London (7 January 2014) – Evidence Submission PIP Action Campaign
ECHA review of Octamethylcyclotetrasiloxane (D4) & Decamethylcyclopentasiloxane (D5)

Are cyclic siloxanes D4, D5 and D6 endocrine disruptor chemicals, reprotoxic or carcinogenic and harmful to women and children? Should they be Restricted/banned in cosmetics and medical devices as well as in shampoo?

> *The following statement can be attributed to* PIP Action Campaign *following the United Kingdom's (UK) recent registration of its intent to submit a restriction proposal under the European Union's chemicals management program (REACH). The restriction would call for limiting D4 and D5* **only** *in rinse-off personal care products. As part of the restriction preparatory phase, ECHA has just launched a Call for Evidence encouraging stakeholders to provide information that would assist the Member State Committee assess whether the REACH Annex XIII criteria for PBT/vPvB are met for these substances. The proposed restrictions have not yet been finalised nor approved and may be further amended based on information provided in response to this call for evidence or subsequent public consultation.*

For many years the testimonies of women and doctors have established there are serious health consequences for women with silicone breast implants.

Women's symptoms are consistently undermined by claims that either, i) there is no evidence of a causal link with breast implants[1], or ii) a wealth of data about the health and safety of silicones has been accumulated and no such link is apparent.[2]

These claims, along with failed regulation of chemicals in cosmetics and medical devices have resulted in many hundreds of thousands of women suffering debilitating symptoms for which doctors have no answers and few reliable points of reference.

For many years it has been known that D4 and D5 together with other cyclic siloxanes are found in silicone breast implants. In tests on very limited numbers of, mostly, sterile unused PIP implants, approximate levels of D4, D5 and D6 have been published.

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[1] Silicone Gel Breast Implants The Report of the Independent Review Group (IRG) http://www.mhra.gov.uk/home/groups/dts-bi/documents/websiteresources/con2032510.pdf

[2] **Biomaterials in Plastic Surgery: Breast Implants** edited by W Peters, H Brandon, K L Jerina, C Wolf, V L Young page 57

Fig 1. **SCENIHR Final Report[3] on PIP Breast Implants**

Table 4:Levels of D4, D5 and D6 in devises from various manufacturers

	D4 (ppm)	D5 (ppm)	D6 (ppm)
TGA – PIP*	136	434	474
TGA – Nusil	ND**	ND	ND
MPA – PIP2*	134	457	604
MPA – PIP Nusil*	ND	18	30
MPA – Brands A and B	ND	20	22
MPA – Brand C	30	72	132

* ***TGA tested several samples – the median result is quoted here. MPA tested one new implant and one explant of each PIP2 and PIP-Nusil; the highest result is quoted here.***
** ***ND = not detected***

The SCENIHR committee who published the table above, has concluded there is no evidence PIP are toxic or carcinogenic. Even though PIPs manufacturing experiments with unknown methods, chemistry and raw materials are acknowledged, the SCENIHR have failed to recommend preventative removal of PIP implants in Europe.

The SCENIHR committee is able to refer to other EC agencies for contributory expertise such as ECHA and REACH with regard to chemical toxicity however did not do so on this occasion relying instead on the Opinion of SCCS 2010[4].

The SCCP, SCCS & SCENIHR : European Commissions's scientific committees

In 2008, the SCCP's name was changed into SCCS (Scientific Committee on Consumer Safety). *In addition to the SCCS, SCENIHR and SCHER, a Pool of scientific advisors on risk assessment was also established, with the specific task to assist the members of the scientific committees in their work.*

At the time of the first review of D4 by the SCCP in 2005[5] **Octamethylcyclotetrasiloxane was classified as toxic for reproduction category 3**. *The substance was not regulated in an Annex to the Cosmetics Directive nor had it been evaluated by the Scientific Committee on Cosmetology (SCC) /SCCNFP before.*

*In 2005 the European Commission received a submission from the Centre Européen des Silicones (**CES**) in co-operation with the European Cosmetics Toiletry and Perfumery Association (COLIPA)*

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[3] http://ec.europa.eu/health/scientific_committees/consultations/public_consultations/scenihr_cons_14_en.htm

[4] http://www.mychemicalmonitoring.eu/Files/News/sccs_o_029.pdf

[5] http://ec.europa.eu/health/ph_risk/committees/04_sccp/docs/sccp_o_035.pdf

which concluded that Octamethylcyclotetrasiloxane was safe for continued use in cosmetic products.

However, on the basis of provided data, the SCCP was unable to assess the risk to consumers when Octamethylcyclotetrasiloxane (D4) was used in cosmetic products.

In its conclusion the SCCP stated that despite the size of the dossier submitted by industry for evaluation, ***it was unfortunate that the dossier lacked meaningful information/data on actual consumer exposure to D4.***

The SCCP added the following information was required for further consideration:

+ Adequate information on the use of D4 in cosmetics in particular in different cosmetic products;
+ Relevant/appropriate percutaneous absorption studies at different use concentrations;
+ Information on the co-use, and hence consumer exposure, of related organosiloxanes, in particular decamethylcyclopentasiloxane (D5).

The SCCP requested this information be supplied by 1 October 2006.

In 2010, the Scientific Committee on Consumer Safety SCCS published its OPINION ON Cyclomethicone Octamethylcyclotetrasiloxane (Cyclotetrasiloxane, D4) and Decamethylcyclopentasiloxane (Cyclopentasiloxane, D5)[6] Drawing heavily on the work in Canada of the **(SEHSC)** the trade association comprised of North American silicone chemical producers and importers, the SCCS concluded:

The SCCS is of the opinion that cyclomethicone (D4, D5) does not pose a risk for human health when used in cosmetic products. Other uses were not considered in this risk assessment. (page 102)

Trade organisations such as **CES** representing all major producers of silicones, silanes and siloxanes in Europe and **SEHSC** in North America with a similar membership profile are the voices of the chemicals industry.

The silicones/chemical industry[7] **does** ***not believe there is a need to restrict the use of D4 or D5 in any application and makes claims that the weight of the evidence of the currently available data does not warrant any regulatory action.*** In addition, they claim *the concentrations of these materials that have been measured and continue to be measured in the environment via a global voluntary monitoring program are substantially below the levels that might pose a risk to the environment and/or humans*. **They go further saying:** ***Imposing restrictions would unnecessarily hamper international trade, economic growth, stifle innovation and would not be proportionate to the lack of risk.*****"** In their view *D4 and D5 are not PBT or vPvB*[8]. They insist *the weight-of-evidence indicates that these substances are safe for human health and the environment in their intended uses.*

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[6] http://www.mychemicalmonitoring.eu/Files/News/sccs_o_029.pdf

[7] http://www.silicones.eu/uploads/Modules/Newsroom/ces-d4-d5-holding-statement.pdf

[8] Persistent, Bioaccumulative, Toxic (PBT) 2 Very Persistent, Very Bioaccumulative (vPvB)

The silicone and chemical industries' lobbies are always heavily engaged in influencing the regulation of these chemicals as the markets for surgical implants and cosmetics continue to grow The industry claims *environmental monitoring data collected by the global silicones industry demonstrate that D4 and D5 are not found at, nor will be found at, levels that pose a risk to the environment* based on assessment in Canada.

CES claims *Environment Canada having reviewed the environmental data available for D4, has not imposed any product concentration restrictions on the use of D4 in any application.*
However, **a Final Order adding D4 to the List of Toxic Substances in Schedule 1 under the Canadian Environmental Protection Act, 1999(CEPA 1999) was published in Part II of the Canada Gazette on February 16, 2011.**[9]

CES also states that in addition, *a comprehensive, risk-based assessment of the data conducted by an independent, group of* ***leading scientific experts selected by the Canadian Government concluded that D5 does not pose a risk to the environment now, or in the future.***

This is a CES reference to an Objection submitted to Environment Canada[10] by the Silicones Environmental, Health and Safety Council of North America (**SEHSC**)[11] run by The American Chemistry Council (ACC) which represents the leading companies in the business of chemistry.[12]

In a letter of 10 July 2009 to the Canadian Minister for the Environment Jim Prentice, Karluss Thomas Executive Director Silicones Environmental, Health and Safety Council of North America made a Notice of Objection and Request for Board of Review in relation to the Proposed Order to add Cyclotetrasiloxane, octamethyl- (D4) and Cyclopentasiloxane, decamethyl- (D5) to Schedule 1 to the Canadian Environmental Protection Act, 1999; Canada Gazette Vol. 143, No. 20 — May 16, 2009[13]

To which the minister replied[14] that **a Board of Review would not be established for D4 as the Notice did "not bring forth any new scientific data or information that would likely lead to a different conclusion" but agreed that "*a further inquiry into the nature and extent of danger posed by D5 (was) warranted*" and a review was undertaken.**[15]

Environment Canada's Screening Assessment of D5 November 2008[16] **found *no international agency had classified D5 for carcinogenicity, genotoxicity or reproductive/developmental toxicity. Only one national review on the health effects of cyclosiloxanes was identified to***

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[9] https://www.ec.gc.ca/toxiques-toxics/Default.asp?lang=En&n=71D7177A-1

[10] http://www.ec.gc.ca/lcpe-cepa/default.asp?lang=En&n=6E52AE02-1

[11] http://sehsc.americanchemistry.com/

[12] http://www.americanchemistry.com/Membership/MemberCompanies

[13] http://www.ec.gc.ca/lcpe-cepa/documents/consultations/avis-notices/20090710_siloxanes_avis-notice.pdf

[14] http://www.ec.gc.ca/lcpe-cepa/documents/consultations/avis-notices/20100720_siloxanes_min.pdf

[15] http://www.ec.gc.ca/lcpe-cepa/default.asp?lang=En&n=515887B7-1&offset=9&toc=show

[16] http://ec.gc.ca/ese-ees/13CC261E-5FB0-4D33-8000-EA6C6440758A/batch2_541-02-6_en.pdf

date, that of the Danish Environmental Protection Agency (EPA). They reviewed health effects for D4 and D5 *(Lassen et al. 2005[17])***.**

The industry lobbies SEHSC & CES continue to make claims surrounding the safety of D4 and D5, and have already had some success in preventing regulators acting in the interests of the public and the environment and in particular for the protection of women and children. **As women exposed to toxic D4 and D5 we take this opportunity to draw the following concerns to your attention.**

HAZARD IDENTIFICATION

based on the results of in vivo tests, in vitro tests, clinical studies, accidents, human epidemiological studies and, when available, quantitative structure activity relationship (QSAR) studies. The intrinsic physical, chemical and toxicological properties of the molecule under consideration are studied to identify whether the substance has the potential to damage human health.

D5 - carcinogenic, reprotoxic, cytotoxic, dopamine agonist & endocrine disruptor?

