presence of urinary metabolites of phthalates in the general population.

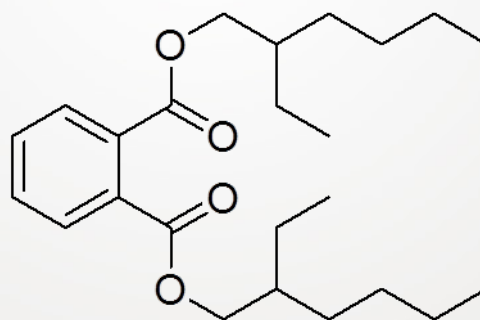
Attested presence in:

amniotic fluid, breast milk, umbilical cord, fetus ...

Field studies

- **Dirven** (1993) measured several urinary metabolites of DEHP and the exposure levels of DEHP (individual samples) in PVC industry workers
-> no correlation
- **Pan** (2006) observed a small, but significant, decrease in plasma testosterone levels for Chinese workers heavily exposed to DEHP and DBP
- Risk assessments point to a lack of occupational exposure data (EU, USA)
- In France, no occupational data (but data concerning transfused and dialyzed individuals)

Biological monitoring of occupational exposure to di(2-ethylhexyl) phthalate (DEHP)



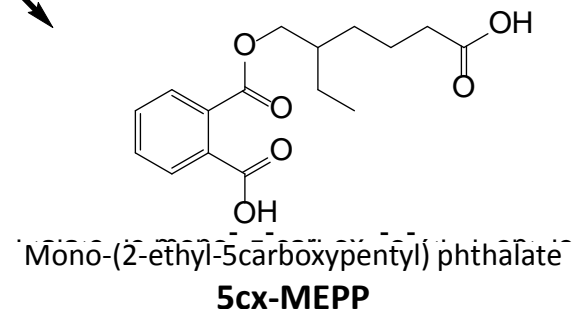
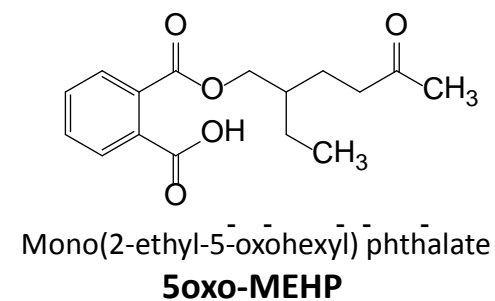
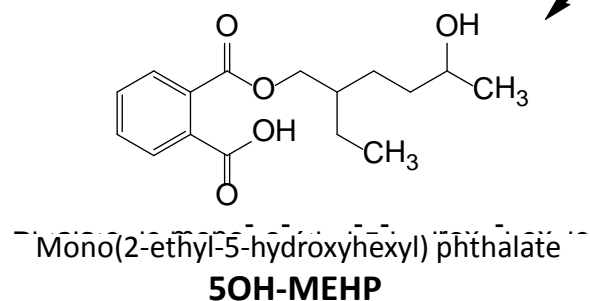
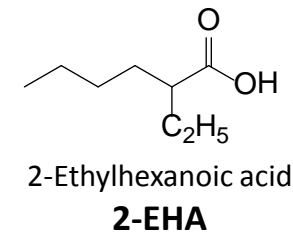
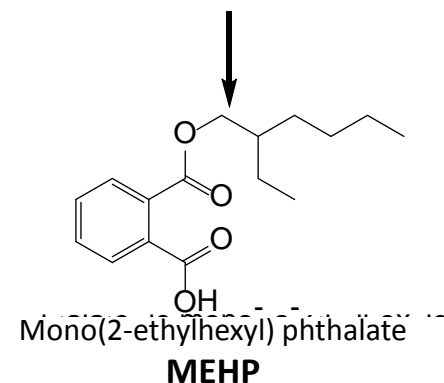
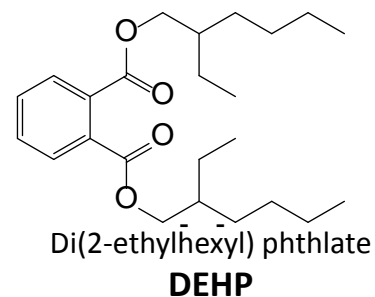
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Analyzed urinary metabolites

DEHP metabolism in Human
(Koch *et al.* 2006)

HPLC-MS/MS analysis with « on-line »
urine preparation after enzymatic
hydrolysis
CEA Saclay France (2002-2004)
External quality control



A vertical strip on the left side of the slide shows a close-up of industrial machinery, likely a green-painted metal structure with various pipes and components.