Decamethylcyclopentasiloxane (**D5**) CAS 541-02-6

Like Environment Canada, Lassen et al. 2005[18] noted screening did not reveal any data on human toxicity either. "***The main source of information has been the*** *Siloxane Research Program. The program run by The Silicones Environmental, Health and Safety Council of North America* ***(SEHSC)"*** *the trade association comprised of North American silicone chemical producers and importers* **who are opposed to the regulation of D4 and D5.**

Lassen et al 2005 notes ***In the discussion of the possible health problems related to the use of silicone breast implants, diffusion of low molecular weight siloxanes plays an important role****. At 3.2 on the Toxicity of siloxanes it is stated* ***there is relatively little information available about their toxicity apart from the information provided by the Siloxane Research Program (SEHSC). However, siloxanes have generally been regarded as safe in consumer products, but new uses, e.g. in breast implants and focus on reproductive toxicity and possible endocrine disrupting effects have focussed attention on this group of substances.*** *(page45)*

At 3.2.6 Carcinogenicity Lassen et al state ***Very little information is available on carcinogenicity of siloxanes. The only information identified is a report from Dow Corning received by EPA with preliminary results from a two-year chronic toxicity and carcinogenicity study in rats exposed to vapour concentrations of 0, 10, 40 or 160 ppm of D5 for 6 hours per day, 5 days per week, for 24 months. The preliminary results show that female rats in the highest dose group had a statistically significant increase of uterine tumours. These findings may indicate that there is a potential carcinogenic hazard associated with D5 (EPA. 2003).*** *(page 48)*

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[17] **Siloxanes - Consumption, Toxicity and Alternatives** Lassen et al, 2005 http://www.miljoestyrelsen.dk/udgiv/publications/2005/87-7614-756-8/pdf/87-7614-757-6.pdf

[18] http://www.miljoestyrelsen.dk/udgiv/publications/2005/87-7614-756-8/pdf/87-7614-757-6.pdf

Lassen et al 2005 at 3.3 Concludes: ***Based on the reviewed information, the critical effects of the siloxanes are impaired fertility (D4) and potential carcinogenic effects (uterine tumours in females) (D5). Furthermore there seem to be some effects on various organs following repeated exposures, the liver (D4), kidney (HMDS) and lung (D5 and HMDS) being the target organs.*** *(page 50)*

ECHA Data Dossier

In the 6-year study report which appears in brief in ECHA's registered data dossier on D5 Carcinogenicity **Exp Key Carcinogenicity.001**[19] it has been noted that:

> *due to the complexities surrounding the relevance of the observed uterine tumours to humans,* ***a summary report has been prepared by the Silicone Industry that summarises current understanding of the scientific basis for disregarding these tumours when considering risk characterisation for humans****. The summary was attached to the endpoint summary for carcinogenicity, and the conclusion from this summary was "that the tumorigenic effect of D5 in female rats exposed to very high concentrations for two years is related to a* ***rodent- specific imbalance*** *in the normal hormonal milieu that occurs in aging female Fischer 344 rats.* ***These imbalances are common in rodents and are of no relevance to humans****". Findings of* ***uterine tumours following 24 months exposure to 160 ppm of D5 were not considered being not relevant to humans****.*

We wonder why the rodent-specificity was unknown to those conducting the experiment? Exposing female rodents to 160ppm over 24 months, sufficient for them to develop uterine tumours, seems cruel and unnecessary if the findings where known to be irrelevant in humans.

Virtually all the evidence on the carcinogenicity of D5 in humans is based upon animal data. However, D5 and human health concerns are known and reported:

In a MEMORANDUM of September 13, 2007 addressed to Robert Barham, Ph.D. Assistant Chief, Stationary Source Division Air Resources Board, **George Alexeeff, Ph.D**. Deputy Director for Scientific Affairs USA **contributed to the OEHHA Review on the toxicity of D5**[20].

D5 human health concerns

> *Even if the uterine adenocarcinomas seen at 160 ppm in the 2-year study are due to a carcinogenic mechanism which is rodent specific,* ***there is still concern that D5 could be a dopamine agonist and result in other adverse effects in humans.***

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[19] http://apps.echa.europa.eu/registered/data/dossiers/DISS-9d82d68d-a71c-2317-e044-00144f67d249/AGGR-0440ce3e-201e-4fa5-bf0d-5713a8fe622e_DISS-9d82d68d-a71c-2317-e044-00144f67d249.html#AGGR-0440ce3e-201e-4fa5-bf0d-5713a8fe622e

[20] See Appendix 2

Dopamine is a major neurotransmitter, involved in many brain functions and downstream physiological processes. ***Dopamine has been demonstrated to affect brain neural architecture during development*** *(Todd, 1992; Swarzenski et al., 1994; Song et al., 2002).* ***Data described above indicate that brain levels of D5 in rats exposed to 160 ppm D5 were approximately twice as high as corresponding blood levels. This raises the possibility that in utero exposure to D5 could result in adverse effects on brain neural development. Dopamine D2 receptors, with which D5 interacts, have a role in neurological disorders and mental illness*** *(Ben-Jonathan and Hnasko, 2001; Seeman et al., 2006). For example, administration of the dopamine agonist bromocriptine may exacerbate schizophrenia (Ben-Jonathan and Hnasko, 2001) or it may produce improvements in negative symptoms (Lindenmayer, 1995).*

Dopamine acts on the endocrine system by inhibiting prolactin release *(Ben-Jonathan and Hnasko, 2001).* ***In humans prolactin induces and maintains the secretion of milk (lactation) and during lactation decreases reproductive function and suppresses sexual drive in the mother.*** *Drugs used to treat hyper-prolactinemia, such as cabergoline and bromocriptine, are dopamine receptor agonists (Melmed and Jameson, 2005).*

Dopamine can activate dopaminergic receptors in normal human T-cells, and trigger the selective secretion of IL-10 and/or TNF (Besser et al., 2005). ***Assuming D5 has dopamine agonist properties, this could have detrimental consequences in various immunological diseases, injuries and cancers.***

Prolactin has been reported to affect a variety of other cells including human adipocytes *(Asai-Sato et al., 2006; Nilsson et al., 2005), mouse adipocytes (Flint et al., 2006) rat cholangiocytes (Bogorad et al., 2006a, b), rat chondrocytes (Zermeno et al., 2006), human natural killer (NK) cells (Sun et al., 2004),* ***developing human thymocytes*** *(Carreno et al., 2005), and rat pancreatic islet cells (Amaral et al., 2004).*

In vivo, in rodents, prolactin has a synergistic relationship with the glucocorticoids and adrenal function, possibly acting to determine adrenal size and function (Silva et al., 2004). A recent report that alactogenesis resulting from an inherited defect in prolactin secretion also has an adrenal component in humans (Saito et al., 2006) ***raises the possibility that adrenal function and carbohydrate metabolism could be adversely affected by chronic suppression of prolactin in humans.***

Thus, ***even if D5 does not induce uterine or other tumors in humans, if D5 acts as a dopamine agonist it may therefore have other adverse health impacts.***

As D4, D5 and D6 have been found in silicone implants to varying degrees and at high levels in PIP implants, there is valid human exposure data. **George Alexeeff, Ph.D**. Deputy Director for Scientific Affairs continues:

D5 Human Exposure[21]

*In addition to detection in the breathing space of people working with **D5**, this compound **has been detected in the fat of members of the general population, in human breast milk and in women with breast implants.***

*A national survey of human adipose tissue in 1982 found D5 in 28 of 46 people sampled (US EPA, 1987). Kaj et al. (2005) reported levels of D5 as high as 4.5 µg/L in samples of human breast milk in Sweden. Neither D5 nor any other siloxane was measured for the recent Second National Report on Human Exposure to Environmental Chemicals released in January 2003 by the National Center for Environmental Health. **D5 and its structural analog D4, which has one less dimethylsiloxane group than D5, occur together in breast implants and are often investigated together because of their structural similarities. However, D4 has some activity mimicking the female hormone estrogen, so any contamination of D5 by D4 is cause for concern.***

*Flassbeck et al. (2001)[22] analyzed plasma and blood of women exposed to silicone gel-filled implants (n = 14) and of control subjects (n = 2) for low molecular weight silicones. D5 and its structural analogs D3, D4, and D6 were not detectable in control plasma or blood. **The numbers of patient samples were limited, but the data showed an increase in the amount of low molecular weight cyclic siloxanes in the bodies of women with silicone implants. Many years after the removal of ruptured silicone implants, siloxanes were still in blood samples from several women.** D3 varied from 6 to 12 ng/mL in plasma and from 20 to 28 ng/mL in blood. **The range of D4 was 14-50 ng/mL in plasma and 79-92 ng/mL in blood.** D5 (28 ng/mL) and D6 (17 ng/mL) were detected in the plasma of one patient. Possible shortcomings in the data, which were noted by Smith (2002), included only two controls, possible inadvertent contamination, and some values near or at the limit of detection.*

Flassbeck et al. (2003) used a sophisticated combination of mass spectrometry and gas chromatography to analyze siloxanes (D4, D5, D6) in prosthesis capsule, muscle, and fat of 3 women who had silicone gel-filled breast implants and in breast tissue of 3 control women. In all tissues of women with breast implants, D4, D5 and D6 were identified. Depending on the siloxane species and type of tissue analyzed, siloxane levels in the range of 10-1,400 ng/g were detected. The highest level of D5 was 637±100 ng/g (637 ppb) in the fat tissue of one woman. This investigation shows that siloxanes leak from prostheses and accumulate in surrounding tissues.

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[21] MEMORANDUM To: Robert Barham, Ph.D. Assistant Chief, Stationary Source Division Air Resources Board From: **George Alexeeff, Ph.D. Deputy Director for Scientific Affairs** September 13, 2007 REVIEW OF TOXICITY INFORMATION ON D5 13.09.2007 OEHHA Review of Toxicity Information on D5

[22] **Determination of low molecular weight silicones in plasma and blood of women after exposure to silicone breast implants by GC/MS** http://www.ncbi.nlm.nih.gov/pubmed/11217769

D4 - Endocrine disruptor, reprotoxic, genotoxic, cytotoxic?

octamethylcyclotetrasiloxane (**D4**) CAS 556-67-2

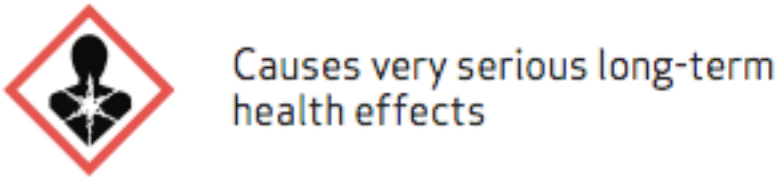
In Europe, D4 has been classified as R53, "may cause long-term adverse effects in the aquatic environment," and R62, "possible risk of impaired fertility" (ECB 2007). Four companies have been identified as producers/importers of D4 by the European Chemicals Bureau: ***Bayer AG*** *and* ***Wacker-Chemie GmBH of Germany****,* ***Rhone-Poulenc Chimie of France*** *and* ***Dow Corning Europe of Belgium*** *(ECB 2007).* ***The quantity of D4 used in the European Union*** *as a site-limited intermediate and in household products* ***during 2003-2004 is confidential information****.*[23]

D4 is on Annex I to the Substance Directive (67/548/EEC) with a health classification as toxic to reproduction in category 3[24]

D4 is classified labelled **: Repr. Cat. 3; R62 R53, Xn R: 53-62 S: (2-)36/37-46-51-61**

D4 is an Endocrine Disrupting Chemical Category 1

Fig 2. ECHA label for D4



The reproTOXIC effect of D4 is both well-known and well documented.

Octamethylcyclotetrasiloxane (**D4**) appears on various lists of substances for concern including:

1. Safer Chemicals.org

The Hazardous 100+ List of Chemicals of High Concern[25]

Octamethylcyclotetrasiloxane (D4) **endocrine disruption (Cat 1)**

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[23] Screening Assessment for the Challenge Octamethylcyclotetrasiloxane (D4)Envrionment Canada Archive November 2008 http://www.ec.gc.ca/ese-ees/default.asp?lang=En&n=2481B508-1

[24] http://www.greencouncil.org/doc/resourcescentre/annex1.pdf

[25] http://saferchemicals.org/methodology/

2. Maine Government USA

Chemicals of High Concern[26]
Maine law requires the Department of Environmental Protection to publish a list of no more than 70 chemicals of high concern. Development of Maine's list of Chemicals of High Concern (CHC) is to be cooperatively determined by the Maine Department of Health and Human Services, Maine Center for Disease Control and Prevention ("Maine CDC"), and the Maine Department of Environmental Protection ("Department"). (38 M.R.S.A. § 1693-A(1)). ***A chemical currently listed on Maine's chemicals of concern list may be included on the CHC list if there is a determination of strong, credible scientific evidence that the chemical is a reproductive or developmental toxicant, endocrine disruptor or human carcinogen, AND there is strong, credible scientific evidence that the chemical meets one or more of the following criteria:***

- ***The chemical has been found through biomonitoring studies to be present in human blood, human breast milk, human urine or other bodily tissues or fluids;***
- *The chemical has been found through sampling and analysis to be present in household dust, indoor air or drinking water or elsewhere in the home environment; or*
- *The chemical has been added to or is present in a consumer product used or present in the home.*

Deriving Chemicals of High Concern Process Documentation
Appendix II - Final List of Chemicals of High Concern[27]
Octamethylcyclotetrasiloxane (D4) page2

3. Washington State Department of Ecology USA
The Reporting List of Chemicals of High Concern to Children (CHCC)[28]
Each of the chemicals on this list meets the criteria established by the Children's Safe Product Act (RCW 70.240.030).
Rationale for Reporting List of Chemicals of High Concern to Children Prepared by the Washington State Department of Health for the Children's Safe Product Act – 4/18/2011
CAS 556-67-2 Substance name Octamethylcyclotetrasiloxane[29]

[26] http://www.maine.gov/dep/safechem/highconcern/index.html

[27] http://www.maine.gov/dep/safechem/highconcern/documents/Appendix%20II%20Final%20List%20of%20CHC.pdf

[28] http://www.ecy.wa.gov/programs/swfa/cspa/chcc.html

[29] http://www.ecy.wa.gov/programs/swfa/cspa/pdf/556672.pdf

4. California Environmental Contaminant Biomonitoring Program (CECBP) Scientific Guidance Panel (SGP)

Materials for the December 4-5, 2008 Meeting of the California Environmental Contaminant Biomonitoring Program (CECBP) Scientific Guidance Panel (SGP)[30]

> ***Need to assess efficacy of public health actions**:*
> ***Cyclosiloxanes appear to be persistent and to have long half-lives in people. The weak estrogenic activity of D4, in combination with its long half-life, poses potential concerns for exposed individuals. While studies have not shown D5 to be estrogenic, it nonetheless increased uterine tumors in animal studies. In addition, there are potential concerns related to effects of D5 on the neurotransmitter dopamine and the hormone prolactin.** (page 1)*

The concerns over EDC Exposures & Regulation are Growing:

5. Danish Environmental Protection Agency

Exposure of pregnant consumers to suspected endocrine disruptors[31]

Survey of chemical substances in consumer products no. 117 (page 101)

> *The data showing endocrine disruptive (estrogenic) effects of Siloxane D4 is considered to be robust. 6.13 pg 112*

6. Breast Cancer UK

> ***Breast Cancer UK's Manifesto calls on policy makers to move beyond breast cancer 'awareness' and to take political action on the chemical causes of the disease**.*[32]

7. European Environment Agency on The Weybridge+15 (1996–2011) report

> *Rates of endocrine diseases and disorders, such as **some reproductive and developmental harm in human populations, have changed in line with the growth of the chemical industry, leading to concerns that these factors may be linked.**[33]*

8. The Berlaymont Declaration 2013[34]

> *As scientists actively engaged in endocrine disrupter research we welcome the initiatives of the European Commission. **European Union (EU)-funded research was instrumental in substantiating the plausibility that endocrine disrupters might lead to serious, irreversible human and wildlife health effects.** As the first major economic area to target endocrine disrupters, the EU has the opportunity to put in place standards that will be exemplary for health and environmental protection policies in other regions of the world. We wish to express our views on this important topic and call on the European*

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[30] http://oehha.ca.gov/multimedia/biomon/pdf/1208cyclosiloxanes.pdf

[31] http://www2.mst.dk/Udgiv/publications/2012/04/978-87-92903-02-0.pdf

[32] http://www.breastcanceruk.org.uk/our-campaigns/prevention-is-better-than-cure/

[33] http://www.eea.europa.eu/publications/the-impacts-of-endocrine-disrupters

[34] http://www.brunel.ac.uk/__data/assets/pdf_file/0005/300200/The_Berlaymont_Declaration_on_Endocrine_Disrupters.pdf

Commission to implement regulatory measures that are in line with the best available science.
Scientists are concerned that the prevalence of endocrine-related diseases is higher than it has ever been. The disease burden continues to increase in the EU and globally.
Evidence is strengthening that environmental factors, including chemical exposures, play a role in these phenomena.

10. United Nations Environment Programme [35]
Effects of Human and Wildlife Exposure to Hormone-Disrupting Chemicals Examined in Landmark UN Report

11. WHO - World Health Organisation
State of the science of endocrine disrupting chemicals - 2012 [36]
An assessment of the state of the science of endocrine disruptors prepared by a group of experts for the United Nations Environment Programme (UNEP) and WHO

Dose-response assessment:

*in which **the relationship between the toxic response and the exposure** is studied. In the case of an effect with a threshold, the dosage at which no adverse effects are observed (NOAEL), is determined. If the NOAEL is not available, the lowest dosage at which an adverse effect is observed (LOAEL) is used. In the case of non-threshold carcinogens, a dose-descriptor (e.g. T25) is determined [Dybing et al. 1997].*

Women globally share Drs Menache and Martindale's concerns outlined in **'The PIP scandal: an analysis of the process of quality control that failed to safeguard women from the health risks'**.[37]

*The PIP implants were found to contain a higher proportion of small-sized molecules **D4, D5, D6 than the norm.8 D4 (octamethylcyclotetrasiloxane) was identified as an endocrine disrupting chemical (EDC) of 'high concern' in 2007 by a report commissioned by the European Commission entitled 'Study on enhancing the Endocrine Disrupter priority list with a focus on low-production chemicals'. The effects of low doses of such chemicals, particularly on the developing fetus, have been well documented**. While most regulatory levels of impurities in breast implants are considered acceptable in the range of a few parts per million, **Le et al. showed that EDCs are capable of affecting developing neurons in vitro at concentrations of less than one part per trillion.***

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[35] http://www.unep.org/Documents.Multilingual/Default.asp?DocumentID=2704&ArticleID=9403&l=en&t=long

[36] http://www.who.int/ceh/publications/endocrine/en/

[37] **The PIP scandal: an analysis of the process of quality control that failed to safeguard women from the health risks** Victoria Martindale, Andre Menache http://jrs.sagepub.com/content/106/5/173.long

Even at the tiniest doses, EDCs delivered during a particular time frame can be harmful. **The migration of EDCs can be relative to temperature**. Le et al[38] observed *exposure to boiling water (100 degrees C) increased the rate of BPA migration by up to 55-fold.*

Human Exposures to D4 and D5

Air Contamination

Concerns about air contamination have been raised in the USA. **Chemicals from Personal Care Products Pervasive in Chicago Air:** by Brian Bienkowski published April 30, 2013 in Environmental Health News and Scientific American writes:[39]

> ***On the brink of federal regulatory review, chemicals in deodorants, lotions and conditioners are showing up in Chicago's air at levels that scientists call alarming.*** *The airborne compounds – cyclic siloxanes – are traveling to places as far as the Arctic, and can be toxic to aquatic life.*
> *"These chemicals are just everywhere," said Keri Hornbuckle, an engineering professor at the University of Iowa and senior author of a new study.*
> *Concentrations were 10 times higher in Chicago's air than in the air of West Branch, Iowa, and four times higher than in Cedar Rapids, Iowa.*
> *Hornbuckle said* ***the findings are worrisome because the compounds are ubiquitous and have been detected at much higher levels than other common environmental contaminants.*** *"These are big concentrations and, truthfully, are concerning to me," she said...*
>
> ***...In Chicago's air, the most prevalent compound, known as D5****, was at levels three times greater than what polychlorinated biphenyl (PCBs) typically are there. PCBs are persistent chemicals banned in the 1970s.* ***D5 is most commonly used in soaps, lotions, shampoos and conditioners...***
>
> ***... D4 – used in polishes, detergents, sealants, adhesives and plastics -- is toxic to wildlife, according to the EPA.*** *Previous lab studies found the compound toxic to certain species – small rainbow trout and water fleas – at concentrations that are expected in the environment.*
>
> *In addition,* ***D4 causes tumors, reproductive problems, altered organ size and acts like a weak estrogen in studies of lab animals. D5 has caused changes in the nervous systems, livers and immune systems of lab animals****.*
>
> ***D4 and D5 are not currently regulated anywhere in the world.*** *But the EPA announced last year that it would evaluate whether D4 should be regulated under the Toxic Substances and Control Act. However, the agency is less concerned about outdoor air*

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[38] http://www.ncbi.nlm.nih.gov/pubmed/18155859

[39] Scientific American http://www.scientificamerican.com/article/chemicals-from-personal-care-products-pervasive-in-chicago-air/

concentrations than it is about the risks to water-dwelling creatures, an EPA spokesperson said in an email.

The accumulation potential and toxicity of cyclic siloxanes are debated by scientists and industry representatives.

Both D4 and D5 are "safe for human health and the environment when used as intended," ***Karluss Thomas, senior director of*** *the American Chemistry Council's Silicones Environmental, Health and Safety Center* ***(SEHSC),*** said in an emailed response.
He also said ***higher levels of the compounds in places such as Chicago are not cause for concern because there is no evidence they harm humans.***

...**California health officials have expressed concern about this growth in use of D5, saying in 2007 that "*it has potential public health impacts*"** and "*has been measured in several aquatic species at parts per million concentrations, and appears to have a long half-life in humans. Thus,* ***D5 persistence in the environment and in animal and human tissues is a concern****."*

...according to work by Michael McLachlan and Stockholm University colleagues.
McLachlan said ***the compounds have an odd structure that makes it difficult to understand them, but he said that most scientists say they are accumulating****.*
"Standard chemicals usually mostly end up in sediment," McLachlan said. "However, with cyclic siloxanes, a much smaller portion ends up in sediment and a much larger portion ends up in fish."

*..."****They [cyclic siloxanes] are much different compared to other environmental chemicals," McLachlan said. "We're really just starting to understand how they behave."*** **...**[40]

The potency, safe levels and margins are impossible to accurately predict.