Study design

Preliminary actions

- Agreement of the French National Commission for Computing and Liberties (CNIL)
- Choice of factories or establishments - involvement of occupational medicine and CARSAT*
- Agreement of the factories, information, presentation of the study in HSC, informed consent of employees

Methodology

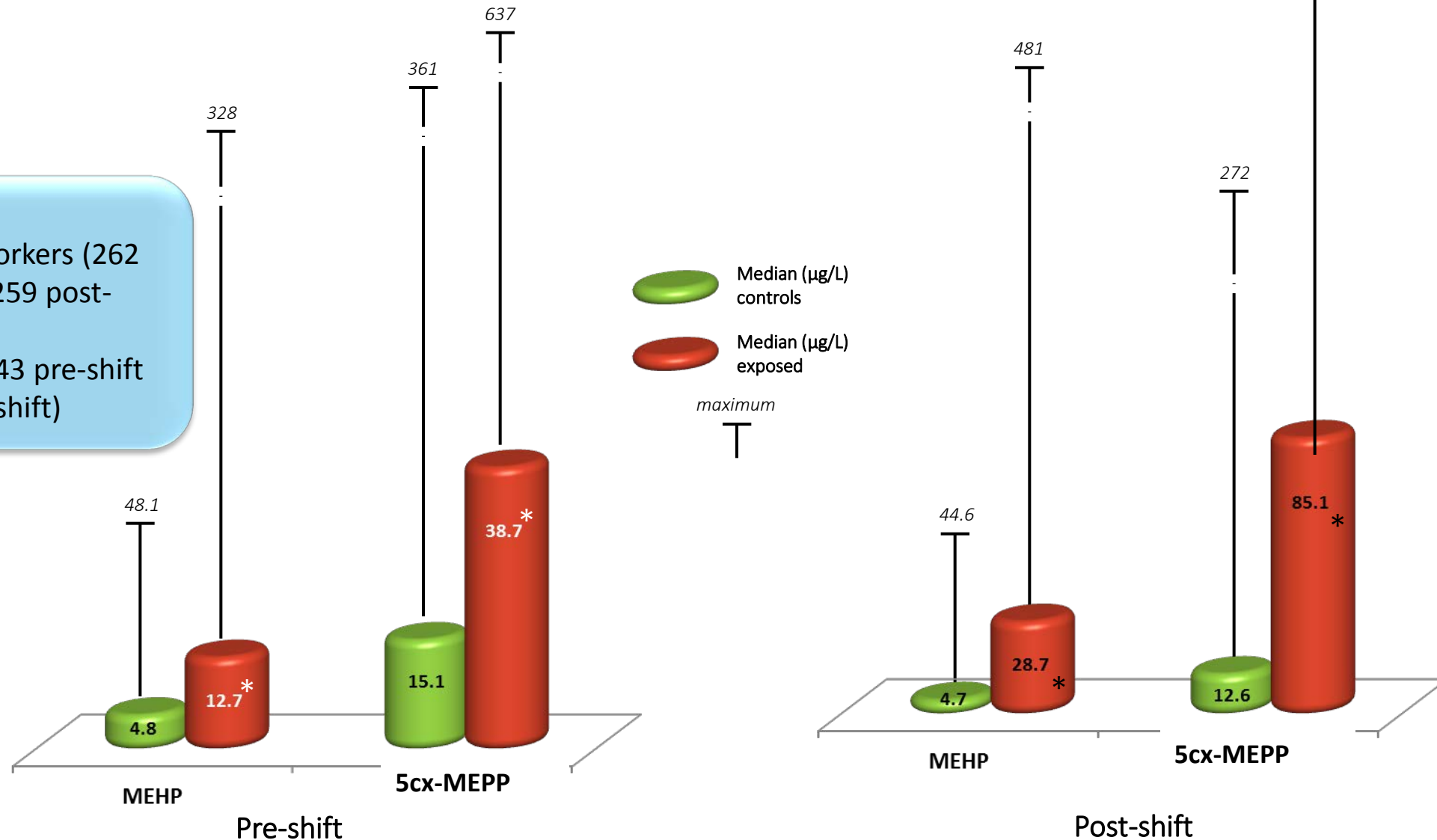
- Pre- and post-shift urine samples collected during a week of work, exposed workers and controls (administrative departments)
- Questionnaire : job, tasks, protective equipment...