Exposure assessment:

in which the amount and the frequency of human exposure to the compound are determined (including potential specific groups at risk, e.g. children, pregnant women, etc.).

D4 is a known endocrine disruptor, it is toxic to reproduction, bioaccumulative in human tissue, women and children are most vulnerable, the majority of women exposed to D4 in PIP breast implants are of reproductive age. D5 is a known carcinogen. ***Dopamine D2 receptors, with which D5 interacts, have a role in neurological disorders and mental illness. D5 has*** **dopamine agonist properties,** ***this could have detrimental consequences in various immunological diseases, injuries and cancers.***

[40] http://www.environmentalhealthnews.org/ehs/news/2013/siloxanes-in-the-air

D4 & D5 in Cosmetics and Person Care Products (C&PCPs)

A 2013 study, **Concentrations of cyclic volatile methylsiloxanes in European cosmetics and personal care products: Prerequisite for human and environmental exposure assessment** [41] observes the magnitude of the increase in D5 exposure:

"Overall, our findings are in agreement with the results of Horii and Kannan (2008) and Wang et al. (2009), who ***report that D5 and D6 are the two predominantly used cyclic siloxanes in cosmetics and personal care products****; D4 was found in smaller amounts and presumably in most cases as an impurity of D5 or D6. On the other hand, the maximum cVMS concentrations that we determined for skin care, hair care, deodorants and cosmetics were generally higher compared to those found in previous experimental studies (Horii and Kannan, 2008; Lu et al., 2011; Wang et al., 2009).* ***For example, our maximum D5 concentrations in all product categories are approximately five times higher than those reported by Horii and Kannan (2008). The same tendency is observed when we compare our values with the results published by Wang et al. (2009), who analyzed 252 C&PCPs bought in Canada."***

D4 & D5 in Silicone Breast Implants

It has long been known that women are particularly vulnerable to D4 exposures. In 1991 Hoan-My Do Luu and Joseph C. Hutter from the Center for Devices and Radiological Health, U.S. Food and Drug Administration, USA, conducted research on D4 and published **Bioavailability of Octamethylcyclotetrasiloxane (D4) After Exposure to Silicones by Inhalation and Implantation**[42] [43]

> ***Women are prone to bioaccumulate D4 when exposed daily to such multiple personal care products as antiperspirants, skin care, or hair care products.*** *A mean dose of 0.158 mg/kg D4 per day by inhalation was reported in a recent abstract by Shipp et al. (4). Added to this would be the estimated dose (10.4 mg/30 days/60 kg = 0.0057 mg/kg/day) of D4 leached from the saline- filled silicone breast implants (5–9). For the first time, the results of the PBPK model suggest that* ***women accumulate D4 in their fatty tissues (e.g., breasts), richly perfused tissues, liver, and kidneys. The D4 accumulation increases with the dose, the regimen of dosing (single vs. repeated), and the routes of exposure (inhalation vs. implantation)****.*
>
> *The resulting tissue distribution is attributed to the physical properties of D4, which is highly lipid soluble and very insoluble in water (Figure 1, Table 1). Thus,* ***once lipid- containing tissue (e.g., breast tissue) is exposed to D4—as occurs when D4 leaches from breast implants—D4 is rapidly absorbed and only slowly desorbed with a very long half-life***

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[41] Concentrations of cyclic volatile methylsiloxanes in European cosmetics and personal care products: Prerequisite for human and environmental exposure assessment http://www.ncbi.nlm.nih.gov/pubmed/24184663

[42] Bioavailability of Octamethylcyclotetrasiloxane (D4) After Exposure to Silicones by Inhalation and Implantation Luu HM, Hutter JC 2001 http://www.ncbi.nlm.nih.gov/pubmed/11712992

[43] **See Appendix 3 Comments Bioavailability of Octamethylcyclotetrasiloxane (D4) After Exposure to Silicones by Inhalation and Implantation** See letter from Luu HM, Hutter JC

> ***(fat t1/2 = 18.2 days). D4 is retained in the body if during exposure it contacts the lipophilic tissues.*** *Thus neither inhalation exposure (about a 10% capture of the intake dose) nor dermal contact (0.5% absorption) is an efficient way to deliver D4 into internal target organs in the body (17,28). By contrast,* ***leaching from an implant directly into breast tissue (mostly fat) would have great potential for allowing accumulation of D4 in the body.*** *Repeated exposures increase accumulation in target tissues since the frequency of exposure is shorter than the elimination half-life, especially in certain target tissues.*

More recent research from Danish Environmental Health Protection agency noted in:

Exposure of pregnant consumers to suspected endocrine disruptors[44]
Survey of chemical substances in consumer products no. 117

> ***6.13 Octamethylcyclotetra-siloxane(D4)***
> *DNELE of 195 µg/kg bw/day is based on a NOAEL of 19.5 mg/kg bw/day for changed estrous cycle, reduced fertility and reduced litter size in a 2-generation study (inhalation) in rats (Siddiqui et al., 2007). The NOAEL of 19.5 mg/kg bw/day is an internal dose calculated from an inhalation dose of 300 ppm, and by means of a calculation method used in SCCS' risk assessment for D4 (SCCS 2010b).* ***The estrogenic mode of action is supported by findings of increased uterine weight and reduced estradiol in the blood in screening studies for estrogenic effect in mice (He et al., 2003), and increased uterine weight and changed hormone levels and changed uterine histology in rats (McKim et al., 2001; Quinn et al., 2007)****. DNELT has not been determined, as no data for effects on the thyroid hormone system was located.* ***The data showing endocrine disruptive (estrogenic) effects of Siloxane D4 is considered to be robust****.*

Results from the Swedish National Screening Programme 2004[45]

> ***One or more of D4, D5 and D6 were found in 11 out of 49 samples of human breast milk. The maximum concentration of D4 was 10 µg/L, of D5 4.5 µg/L and of D6 4.8 µgL.***
>
> ***The substances included were three cyclic polydimethylsiloxanes (D4, D5, and D6) and four linear analogues (MM, MDM, MD2M and MD3M)...***
>
> *...D4 is classified as R62 "possible risk of impaired fertility" and as R53 "may cause long-term adverse effects in the aquatic environment" (KemI, 2004).* ***D4 is also classified as a PBT/vPvB substance and hence as a phase-out substance in the priority data base of the Swedish Chemicals Inspectorate and as such not supposed to be used in any new chemical applications within Sweden. MM is included on the OSPAR candidate list for dangerous substances.***

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[44] http://www2.mst.dk/Udgiv/publications/2012/04/978-87-92903-02-0.pdf

[45] http://www.imm.ki.se/Datavard/PDF/B1643_siloxaner.pdf

The Swedish screening programme results[46] are cited by both the UK and SCENIHR reports as evidence of the ubiquity of D4 and D5 in breast milk: they say *"siloxanes have been found at detectable levels in over 20% of breast milk samples taken from women without breast implants."* However, the Swedish Report states **"*The obtained samples were marked with numbers and carried no personal information or medical history."***

Risk characterisation:

the probability that the substance under investigation causes damage to human health and the level of risk, are examined. In the case of a threshold effect, the Margin of Safety (MoS) is calculated according to the formula: MoS = NOAEL where SED represents the Systemic Exposure Dosage.

In 1994, an important epidemiological study by JJ Levine, a Paediatrician, and NT Llowite was published following observations of Sclerodermalike esophageal disease in children breast-fed by mothers with silicone breast implants.[47]

The case report **Scleroderma and breast implants**[48] published in 2014 provides the background history of the association between Scleroderma and breast implants in women and two of the most influential safety reviews of silicone implants are referenced: in (1). The UK's Independent Review Group (**IRG**) and (2). the review of the **National Science Panel** in the USA.

> ***Chemically induced scleroderma***[49]
> *The role of silicone in relation to idiopathic or atypical connective tissue diseases is not clear. There have been a number of studies associating silicone breast implants with the development of connective tissue diseases. Case reports of women with silicone breast implants developing scleroderma began to appear in the US medical literature in the 1980s. However, other studies have suggested little or no relationship. In 1994, the Department of Health stated that there was no evidence of association between silicone implants and connective tissue diseases. In 2001, a US District Court Order established a National Science Panel to assist in lawsuits brought against silicone implant manufacturers, and f****ound no evidence of association between silicone breast implants and connective diseases.***

The Independent Review Group (IRG) was established in May 1997 in response to concerns expressed by women in relation to silicone gel breast implants.

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[46] **Results from the Swedish National Screening Programme 2004 Subreport 4: Siloxanes** Breast Milk at 6.1.6 pg15 http://www.imm.ki.se/Datavard/PDF/B1643_siloxaner.pdf

[47] http://www.ncbi.nlm.nih.gov/pubmed/8277548

[48] http://qjmed.oxfordjournals.org/content/early/2014/08/19/qjmed.hcu156.long

[49] Scleroderma and breast implants http://qjmed.oxfordjournals.org/content/early/2014/08/19/qjmed.hcu156.long

*The then Chief Medical Officer set up the IRG with the remit: '**to review the evidence relating to the possible health risks associated with silicone gel breast implants**, to examine the issues relating to pre-operative patient information, and to report to the Chief Medical Officer on its conclusions."*[50]

The report of the IRG was available to the IOM Committee on the Safety of Silicone Breast Implants in July 1998.[51]

In 1999 the (US) **Institute of Medicine: Committee on the Safety of Silicone Breast Implants** reviewed the work of both the IRG and and the National Science panel: ***IRG concluded that "there was no evidence that children of women with silicone gel-filled breast implants are at increased risk of connective tissue disease** and that the overall biological response to silicone is consistent with conventional forms of response to foreign materials, rather that an unusual toxic reaction. **In the section on toxicology, it might have been preferable to have relied on information that is available to and reviewable by others, rather than citing data that are confidential."*** [52]

Human exposures to D4 and D5 have been under investigation for decades.