* Regional Health Insurance Funds

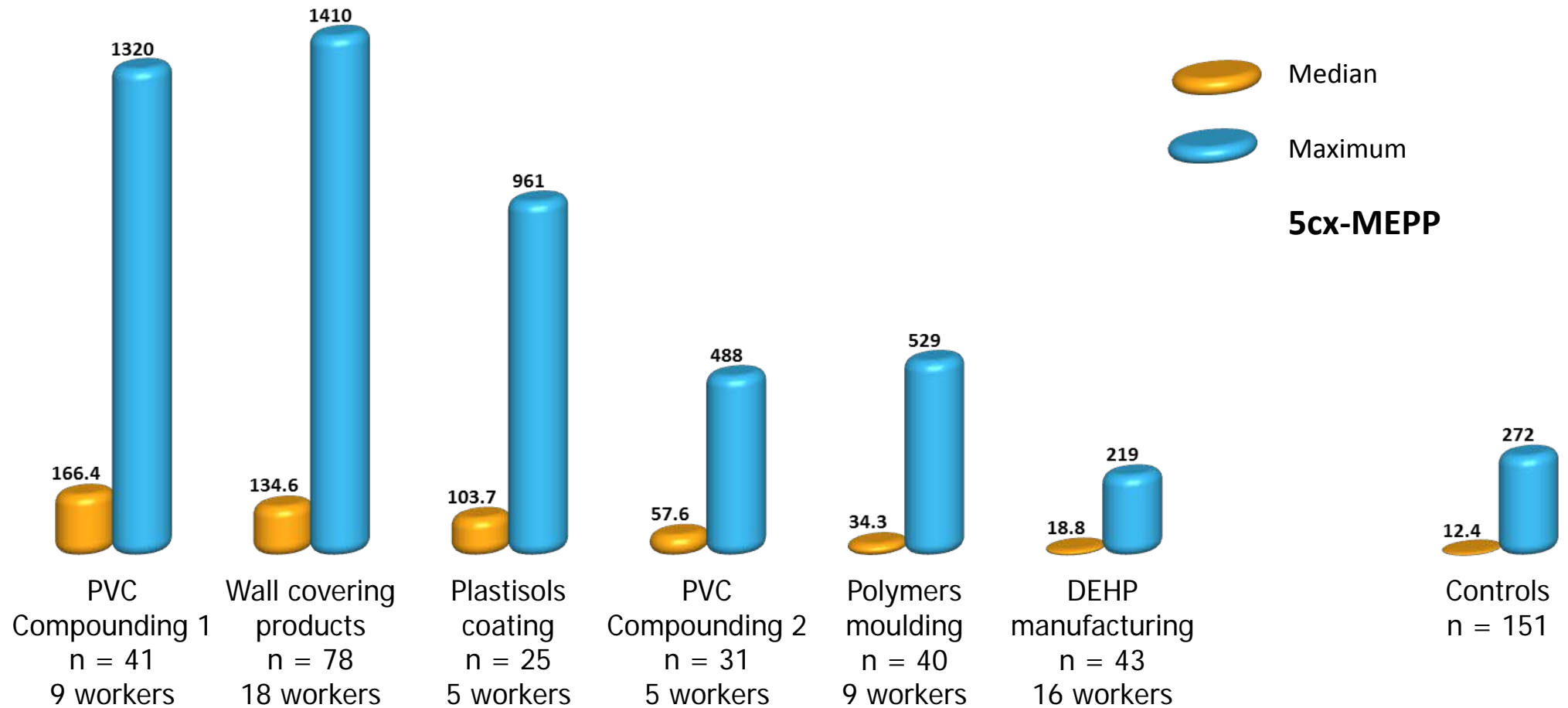
Results (2005-2008): evident occupational exposure to DEHP

- 6 factories
- 62 exposed workers (262 pre-shift and 259 post-shift)
- 35 controls (143 pre-shift and 139 post-shift)

* $P < 0.05$
Mann-Whitney Test



Industry sectors : highly variable occupational exposures



Data in reference populations

		MEHP (µg/L)		5cx-MEPP (µg/L)	
		Median	95th	Median	95th
US population	• NHANES* 2005-2006, n=1490, 20 years old and more.	2.3	41.5	35.1	377.0
	• BLOUNT et al. 2000 1988-1994, n=298 from 20 to 60 years old	2.7	21.5	-	-
	• SILVA et al. 2006 2003-2004, n=129, adult military	3.1	17.0	15.6	159.0
German population	• Koch et al. 2003 1999-200, n=85	10.3	37.9	-	-
	• WITTASEK et al. 2007 1988-2003, n=60, students	4.6	25.2	17.5	61.6
Controls INRS	• GAUDIN et al. 2001 2005-2007, n=282, administrative staff	4.7	24.3	14.1	102.3

Pan (2006), chinese population, n=63, MEHP, median 7.6 and 95th 32.5 µg/L

* National Health and Nutrition Examination Survey

Data in industry sectors

		MEHP		5cx-MEPP	
Industry sector		Median	Maximum	Median	Maximum
DIRVEN 1993	Boot factory (n=9)	169.8		124.7	-
	Cable factory (n=6)	119.8		48.4	-
PAN 2006	PVC flooring (n=74)	787			
Hines 2009	DEHP manufacturing (n=9)	7.6	28	-	-
	PVC film (n=25)	37.3	257	283	2030
	PVC compounding (n=12)	29.2	220	391	1080
	Vehicle filter (n=18)	11.1	67	-	-
	Rubber hose (n=25)	7.6	107	51.4	497
	Rubber boot (n=21)	12.5	117	132	3520
GAUDIN 2011	DEHP manufacturing (n=16)	5.6	104	18.8	219
	Plastisols coating (n=5)	55.9	303	103.7	961
	PVC compounding 1 (n=9)	52.0	467	166.4	1310
	PVC compounding 2 (n=5)	17.3	90	37.6	488
	Polymers moulding (n=9)	18.3	248	34.3	529
	Wall covering products (n=18)	41.9	481	134.6	1410

Daily intakes (DI)

- The DI can be calculated from the concentrations of urinary metabolites
- Comparison to the recommended guiding values

- TDI of 50 µg/kg/day (EFSA* – EU)
- RfD of 20 µg/kg/day (US EPA°)

Tolerable Daily Intake : no adverse effect on reproductive system

Reference Dose : liver cancer

* European Food Safety Authority (EFSA)

$$DJ(\mu\text{g}.\text{kg}^{-1}.\text{j}^{-1}) = \frac{CU(\mu\text{g}.\text{g}^{-1}) \times CE(\text{mg}.\text{kg}^{-1}.\text{j}^{-1}) \times Md}{FUE \times 1000(\text{mg}.\text{g}^{-1}) \times Mm}$$

David, Kohn et al.
(2000)

Hines et al. (2011)

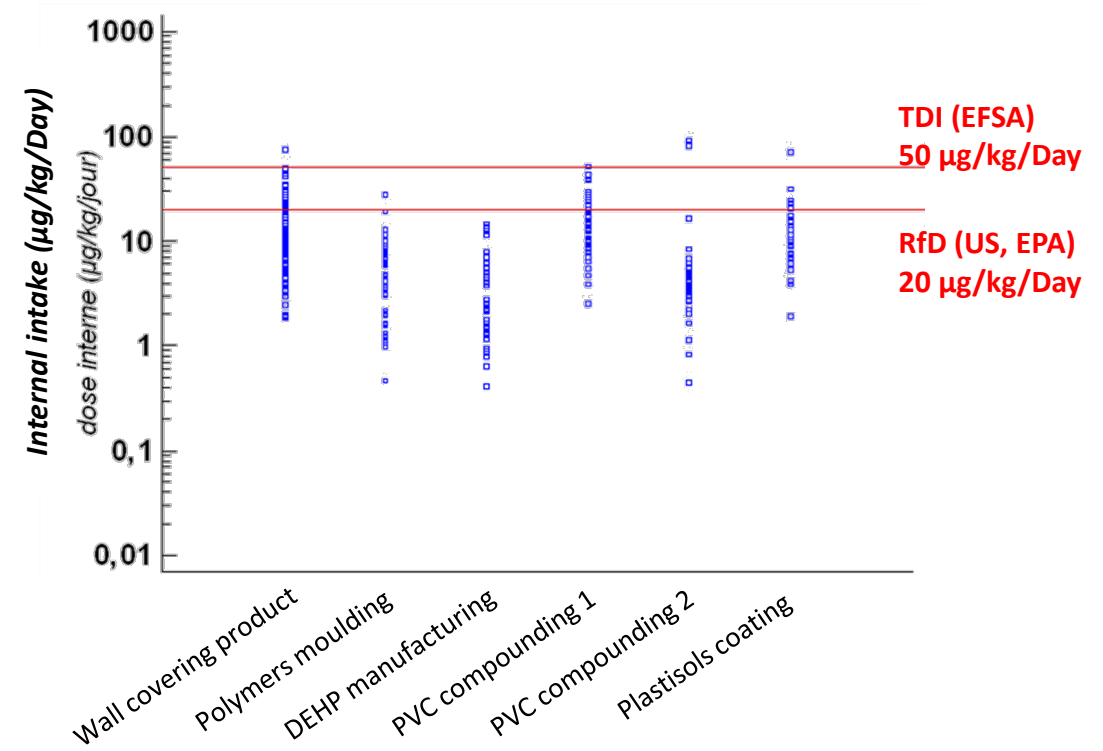
CU : urinary concentration of metabolite en µg/g de creatinine (post-shift)

CE : creatinine excretion rate normalized by body weight (23 and 18 mg/kg/day for men and women respectively)

FUE : molar excretion fraction of metabolite determined after oral absorption (%)

Md : molecular weight of diester

Mm : molecular weight of monoester

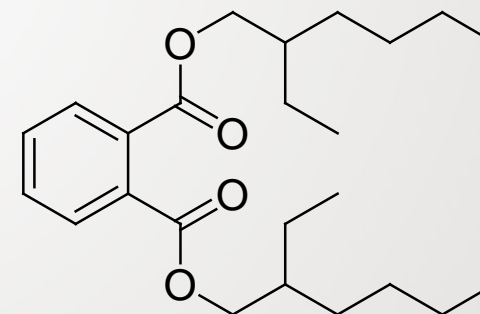


Proposition ANSES* (2011)

- Biologic Exposure Indice (BEI) : 5cx-MEPP
- No Biologic Limit Value (BLV)
 - Based on a health effect (aspermatogenesis)
 - Based on an time-weighted average (TWA) value (0,8 mg/m³)
- Reference Biologic Value (RBV) in the general population (95th percentile)
200 µg/g de creatinine

* French Agency for Food, Environmental and Occupational Health & Safety

Biological evaluation of occupational exposure to di(2-ethylhexyl) phthalate (DEHP) linked to wearing vinyl gloves



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Why this study ?



- Question of an occupational physician :

Does the use of vinyl gloves expose workers to DEHP ?