Dow Chemical Deceived Women On Breast Implants, Jury Decides
By BARRY MEIER NYC Times Published: **August 19, 1997**
Read more:
http://www.nytimes.com/1997/08/19/us/dow-chemical-deceived-women-on-breast-implants-jury-decides.html
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> *'... the jury found after a five-month trial that Dow Chemical had been involved in testing silicone for human implants, had been negligent in those activities and had remained silent about the dangers of silicone for humans. The jury also found that the company (Dow Chemical) had conspired with Dow Corning and that it had intentionally made misleading statements about silicone's safety.'* [53]

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[50] http://www.mhra.gov.uk/Committees/Devices/IndependentReviewGrouponsiliconegelbreastimplants/index.htm

[51] **Safety of Silicone Breast Implants** http://www.ncbi.nlm.nih.gov/books/NBK44797/

[52] **Institute of Medicine (US) Committee on the Safety of Silicone Breast Implants**; Bondurant S, Ernster V, Herdman R, editors. Safety of Silicone Breast Implants. Washington (DC): National Academies Press (US); 1999. C, Review of the Reports of the Independent Review Group and the National Science Panel. Available from: http://www.ncbi.nlm.nih.gov/books/NBK44797/

[53] NEW YORK Times **Dow Chemical Deceived Women On Breast Implants, Jury Decides** by BARRY MEIER Published: August 19, 1997 http://www.nytimes.com/1997/08/19/us/dow-chemical-deceived-women-on-breast-implants-jury-decides.html

Court documents (see Appendix for citations) reveal much of the confidential data from Dow Corning's own testing programme, pointing to the dangers to women from D4 and D5 in silicone breast implants:

> *By the early 1970's,* ***Dow Corning was focusing on the effectiveness of various polydimethylsiloxanes, including D4****, as adjuvants. Initial studies in Dow's laboratory, from 1971, established that silylated bacterial cells evoked an antibody response which differed from that of the unsilylated control with the response remaining higher than in control cells for the period studied.* ***By 1974, the Dow researchers concluded that "from a modest number of compounds examined over a period of ten months we have data indicating that organosilicon compounds can stimulate the immune response****."*
>
> *By January, 1975, Dow had found that "[v]arious organosilicon fluids [including polydimethylsiloxane fluids contained in breast implants]* ***potentiated the formation of humoral antibody, modulated cell mediated immunity and promoted the induction of interferon by stimulation of the immune system****." Later that same year,* ***testing by a Dow Corning virologist revealed that*** *some of the polydimethylsiloxanes in breast implants also produced eosinophilia, and that* ***the low molecular weight silicones impaired the phagocytic ability of macrophages****.*

In a report **In vitro metabolism of octamethylcyclotetrasiloxane (D4) by human liver microsomes**[54] released by Dow Corning to the US Environmental Protection Agency, in 2001, it is clear D4 interconversion is a strong probability:

> *Based on the results of experiments with recombinant human CYP enzymes and polyclonal antibodies, it was concluded that [^{14}C]-****D_4 is primarily metabolized in vitro to M8*** *and that CYP2B6 and CYP3A4 are largely responsible for its formation.*

In another report **Non-Regulated Study: in vitro effects of siloxanes on human immune cells**[55] submitted by Dow to the EPA in 2001 the reports author made this observation:

> *For example, if D4 or D5 are injected subcutaneously or into a body cavity, or when large quantities of D4 or D5 are ingested, or if droplets of D4 and D5 impact onto the respiratory mucosa,* ***the local concentration of lipid may be insufficient to neutralize the effects of D4 or D5, and the resultant cellular damage may lead to inflammation or fibrosis****.*

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[54] **In vitro metabolism of octamethylcyclotetrasiloxane (D4) by human liver microsomes** Dow Corning 2001 http://www.epa.gov/oppt/tsca8e/pubs/8ehq/2002/jan02/fyi_0102_01418a.pdf

[55] **Non-Regulated Study: in vitro effects of siloxanes on human immune cells** Dow Corning 2001 http://www.epa.gov/oppt/tsca8e/pubs/8ehq/2002/jan02/fyi_0102_01420a.pdf

Regulatory Delays

In 2012, EPA gave notice of a public meeting to negotiate an enforceable consent agreement (ECA) **to collect certain environmental monitoring data on octamethylcyclotetrasiloxane (D4) and decamethylcyclopentasiloxane (D5).** *A private organization had submitted a proposed ECA to EPA.*[56]

February 12, 2014 Lynne Black-Hedges, Economics, Exposure & Technology OPPT wrote to address the details and costs of the testing programme, estimating a budget of USD$1-$1.2m depending on the retention of the samples analysed.[57] In August 2014 the EPA rejected[58] the **SEHSC** request to proposed modifications/delays to the schedule.

The delays in endocrine disruptor regulation in the EU[59] and environmental protection regulations in the USA, pending impact assessments, are having a significant impact on the health of women and children. *Sweden's environment ministry is threatening to sue the European Commission in the European Court of Justice over alleged foot-dragging on endocrine disruptors[60].*

Industry delaying tactics

Momentive and Wacker[61] are amongst the suppliers of raw materials to PIP as well as parties to the Enforceable Consent Agreement: Development for Two Cyclic Siloxanes (D4 and D5) by the USA's Environmental Protection Agency:

> *ENVIRONMENTAL PROTECTION AGENCY [EPA–HQ–OPPT–2012–0209; FRL–9351–1]*
> *Enforceable Consent Agreement Development for Two Cyclic Siloxanes;*
> *AGENCY: Environmental Protection Agency (EPA).*
> *ACTION: Notice.*
> *"**Further information on D4 and D5, including existing test data and a product stewardship program developed by Dow Corning,** can be found in the public docket for this notice." http://www.gpo.gov/fds…/pkg/FR-2012-05-24/pdf/2012-12626.pdf*

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[56] Meetings: Enforceable Consent Agreement Development for Two Cyclic Siloxanes http://federal.eregulations.us/rulemaking/document/epa-hq-oppt-2012-0209-0001

[57] EPA (USA) Testing Consent Order for Certain Siloxanes http://www.noticeandcomment.com/EPA-HQ-OPPT-2012-0209-fsd-3030.aspx

[58] EPA letter to SEHSC 18 August 2014 http://www.noticeandcomment.com/Letter-to-Silicones-Environmental-Health-and-Safety-Center-SEHSC-Regarding-D4-ECA-Modification-Request-fn-215034.aspx

[59] **EU Commission delays action on EDC criteria** http://chemicalwatch.com/16371/eu-commission-delays-action-on-edc-criteria

[60] Sweden Threatens to Sue EU Over Endocrine Disruptor Inaction http://www.chemanager-online.com/en/news-opinions/headlines/sweden-threatens-sue-eu-over-endocrine-disruptor-inaction

[61] Consent Agreements and Testing Consent Orders: Octamethylcyclotetrasiloxane (D4); Export http://www.noticeandcomment.com/Consent-Agreements-and-Testing-Consent-Orders-Octamethylcyclotetrasiloxane-D4-Export-fn-122089.aspx

Classification, Labelling & Packaging

Women are prevented from making informed decisions and taking steps to protect themselves and their unborn children from toxic cyclic siloxane exposures, as **D4 and D5 in cosmetic products** as defined in Directive 76/768/EEC **and medical devices** which are invasive or used in direct physical contact with the human body **are exempted** from DIRECTIVE 1999/45/EC OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 31 May 1999 *concerning the approximation of the laws, regulations and administrative provisions of the Member States relating to the classification, packaging and labelling of dangerous preparations*[62].

D4 labelling

PIP Breast Implants

More than 400,000 women globally and as many as 100,000 women and their children in the EU have been exposed to D4 and D5 in fraudulent PIP implants. The alert was raised by French health authorities in March 2010 when it was discovered PIP had been using unauthorised materials and experimental manufacturing techniques.

In December 2011, a French woman, with ruptured PIP implants, died from ALCL (Anaplastic Large Cell Lymphoma). It was 22 months after the French alert that the press & media exposed the scandal in the UK, a matter of days before Christmas. **In response to a Freedom of information request, received 19 December 2014, the MHRA confirmed the number of BIA-ALCL reports in the UK had increased from 3 at the time of the second Medical Devices Alert (July 2014) to a total of 8: one case of BIA-ALCL reported every month since the devices alert in July.**

Now, more ALCL deaths have been recorded worldwide, a distinct entity known as **BIA-ALCL Breast implant associated Anaplastic Large Cell Lymphoma** has been identified by medical researchers[63]. BIA-ALCL is not only associated with PIP implants, where significant concentrations of D4 and D5 are found, but also in other brands of silicone breast implants with varying concentrations of D4 and D5[64].

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[62] http://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX:01999L0045-20130701

[63] http://www.ncbi.nlm.nih.gov/pubmed/24878027

[64] **See Appendix: D4 in certified brands**

In the UK where 47,000 women are believed to be affected by PIP implants, the regulatory authority MHRA took a very early position on the issue of safety of PIP implants. And, predictably adhered to the view of the silicone and chemical industries.[65]

UK, SCENIHR & PIP IMPLANTS

The British toxicologist Professor Ian Kimber, was the only toxicologist on the Expert group reporting to the Department of Health in the UK, was also a member of the Working Group of the SCENIHR committee. On the 14th May 2014, **over 4 years after the PIP alert had been sounded by the French Health Authorities**, the SCENIHR, ***mandated to provide rapid advice on the state of scientific knowledge concerning special risks in cases of urgent needs***, published its final report:

Following the SCENIHR opinion on PIP breast implants in February 2012 several cyclic siloxanes (known as D4, D5 and D6) have been identified in PIP devices at higher concentrations than in other silicone breast implants. This has led to investigate the possible toxicological consequences of cyclic siloxanes release from damaged PIP implants. ***It became apparent that these chemicals are commonly present in the bodies of women even without breast implants. This is a consequence of the widespread use of siloxanes in many domestic*** **products. Cyclic siloxanes D4, D5 and D6 are non-toxic and not irritant in standard tests.**[66]

SCENIHR went further saying: *explantation is advised in the case of implant rupture; however, there are* ***no convincing medical, toxicological or other data to justify routine removal of intact PIP implants.*** The SCENIHR committee failed to recommend the preventative removal of all fraudulent PIP implants.

SCENIHR's shocking revelation takes no account of the known reprotoxic and oestrogenic characteristics of D4, or the fact that the majority of women affected are of reproductive age, many have been or would become pregnant and a significant number of women with ruptured and intact PIP implants would be breast feeding infants.

PIP Adverse Events

The array of adverse events in women with PIP breast implants are well-documented in clinical reports in the accompanying Annex. There is a growing body of peer-reviewed literature at odds with the SCENIHR conclusions.

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[65] Environmental Chemistry of Organosiloxanes 2014 Christoph Rücker* and Klaus Kümmerer Institute for Sustainable and Environmental Chemistry, Leuphana University Lüneburg, Scharnhorststrasse 1, D-21335 Lüneburg,Germany http://pubs.acs.org/doi/abs/10.1021/cr500319v

[66] http://ec.europa.eu/health/scientific_committees/consultations/public_consultations/scenihr_cons_14_en.htm

Peer Reviewed Clinical & Epidemiological Evidence

PIP Action Campaign has gathered the peer reviewed clinical evidence on PIP implants. **See Appendix**[67]

These studies & case reports show women with PIP have presented with: **chronic inflammation, silicone embolism, late seromas, prevalence of rupture, sub-clavicular adenopathy, Breast Implant Associated Anaplastic Large Cell Lymphoma, cutaneous manifestation of silicone dissemination, locoregional silicone spread, implant leaks, lymphadenopathies, capsular contracture and biofilm bacterial infections, angiosarcoma, lipogranuloma, and bilateral supra clavicular swelling**.

Self-Reporting Adverse Events

PIP Action Campaign has conducted a Health Survey[68] of members, 206 women affected by PIP implants have taken part. Our evidence should be taken into account and given priority over data derived from animal studies as they demonstrate hazards not identified in any other studies.[69]

Validated percentages[70] of our data show:

Over 50% of women reported suffering one or a combination of the following symptoms; **Blurred vision, dry eyes, cognitive difficulties, shortness of breath, muscle seizures, muscle weakness, dry mouth, dry skin, skin rashes, numb hands, excessive sweating, night sweats, bowel problems, hair loss,**

Over 70% of women reported suffering one or a combination of the following symptoms: **Headaches, memory loss and loss of sex drive**.

Over 80% of women reported suffering one or a combination of the following symptoms: **Poor concentration, depression, anxiety, mood swings, stiff joints and fatigue.**

Over 80% of women **pregnant with PIP experienced difficulties breast feeding**.