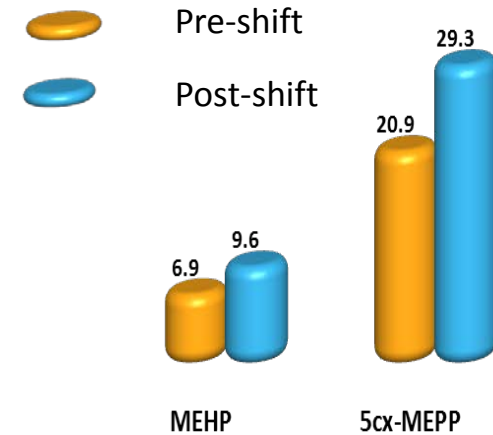
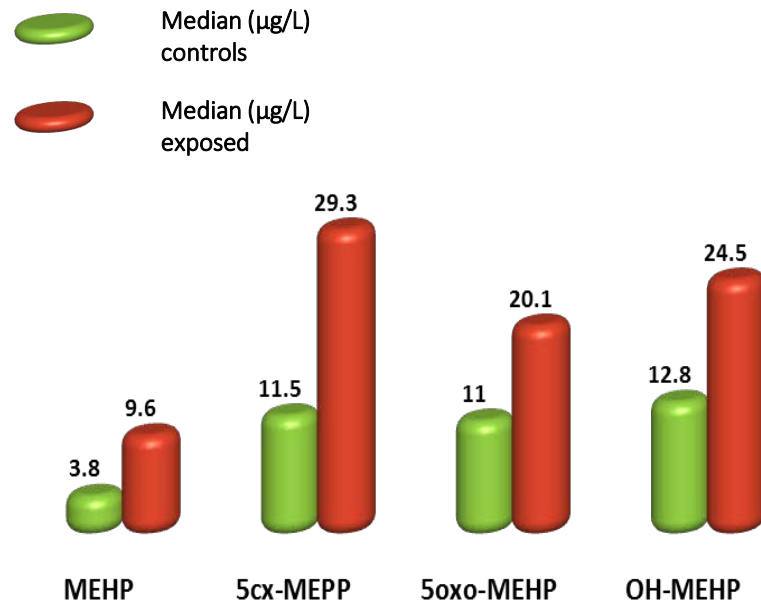
Vinyl gloves

- 20 to 40% of phthalates (mostly DEHP)
- Widely used in hospital and food sectors ; inexpensive ; substitutes for latex gloves (allergies)
- Wearing gloves induce a contamination estimated (theoretical model) to 42-420 µg/day (DEHP Risk assessment, final report 2008, US)
- Vinyl gloves banned in Japan in the food industry
- Restricted use in France: plastics with DEHP prohibited if contact with fat

Results (2009-2012): exposure not negligible to DEHP

- **3** hospitals
- **50** exposed workers (106 pre-shift and 104 post-shift)
- **14** controls (49 pre-shift and 37 post-shift)

- Urinary levels two to three times higher than in controls
- Possible bias : medical equipments, cleaning products
- Shipping time and number of gloves, not significant
- Measures in a poultry slaughterhouse – gloves without DEHP



Daily intakes (DI)

- Median value of DI calculated for all hospitals
4.4 $\mu\text{g/kg/day}$,
- far from the Tolerable Daily Intake (TDI) established by EFSA (no adverse effect on the reproductive system)
50 $\mu\text{g/kg/day}$
- but close to the maximum internal exposure values by dermal contact to gloves from theoretical models (EU risk assessment),
6.7 et 9.3 $\mu\text{g/kg/day}$

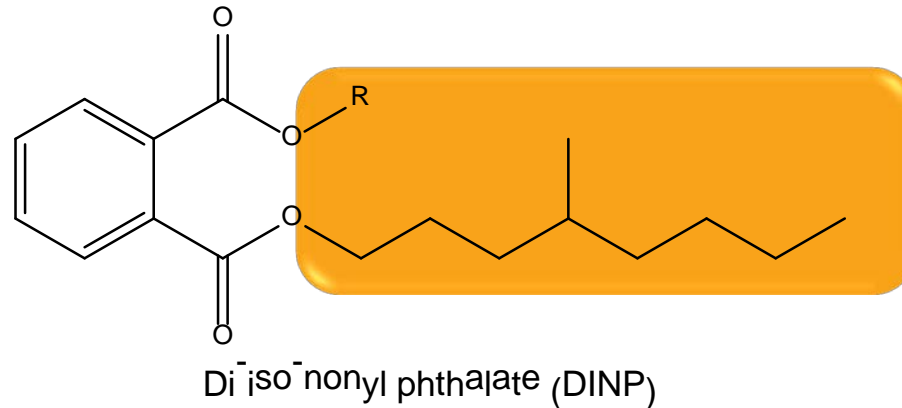
Biological evaluation of occupational exposure to di(isononyl) phthalate (DINP)

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DINP : a complexe mixture of isomers

(alkyl C9 branched)



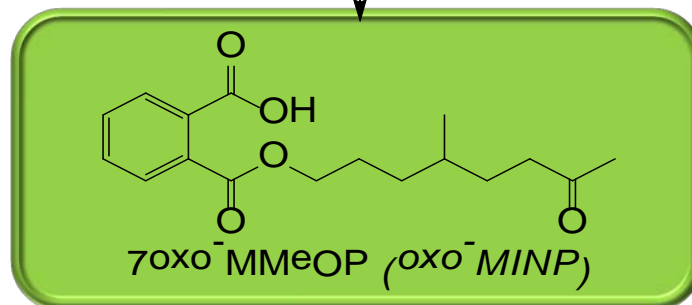
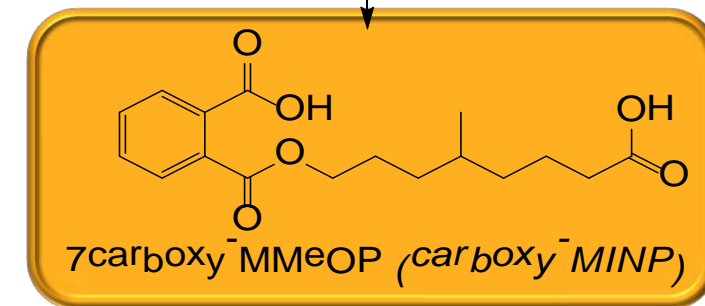
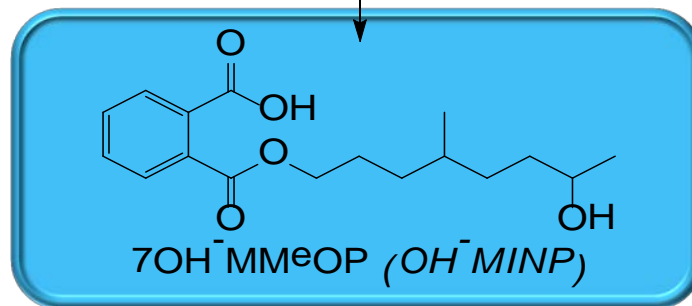
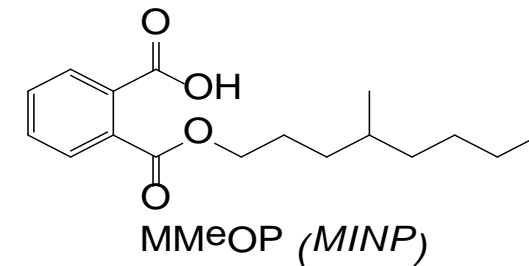
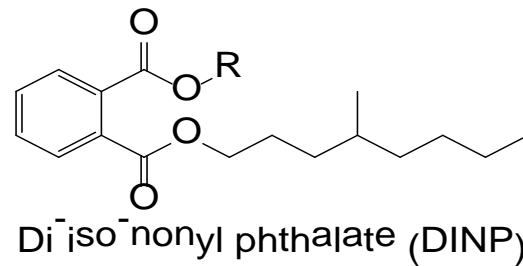
- There is not one DINP, but several DINP, with different CAS numbers, DINP 1 and DINP 2. Other types of DINP have been produced but vanished from the market
- The DINP composition varies depending on manufacturing process: DINP 1, method "polygaz" and DINP 2, method "n-butene"
- Consequence : an analytical challenge, solved by Koch *et al.* (2007)

The effects on health, metabolism, risk assessment

- For rodents: toxic effects on liver (tumors) and kidney, endocrine disruptor (nipple retention and testis atrophy like DEHP)
- Tolerable Daily Intake (TDI) of 150 µg/kg/day edited by EFSA and Acceptable Daily Intake (ADI) of 120 µg/kg/jour edited by CPSC* (USA), based on the same critical endpoint, spongiosis hepatitis
- Human metabolism was investigated by Koch (2007) and Anderson (2011)

* Consumer Product Safety Commission (CPSC)