Women the world over are reporting serious health issues as well as voicing concerns about their children's health.

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[67] See Appendix; **Peer-reviewed Clinical Case Reports & studies PIP implants**

[68] See Appendix : **PIP Action Survey**

[69] Regulation (EC) No 1272/2008 of the European Parliament and of the Council of 16 December 2008 on classification, labelling and packaging of substances and mixtures, amending and repealing Directives 67/548/EEC and 1999/45/EC, and amending Regulation (EC) No 1907/2006 (Text with EEA relevance) **(28)** http://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX:32008R1272

[70] See Appendix: **Validated percentages - PIP Findings**

D4 and D5 In Breast Feeding Mothers with PIP Implants

The UK Government published the MHRA toxicological data[71] on PIP implants on their website 18 December 2014. On many occasions, PIP Action Campaign, supported by experts in the field, have challenged the quality of the toxicological testing, analysis and conclusions of the MHRA and SCENIHR.

The tests undertaken on breast milk of mothers with ruptured or leaking PIP implants stands as an example of the inadequate, self-referenced data relied on by the UK government [72]. In a summary published in 2012, the MHRA[73] noted that ***a single sample of breast milk was obtained from a lactating donor with a ruptured PIP breast implant***. The MHRA press statement adds that *it was relevant that a sample of normal semi-skimmed cows' milk that was used to develop assay method was found to have levels of total silicon of approximately 500 µg/litre (500 ppb)*. The laboratory report, published on the 18th December 2014 states: ***This should not be considered as an accurate result based on this single sample.***[74]

PIP Action Campaign identified several pregnant mothers with PIP implants willing to donate samples of breast milk for testing, the MHRA rejected these offers, saying:

> *The SCENHIR committee considered the levels of siloxanes in breast milk. They noted that Low levels of siloxanes in breast milk have been found in a single subject with a ruptured PIP implant. However, siloxanes have been found at detectable levels in over 20% of breast milk samples taken from women without breast implants. Moreover, commercially available semi-skimmed cow's milk was found to contain considerably higher levels of total silicone than the sample of breast milk taken from women with a ruptured PIP implant. Thus,* ***no identifiable increased risk for the nursing infant is anticipated from breast milk from a mother with ruptured breast implants.*** *The SCENHIR report can be found at : http://ec.europa.eu/health/scientific_committees/emerging/docs/scenihr_o_043.pdf*

Tests on a single sample of breast milk, from a nursing mother with a ruptured PIP implant, are neither evidence of safety nor scientifically valid. The quality of data informing and accepted by the MHRA and the SCENIHR is nothing short of scandalous. Particularly, as both entities are involved in health and safety risk assessments.

Four years on and there are still no answers why PIP implants are significantly more prone to rupture. Nothing is known of the experiments at the PIP manufacturing plant in France. Women with PIP implants are still suffering mental and physical pain.

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[71] https://www.gov.uk/government/publications/poly-implant-prosthese-pip-implants-toxicology-testing/poly-implant-prosthese-pip-implants-toxicology-testing

[72] https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/377372/Determination_of_Total_Silicon_in_Milk.pdf

[73] https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/377373/Silicon_in_Breast_Milk_Summary.pdf

[74] https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/377372/Determination_of_Total_Silicon_in_Milk.pdf

The clear and convincing evidence shows the consequences of human exposure to bioaccumulative D4 and D5 in vivo at body temperature or at critical stages of embryonic development, or ingested by infants in breast milk, is in urgent need of restrictive regulation.

No safe exposures or Margins of Safety can be determined for developing embryos and infants. There is no safe level, Margin of Safety or tests for bioaccumulative D4 and D5 in women who are exposed to a wide range of unlabelled medical devices, consumer, personal care and cosmetic products.

A continual process of risk assessments that are consistently biased towards the chemical manufacturers delays regulation. Only implementing a restriction in shampoo undermines the prospect of the Regulatory protection from EDCs, reproductive toxins and carcinogens, women in Europe are entitled to.

Women exposed to D4 and D5 in PIP are mainly of reproductive age, they are increasingly diagnosed with immune illnesses. As well as a wide range of physical neurological, immunological and toxicological symptoms. Women with PIP are traumatised, some are still battling for access to treatment, many are suffering with symptoms associated with PTSD.

The evidence of physical and mental harm is already well-documented.

Depression & Suicide

In **Mortality among augmentation mammoplasty patients** Brinton et al[75] demonstrate an **excess risk of brain cancer and suicide for women with breast implants**. Dr Diana Zuckerman[76] provides a coherent argument for the interpretation of Brinton's results which resonate with our own experience with PIP:

> *Notably, unlike most other plastic surgery patients, implant **patients suffer from well documented complications such as chronic pain and implant breakage** that increase in likelihood every year. Our centre receives letters every week from women whose implants are broken and who cannot afford explant surgery. **Many of these women are quite desperate, especially when silicone is migrating to other organs or causing pain or deformities.** Even in countries with national health care, these problems can be difficult to remedy and could potentially cause an increase in suicides.*

Weight of Evidence

It is obvious from the informal meta-analysis undertaken by PIP Action on studies on adverse health effects of silicone breast implants there are fundamental flaws in research data, which have been identified many times in the past, namely:

1. Miscalculation of the breast implant population
2. Reliance on studies of limited in size, relevance, questionable methodology or sponsorship

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[75] http://www.ncbi.nlm.nih.gov/pubmed/11337605

[76] BMJ VOLUME 326 7 JUNE 2003 D Zuckerman Letter in response to **Mortality in Swedish women with cosmetic breast implants : see Appendix**

Human health studies on D4 and D5 exposed women with silicone implants are not included in the research or used in calculating harmful exposure levels or *the Margin of Safety (MoS).* In fact, a number of invalid assumptions, experimental and inappropriate methodologies form the basis of many questionable risk assessments on D4 and D5.

In correspondence associated with Luu & Hutter's **Bioavailability of octamethylcyclotetrasiloxane (D4) after exposure to silicones by inhalation and implantation**[77] the authors note:

> *...models should be physiologically realistic and should not be used to predict phenomena beyond the reasonable bounds of the data by "fitting" highly restrictive cases.*
> *In an accurate model, the following problems should be avoided:*
> *•Artificially high pulmonary clearance of D4 resulting from use of a Pb:a that is not comparable to one obtained experimentally.*
> *• Use of unconventional methods to reduce the potential of accumulation in target organs.*
> *• Overestimation of the rate of metabolism, which is caused by a reduced absorbed dose resulting from inhalation exposure.*
> ***•Inappropriate use of the inhalation model for D4 to examine the disposition and fate of D4 leached from silicone breast implants.***
> *Because of these problems with Andersen et al.'s model,* ***the authors underestimated the potential bioavailability of D4 and were unable to predict its bioaccumulation after repeated exposures or long-term exposure that occurs when D4 leaches from silicone breast implants.***

Clear & Convincing Evidence

The clear and convincing evidence is provided by (i) large independent original studies[78] (ii) confidential and/or hidden manufacturer studies (iii) implant registries and adverse event reporting (iv) patient health & death records, most of which is confidential, unavailable or buried beneath the preponderance of meta-analyses of small, limited or manufacturer's/industry regulatory approval data.

Evidence of excess risk, from bioconcentration, biomagnification, bioaccumulation, hydrolysis, migration, in vivo application, low-dose toxicity, Henrys Law Constant, melting temperature and long half life properties, for both D4 and D5, have been known for decades yet women are still being exposed to ever-increasing dosages and presenting with a wide range of serious symptoms.

Peer-reviewed clinical reports and PIP implant adverse event reporting demonstrate links to neurological and immunological pathologies, brain cancer, breast cancer, BIA-ALCL and suicide. This human exposure data combined with evidence from epidemiological and environmental studies of EDCs are irrefutable evidence of the risks and dangers of D4 and D5 to women, developing embryos and breast fed infants. **See Appendices**.

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[77] **Bioavailability of octamethylcyclotetrasiloxane (D(4)) after exposure to silicones by inhalation and implantation.** http://www.ncbi.nlm.nih.gov/pubmed/11712992

[78] Epidemiology. 2001 May;12(3):321-6. Mortality among augmentation mammoplasty patients. Brinton L et Al http://www.ncbi.nlm.nih.gov/pubmed/11337605

Wide scale testing or biomonitoring of women and children exposed to cyclic siloxanes in PIP implants, has not yet been identified as a route to credible human data on toxic exposure levels of D4 and D5. A limited 'Restriction' of D4 and D5 in rinse-off hair products is proposed instead. While a triumph for industry, this would be a disaster for safe regulation of chemicals in the EU and a catastrophe for women. It signals only a very remote possibility of the EU implementing appropriate Restrictions in harmful substances in cosmetics and medical devices in the future,

Current State of Knowledge

In **Environmental Chemistry of Organosiloxanes**[79]**,** (published by Chemical Reviews June 2014) Christoph Rücker and Klaus Kümmerer devote a short chapter to the toxicity of breast implants, acknowledging the increased levels of D4 and D5 in PIP. They note ***ratios of individual cyclosiloxanes may vary over time, which may be due to a selective retention of D5 (and D6) relative to D4, or may be in vivo interconversion of cyclosiloxanes***.

Both selective retention and the interconversion of cyclosiloxanes clearly warrant further urgent investigation. More importantly still, there should be an immediate withdrawal of the SCENIHR final report and a urgent recommendation to remove all leaking and ruptured PIP implants.

In one of two 2013 studies published by Beretta et al[80]. D4 and D5 were found in the peri-prosthetic fluid surrounding the capsules of PIP implants. Evidence that LWM D4 and D5 migrates outside the implant capsule. A gel bleed, which is a phenomenon observed by treating surgeons is a leaking intact shell. This, and other peer-reviewed studies[81] in APPENDIX :**Peer reviewed clinical studies & reports relating specifically to PIP breast implants,** are clear and convincing evidence of toxicity and carcinogenicity in women exposed to D4 and D5 in leaking or ruptured PIP implants.

Both the weight of and clear and convincing evidence shows women and children are particularly vulnerable to and at risk from increasing and prolonged exposures to cyclic siloxanes.

Cosmetic Surgery Industry

In the UK alone, the cosmetic surgery industry is rapidly expanding. The industry was worth an estimated £2.3bn in 2010, and is estimated to rise to £3.6bn by 2015.[82] The global the industry was valued at $6 billion in 2012 according to Reuters[83]

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[79] **Environmental Chemistry of Organosiloxanes** C Rücker, K Kümmerer 2014 http://pubs.acs.org/doi/abs/10.1021/cr500319v

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Beretta G, Richards A, Malacco M. http://www.ncbi.nlm.nih.gov/pubmed/23835059

[81] See Appendix 5 :**Peer reviewed clinical studies & reports relating specifically to PIP breast implants**

[82] http://news.sky.com/story/1187962/breast-implants-plan-for-industry-regulation

[83] Global cosmetic surgery set to grow 10 percent in 2013 Reuters PARIS Thu Jan 31, 2013 http://www.reuters.com/article/2013/01/31/us-cosmetic-surgery-report-idUSBRE90U1FW20130131

Protecting Public Health

The public expects regulations to be put into place to protect human health. If REACH fails to act in the interests of the public, manufacturers will continue to deceive women about the dangers of breast implants[84], toxic medical devices will remain in women's bodies for longer and exposures will continue. Women will need further medical attention. The numbers of Breast Implant Associated Anaplastic Large Cell Lymphoma fatalities will rise[85], suicides, respiratory and brain cancers[86] will rise, developing embryos, breast fed children will be developmentally affected, women's immune illness and symptoms will continue to be dismissed. The public will learn not to expect the chemical regulators to be genuinely concerned with health protection and the proper and necessary regulation of chemicals, but rather with facilitating industry profits and the exponential growth of chemical toxins in our environment and in our bodies.