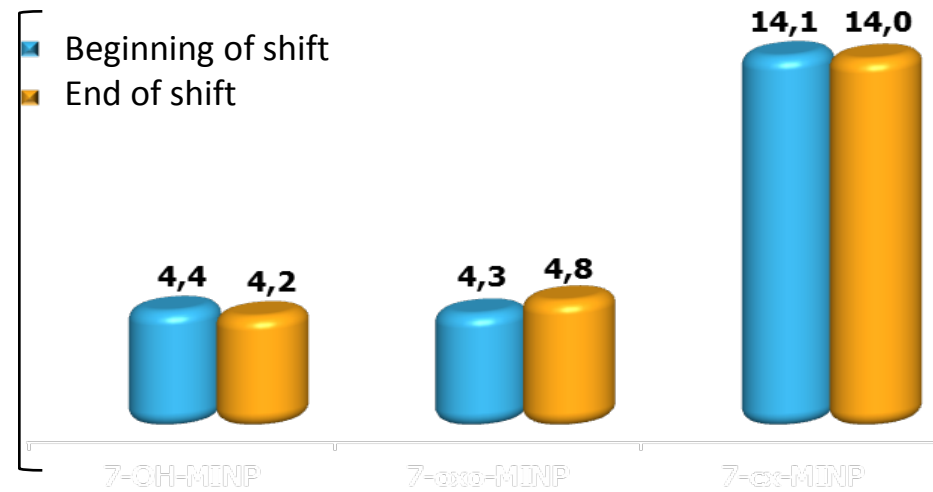
Analyzed metabolites



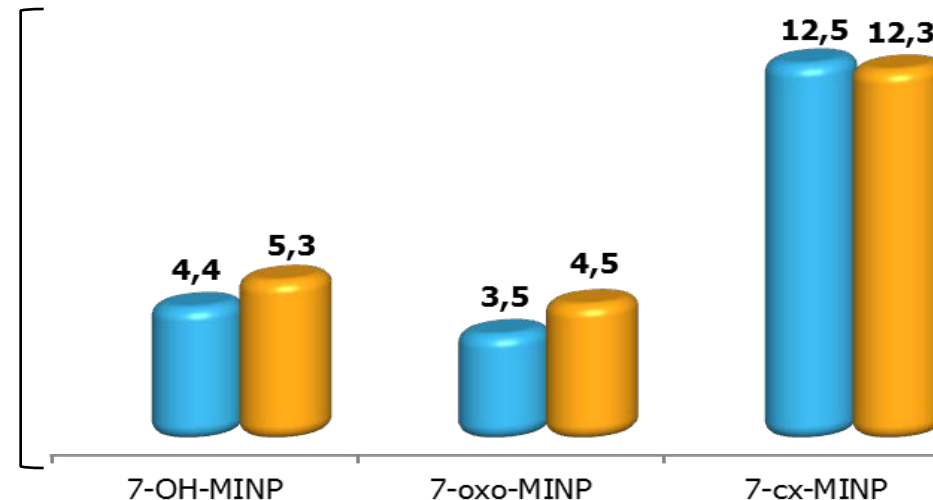
Representative metabolites of exposure to DINP according to Koch et al.

Results (2013-2015) : no occupational exposure to DINP – co-exposure with DEHP

Exposed workers



Controls

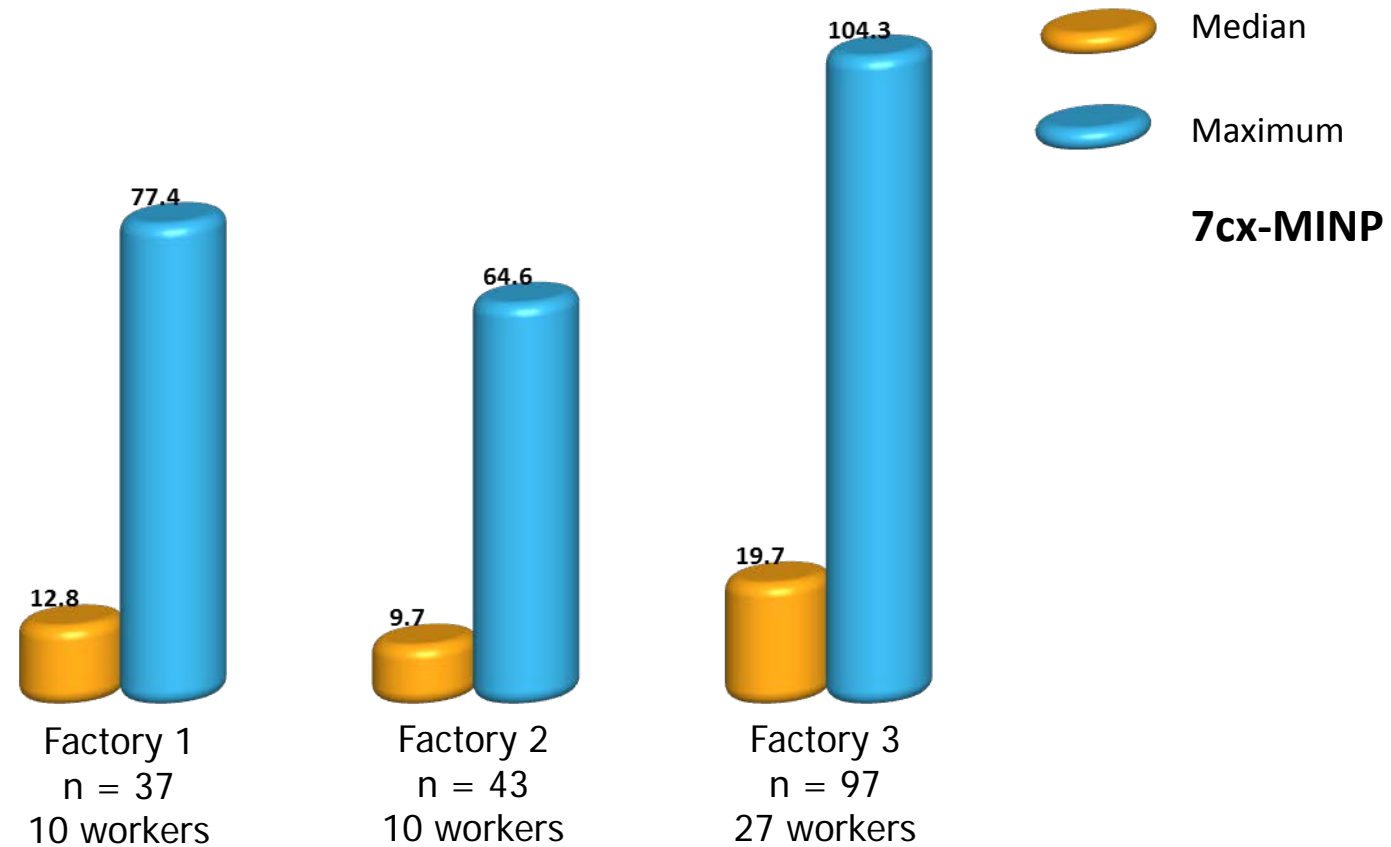


(medians, μg/L)

- 3 factories
- 47 exposed workers (181 pre-shift and 177 post-shift)
- 27 controls (113 pre-shift and 104 post-shift)

- Co-exposure with DEHP
- MEHP : post-shift median, 6.0 vs 24.6
- 5cx-MEPP : post-shift median, 20.1 vs 112.0

Industry sector (PVC compounding) :



Data in reference populations

(controls, post-shift, $\mu\text{g/L}$)

	German population n=45		US population n=129		Controls INRS n=27		Controls Koch et al. n=10	
	<i>Median</i>	<i>Range</i>	<i>Median</i>	<i>Range</i>	<i>Median</i>	<i>Range</i>	<i>Median</i>	<i>Range</i>
7-OH-MINP	4,7	0,4 – 31,1	13,2	-	5,3	0,5 – 223,3	6,2	0,6 – 33,0
7-oxo-MINP	1,7	0,3 – 8,7	1,2	-	4,5	0,5 – 142,8	2,8	< LOQ – 16,3
7-cx-MINP	5,3	0,7 – 16,7	8,4	-	12,3	0,5 – 657,6	6,5	0,3 – 31,1

Calafat *et al.* (2011) : NHANES 2005-2006 n = 1040 / median 7-cx-MINP : 4.70 $\mu\text{g/L}$ / Range: < 0.7 – 4961 $\mu\text{g/L}$

Data in industry sectors

(exposed workers, post-shift, $\mu\text{g/L}$)

	Koch <i>et al.</i> (2012) Cold plastisols n=5		Hines <i>et al.</i> (2012)				INRS (2015) PVC compounding n=54	
	Median	Range	PVC film n=7 Geometric mean	Range	PVC compounding n=12 Geometric mean	Range	Median	Range
7-OH-MINP	117	59,3 – 443	-	-	-	-	4,2	0,5 – 358,9
7-oxo-MINP	44,3	10,7 – 175	-	-	-	-	4,8	0,5 – 263,7
7-cx-MINP	57,8	24,7 - 286	51,0	12,5 - 184	9,5	1,7 – 21,7	14,0	0,5 – 963,4

Daily intakes (DI)

- Recommended Tolerable Daily Intakes (TDI)
 - 150 µg/kg/day (EFSA - EU)
 - 120 µg/kg/day (US - CPSC*)
- Hines *et al.* (2012)
 - PVC film (n=7) : Geometric mean = 8.0 µg/L / Range : 2.4 – 26.0 µg/L
 - PVC compounding (n=12) : Geometric mean = 1,5 µg/L / Range : 0.4 – 4.4 µg/L
- INRS
 - PVC compounding (n=54) : median = 3.4 µg/L / Range : 0.4 – 137.3 µg/L
 - Only one calculated DI higher than US TDI

* Consumer Product Safety Commission

Conclusion

- Occupational exposure to DEHP evident (2005-2008), in all industry sectors visited (excepted DEHP manufacturing)
- Calculated daily intakes (DI) are quite low in comparison to the 50 µg/kg/day intake recommended by EFSA (only 2 % above). The US reference dose (RfD), 20 µg/kg/day, is more protective : 14 % measured values are above, up to 25 % in some industry sectors
- Today, DEHP is still used and occupational exposure to DEHP remain significant in PVC compounding even if 5cx-MEPP urinary median level has been divided by 5,6 during those last ten years
- No VLB available for DEHP – only VBR of 200 µg/g creatinine – 20% of measured urinary levels of 5cx-MEPP are higher than VBR
- Absorption of DEHP through dermal route via vinyl gloves is not negligible - Similar conclusion in recent DEHP skin permeation study (Hopf* *et al.*) - In France, DEHP substitution (by DINP or other) in the vinyl gloves is effective (among the glove samples sent by Occupational Health Services of 25 firms, only 4 of them contained DEHP)
- Occupational exposure to DINP in PVC compounding is not different than environmental exposure – DINP is a good substitute ?
- Relation occupational exposure – health effects ? Results of the INRS epidemiological study.

* N.B. Hopf *et al.* (2014) Skin permeation and metabolism of di(2-ethylhexyl) phthalate (DEHP), Toxicology letters, 224, 47-53

Publications

INTERNATIONAL ARCHIVES OF OCCUPATIONAL AND ENVIRONMENTAL HEALTH
Volume 81, Number 8, 959-966, DOI: 10.1007/s00420-007-0289-6



ORIGINAL ARTICLE

Biological monitoring of occupational exposure to di(2-ethylhexyl) phthalate: survey of workers exposed to plastisols

R. Gaudin, P. Marsan, A. Robert, P. Ducos, A. Pruvost, M. Lévi and P. Bouscaillou

INTERNATIONAL ARCHIVES OF OCCUPATIONAL AND ENVIRONMENTAL HEALTH
DOI: 10.1007/s00420-010-0566-7

Online First



ORIGINAL ARTICLE

Biological monitoring of exposure to di(2-ethylhexyl) phthalate in six French factories: a field study

R. Gaudin, P. Marsan, S. Ndaw, A. Robert and P. Ducos



Surveillance biologique de l'exposition au phtalate de di-(2-éthylhexyle) (DEHP) dans six entreprises françaises

R. Gaudin, P. Marsan, S. Ndaw, A. Robert



Thanks to René Gaudin

Thank you for your attention



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