REACH

REACH was established to make industry responsible for the risks posed by chemicals and ensure a high level of protection for the public. It has a duty to protect women and children from the increasing toxic burden forced on them by D4 and unregulated D5 in consumer products, cosmetics and medical devices.

ECHA

ECHA now has a responsibility to assess these toxins based on clear and convincing evidence and ensure that it is not simply facilitating industry in seeking not only fewer regulations but even greater influence over chemical regulation in Europe.

VICTIMS of PIP FRAUD & REGULATORY FAILURES

Victims of the PIP fraud have become unwittingly embroiled in a much wider issue at the heart of the European Commission: the regulation of chemicals. Failure to regulate the toxic cyclic siloxanes in the light of the evidence is a crime against women.

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Please accept this submission on behalf of all PIP Action Campaign members, exposed to D4 and D5 in fraudulent PIP breast implants, as **clear and convincing evidence for the Restriction of these substances in the environment, personal care products, cosmetics and medical devices.**

PIP ACTION CAMPAIGN

PIP Action Campaign is a small, international social networking group based in the UK. Our members are women, mostly of reproductive age, many are mothers with children exposed during pregnancy, some are recovering breast cancer patients with *oestrogen receptor positive* tumours, all are directly affected and exposed to D4 and D5 in fraudulent PIP implants.

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APPENDIX 1

PIP Action Campaign
(i) HEALTH SURVEY 2014
(ii) PIP Findings Validated Percentages

APPENDIX 2

MEMORANDUM To: Robert Barham, Ph.D. Assistant Chief, Stationary Source Division Air Resources Board from George Alexeeff, Ph.D. Deputy Director for Scientific Affairs
September 13, 2007
REVIEW OF TOXICITY INFORMATION ON D5
OEHHA Review of Toxicity Information on D5

APPENDIX 3

Comments on **Bioavailability of Octamethylcyclotetrasiloxane (D4) After Exposure to Silicones by Inhalation and Implantation** Hoan-My Do Luu and Joseph C. Hutter Center for Devices and Radiological Health, U.S. Food and Drug Administration, Rockville, Maryland, USA Environmental Health Perspectives • VOLUME 109 I NUMBER 11 I November 2001

APPENDIX 4

Re: Mortality in Swedish women with cosmetic breast implants Study found increased risk of suicides and cancer deaths Correspondence from Dr Diana Zuckerman president National Center for Policy Research for Women and Families, Washington, DC 20006, 202 223-4000, USA

APPENDIX 5

Series cyclic siloxanes in FDA approved breast implants

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APPENDIX 6

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APPENDIX 7

Peer Reviewed studies on BIA-ALCL Breast Implant Associated Anaplastic Large Cell Lymphoma

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APPENDIX 8

C. INTERNAL STUDIES CONSISTENTLY DEMONSTRATED ADVERSE REACTIONS
In the 1960's, Dow Corning discovered extreme biological activity in a silicone compound called 2,6-cis, a compound closely related to D4 except that it contains a phenyl component. This development led Dow to begin a research program called the Bioscience Research Department led by a pharmacologist, Dr. Donald Bennett. Dow intended to develop commercial products exploiting the biologic activity of the whole range of silicone compounds. Bennett's lab found various silicones, including polydimethylsiloxanes, to have unexpected effects on the immune system. (28) In fact, by the late 1960's, Dow Corning believed that it might be able to use silicones to cure autoimmune disease.(29)

By the early 1970's, Dow Corning was focusing on the effectiveness of various polydimethylsiloxanes, including D4, as adjuvants. Initial studies in Dow's laboratory, from 1971, established that silylated bacterial cells evoked an antibody response which differed from that of the unsilylated control with the response remaining higher than in control cells for the period studied.(30) By 1974, the Dow researchers concluded that "[f]rom a modest number of compounds examined over a period of ten months we have data indicating that organosilicon compounds can stimulate the immune response."(31)

By January, 1975, Dow had found that "[v]arious organosilicon fluids [including polydimethylsiloxane fluids contained in breast implants] potentiated the formation of humoral antibody, modulated cell mediated immunity and promoted the induction of interferon by stimulation of the immune system."(32) Later that same year, testing by a Dow Corning virologist revealed that some of the polydimethylsiloxanes in breast implants also produced eosinophilia,(33)and that the low molecular weight silicones impaired the phagocytic ability of macrophages.(34)

Concerned about both the ability of silicone to migrate in the body and its local and systemic biological activity, Dr. Bennett recommended the establishment of a patient registry for breast implants.(35) None of the manufacturers established one. In the only long-term clinical study conducted by Dow Corning, fifty women with silicone breast implants were followed for ten years, primarily focusing on aesthetic results. The results, which were never published or disclosed to the FDA during hearings on complications from silicone breast implants during the 1980s,(36) revealed that nine out of forty-two women followed (eight were lost to follow-up) developed many of the same symptoms previously reported in the Japanese literature: (Patient 26 developed arthritis in her fingers twelve years after implantation, and patients 29, 36 and 50 also developed arthritic problems in their upper extremities, back, shoulder and fingers).(37)

In 1970, Dow Corning and Dow Chemical conducted an injection study in albino rats which confirmed the systemic migration of silicone. DC 360 fluid was found to migrate into the bone marrow of animals and affect brain weights.(38) Other internal studies demonstrated migrating silicone particles from a finger joint which were later found in the swollen lymph nodes of human subjects, where they entered the cells and were degraded.(39)

Other manufacturers also internally recognized the problems with silicone gel. By 1975, Heyer-Schulte was exploring the use of alternative materials for breast implants, recognizing that "[t]here is currently a need for a biocompatible and biodegradable organic polymer gel to replace the

polydimethylsiloxane material used in the Heyer-Schulte mammary prostheses . . . there is the possibility of some low molecular weight polymer migrating from the gel through the prosthesis. This material can localize in the body and possibly produce detrimental effects."(40) Heyer-Schulte also confirmed the work of Dow Corning on the subdivision and migration of silicone. In 1978, they found that, over time, the gel was broken up into small particles, and that it was the small particles that provoked the most inflammatory response and had the greatest tendency to migrate.(41)

Bristol-Myers Squibb's subsidiary, Medical Engineering Corporation (MEC/Surgitek), also did early animal testing. MEC's founding president and chief silicone scientist, Wilfred Lynch, testified that the only long-term animal studies MEC ever conducted on silicone were two-year dog studies (in two dogs) and 90-day rabbit studies.(42) MEC's purpose in doing the dog studies was to determine whether the silicone material was biocompatible and safe for long-term use. The dog study showed adverse reactions. Despite this, MEC undertook no additional pathology tests to follow up(43) and, ultimately, MEC determined that the dog studies were useless.(44)

Huntingdon Labs conducted three rabbit tests at MEC's request in the early 1970s. The toxicological reports showed adverse reactions in the brain and other organs, chronic inflammatory reactions, proliferation of connective tissue and formation of giant cells. The response was more prominent in the female animals than in males, particularly in the test sites around the mammary glands.(45) MEC retained an outside consultant to identify the chemical nature of compounds found in the organs of the test animals. He reported "low but definite concentrations of silicone in organs, especially kidney and liver."(46)

Because the local fibrotic reaction leading to significant capsular contracture was now of major concern to the plastic surgeons and manufacturers' sales representatives, MEC's president launched a "Scientific Affairs Committee," or SAC, in 1977. SAC consisted of several prominent scientists outside the company.(47)

In 1977, the manufacturers of silicone breast implants formed an official organization, "Breast Implant Manufacturer's Association," or BIMA, to respond to plastic surgeons' concerns about the formation of capsules in women with breast implants.(48) BIMA held a two-day scientific conference at the University of Michigan in November for plastic surgeons, immunologists, neurologists and other interested physicians regarding capsule formation and the reaction of tissue to silicone gel. Several prominent physicians participated. One of the proposals raised at the conference was to study the immune response of silicone in humans by conducting HLA typing (a lymphocyte study) of 100 patients. Also proposed was the "development of improved analytical techniques for silicone in tissues and biological materials."(49) None of the breast implant manufacturers ever conducted these studies.

Most of the manufacturers also failed to conduct studies on the biodegradation of silicone gel, elastomer and the various other components in the body. Dow, however, did know that silicone undergoes chemical changes in the body. Every test conducted by Dow in the 1970's and 1980's looking for metabolic byproducts had positive findings. Some found depolymerization,(50) the conversion of high molecular weight polydimethylsiloxanes to low molecular weight polydimethylsiloxanes. Others found metabolism to silanols through a hydrolysis reaction.(51) This was of great concern as "[a]ll of the silanols which had been tested had been found to have extreme toxicity."(52)

Other testing indicated that silicone ultimately degraded into silica. In 1979, MEC/Surgitek (later acquired by Bristol-Myers) also tested for metabolic changes of silicone. Transmission electron microscopy and energy dispersive x-ray analysis was conducted of tissue samples obtained from the

liver, kidneys, thyroid and lymph nodes of dogs implanted with silicone. Using a profile for a control silica pattern, "all specimens exhibited an energy pulse in the region of silica compatible with silica migration to these organs. The kidney and liver appeared to have greater peaks than the other tissues though thyroid [from one sample] also exhibited a significant peak."(53) In studies on the effects of silicone in the environment, Dow Corning also confirmed that the ultimate degradation product of silicone was silica.(54)

Meanwhile, in the published literature, case reports of symptoms of disease from silicone gel breast implants and silicone injections were increasingly reported. In 1979, an article was published in which the authors reported that a woman implanted with silicone gel breast implants experienced low grade fevers and joint aches.(55) Silicone was found in various organs throughout her body and upon removal of her implants, her condition improved dramatically.

Between 1979 and 1984, reports by Kumagai, Van Nunen, Baldwin and Okano(56) discussed the occurrence of symptoms of connective tissue disease after silicone gel breast implants and/or silicone injections. After Heggers and Kossovsky published their study in 1983 suggesting that silicone gel breast implants were capable of eliciting a cellular immune response,(57) two of the manufacturers (3M and Heyer-Schulte) left the breast implant business.(58) Dow Corning reviewed its data and acknowledged internally that "only inferential data exists to substantiate the long-term safety of these gels for human implant applications." (59)

In 1984, Dow Corning conducted a ninety-day implant test of silicone gel implanted into the paravertebral muscle and ventral subdural area of male rabbits.(60) After 3, 10, 30 and 90 days, the animals' tissues were examined and compared to USP polyethylene negative controls. The pathologist noted the presence of an eosinophilic infiltrate in the test animals, "considered indicative of an allergic response."

In 1985, Dow Corning conducted a repeat thirty-day test to investigate the possibility of immunological sensitization to a component of the gel formulation.(61) Once again, increased numbers of eosinophils were evident at the gel implant site.(62) The pathologist noted that "eosinophils appeared to diffusely infiltrate around and within the capsule, often being concentrated around vessels on the outer aspect of the capsule."(63) Neither the 1984 study nor 1985 repeat test was ever published.

By 1985, Dow Corning began to consider conducting an immunotoxicology program for silicone gel breast implants. In a project proposal entitled "Investigation of the Effects of Silicone Fluids, Gels and Particles on the Immune System," Dow Corning scientists conceded that "[a]nimal studies . . . also suggest that silicone materials may be able to modify the immune system. The studies have indicated silicone materials may have the ability to elicit a specific immune response to silicone as well as nonspecifically enhance or suppress the immune system."(64) Dow Corning reviewed its internal unpublished research on silicone's adjuvancy properties because of the outside work by Heggers published in 1983 (65) which found a cellular immune response to silicone gel, and Ben-Hur's work from the 1960's which demonstrated the ability of polydimethylsiloxane fluid to prolong mouse skin allograft survival by partial blockage of the lymphatic system.(66) They concluded that "the preponderance of available animal data also suggest a potential for silicone materials to be involved in immunologically mediated disease states."(67)

Other manufacturers reached similar conclusions. In 1985, a small manufacturer, CUI, commissioned a study to characterize its silicone materials. The study confirmed that "oil migration from the gel into the shell degrades the mechanical properties of the shell."(68) The researchers

also conducted biological testing and found tthat "[t]he gel does not appear to be retained within the fibrous capsule. . . ."(69) In fact, the investigators noted that "[s]ome silicone can be observed in close proximity to the vascular system, further substantiating observations by other investigators that silicone can migrate into the bloodstream."(70) They concluded that "the use of silicone gel prosthesis represent a significant risk to the patient. The literature suggest that individuals can develop an allergic and immunologic reaction to silicone and oil."(71) Similarly, an "Infor-Med" put out by one manufacturer stated that: "[t]he hazards of free silicone, well documented in silicone injections, are leading to more granulomas and silicone gorged [sic] lymph nodes. The damaging sequelae from these implants ask questions that remain unanswered and although doctors are using the product, plastic surgeons and the FDA continue to raise doubts about its safety and efficacy."

Further:

[s]mooth surfaced silicone polymers do not yield benign histological conditions as a result of their implantation. Silicone granulomas in the lymph and capsule, calcification, and recently 'arthritis' are hazards of direct cellular contact with this smooth polymer material.(72)
In late 1986, Dow Corning conducted a comprehensive review of all internally conducted safety studies of silicone materials to date and noted that "[s]ilicone gel contained within a silicone elastomer shell induces a chronic inflammatory reaction with the same characteristics as noted for free gel. It is probable, however, that resolution is never entirely achieved because the permeation of fluid through the shell is very slow and constitutes a rate-limiting process. That is, the contained gel functions as an infinite sink."(73) At least internally, Dow Corning also acknowledged that the gel from an implant was not contained within the fibrous capsule: "[r]eleased polydimethylsiloxane (and probably gel in the case of a rupture) is phagocytized in part by macrophages, giant cells, and possibly, PMN's. Phagocytic cells transport engulfed silicone to at least regional lymph nodes."(74) Dow scientists "postulated that phagocytized silicone will accumulate in draining lymph nodes followed by slow transport to the liver. It is anticipated that the liver will function as a secondary long-term storage site from which phagocytic bearing silicone will cycle to other tissues of the reticuloendothelial system. Elimination is postulated to occur at a slow rate via lung alveolar phagocyte migration up the respiratory tree to the esophagus."(75)

Concerning the formally-conducted toxicity studies done to date, Dow admitted that the majority "were conducted for the purpose of evaluating local implantation site reactions [and that] [t]he local reaction has been characterized only with regard to incidence and broad levels of severity."(76) Notably, Dow admitted that "[i]n no case are the local inflammatory reactions described and classified according to criteria employed by researchers expert in the study of inflammation nor have any studies been designed to detect the range of systemic effects that could attend a chronic inflammatory state."(77) In summarizing the major deficiencies in the toxicological studies performed on silicone up through 1986 Dow Corning noted:

A. The histopathology of the reticuloendothelial system has not been adequately assessed in any long-term study including determination of the organ distribution of silicone materials.
B. None of the existing studies critically assess possible systemic effects arising from the local inflammatory reaction or from material transport. These substantive issues are specifically relevant to current claims and suspicions of autoimmune-like disorders linked to silicone fluid and gel and to synovitis and lymphadenopathy associated with elastomer abrasion particles.(78)
In the late 1980's, Dow Corning began to conduct toxicological testing of

some of the various polydimethylsiloxanes present in silicone gel breast implants. A series of studies on D4and other low molecular weight silicones confirmed increased liver weights in animals(79) and more recent studies have found a prenatal and/or neonatal toxicity as compared to controls with a reduction in mean live litter size and pup viability indices.(80)

D5, another component, was found to induce the production of drug metabolizing microsomal enzymes in the liver(81) and also to result in reduction in P-450 hemoprotein content and hepatomegaly. Studies on D4produced similar results.(82)

In 1988, the FDA classified silicone gel breast implants as Class III devices requiring the manufacturers to produce data establishing their safety and effectiveness. Dow Corning, Bristol-Myers, Mentor and McGhan submitted Pre-Market Approval Applications on their "low-bleed" implants in July 1991. All were rejected by the FDA and, in February 1992, a moratorium was imposed.

D. THE MANUFACTURERS' LITIGATION STRATEGY

In reaction to an increasing number of lawsuits, the manufacturers developed a "litigation strategy" of designing and funding epidemiological studies with the purpose of giving silicone gel breast implants a clean bill of health.(83) Before agreeing to funding any studies, Dow's litigation attorneys reviewed them to judge their impact on the litigation.(84) Epidemiology studies were also funded through the Plastic Surgery Education Foundation, an organization to which the manufacturers contributed and in which the attorneys for the manufacturers had direct input into selecting which studies to fund. As the attorneys noted at one meeting, "[t]he strategydirectly relates to which study should be funded."(85) Four conditions were apparently required before funding approval was given:

1. that the studies look at classical, traditional connective tissue diseases (and not the atypical symptomatology reported by clinicians and found in the literature).
2. that the studies include saline implants which do not contain silicone gel or oil inside.(86)
3. That the studies use a two-tailed test of significance instead of a one-tail test which had been recommended by investigating institutions;(87) and
4. that all women who exhibited symptoms after 1991 be excluded from the study although including all women implanted through 1991.(88)

In the early and mid-1990's independent research on silicones has proliferated. From clinicians' documentation of their clinical experience with thousands of ill women with breast implants to laboratory studies exploring the immunological effects of silicones in the body, the science continues to develop to this day.

E. RECENT DEVELOPMENTS

There have been a few important new developments on a variety of scientific issues since the July, 1997 Birmingham presentations. In the area of immunology, Schaefer recently reported the first animal model showing increased incidence and severity of autoimmune disease in susceptible mice induced by exposure to silicones nine months prior to immunization with antigen. The same study detected multiple perturbations in more than six different cytokines, autoimmune biomarkers, and antibodies to different silicone-bound proteins.(89) Naim reported that human monocytes compared to other materials, cultured on silicone, produced two times the amount of 3 cytokines,(90) and an Austrian research group confirmed Claman's findings of excess high titer ANA's in non-symptomatic implanted women.(91)

In addition, new clinical studies show a correlation between levels of silicone in the liver and ANA's and with peripheral neuropathy in implanted women vs. controls. A correlation was also shown between cognitive impairment and two brain metabolic dysfunctions, with one of the dysfunctions improving after explantation.(92) Finally, two large German studies recently found powerful associations between silica inhalation and scleroderma.(93)

Continue to Section II of Plaintiffs' Submission.

1. Rowe, V.K., Spencer, H.C., Bass, S.L., "Toxicological Studies on Certain Commercial Silicones and Hydrolyzable Silane Intermediates," Journal of Industrial Hygiene and Toxicology 30(6):332-352 (1948) [Record No. 0004].

2. The Dow Chemical Company and Corning, Inc. created Dow Corning Corporation in 1943. Each of the parents owns 50% of the stock in Dow Corning.

3. Chenoweth, M., Holmes, R., Stark, F., "The Physiological Assimilation of Dow Corning 200 Fluid" (1956) [Record No. 0006].

4. Dow Chemical Letter to McGregor, R.R., Re: Comparative eye irritation of specially prepared Dow Corning 200 fluids (9/1/59) [Record No. 0011].

5. Kumagai, Y., Shiokawa, Y., Medsger, T.A., et al., "Clinical Spectrum of Connective Tissue Disease After Cosmetic Surgery: Observations on Eighteen patients and a Review of the Japanese Literature," Arthritis & Rheumatism 27(1):1-12 (1984) [Record No. 1111].

6. Kumagai, Y., Shiokawa, Y., Medsger, T.A., et al., "Clinical Spectrum of Connective Tissue Disease After Cosmetic Surgery: Observations on Eighteen Patients and a Review of the Japanese Literature," Arthritis & Rheumatism 27(1):1-12 (1984) [Record No. 1111]; See, Travis, W., Balogh, K., Abraham, J., "Silicone Granulomas: Report of Three Cases and Review of the Literature," Human Pathology 16(1):19-27 (1984) [Record No. 2474].

7. "Silastic" is the Dow Corning registered trademark used to refer to all Dow Corning silicone-containing products. It is frequently used interchangeably with the word "silicone" to refer to the composition of a medical device such as "silastic implants," "silastic shunts," or "silastic tubing."

8. There are four main types of silicone gel breast implants: (1) Single-lumen - the most common breast implant, consisting of a gel/fluid matrix encased by a single silicone elastomer shell; (2) double-lumen - a double walled implant consisting of a gel/fluid matrix encased in a silicone elastomer that was, itself, surrounded by a saline filled chamber enclosed in an outer silicone elastomer shell; (3) polyurethane - a foam covered implant consisting of a gel/fluid matrix surrounded by a silicone elastomer one totally encased in an outer covering of polyurethane; and (4) a low bleed implant introduced in the early 1980's which was an alternative implant with an additional liner comprised of either thriflouropropy or additional methylphenyl material. There were variations which included textured shells introduced in the late 1980's in an attempt to reduce capsular contracture. Saline implants have only a silicone elastomer but no gel matrix, instead being filled with a saline solution.

9. Heyer-Schulte and MEC began manufacturing silicone gel breast implants in 1970 and, until 1976, received their silicone components from General Electric. McGhan Medical began manufacturing in 1975 and for the first year purchased its silicone components from General Electric. In 1976 General Electric ceased selling silicone for use in medical implantation.

10. Frugard, G., Memo to Koorajian and Rudy re: Trip to Dow Corning (7/14/76) [Record No. 2632].

11. Biotech Report to Heyer-Schulte re: 90-Day Animal Implantation Study with Histopathology, MC 236914-918 (1/26/77) [Record No. 7029].

12. Winn, R.A., memo to Tom Hyans re: Silicone gel technology for July meeting of FDA gel mammary panel (6/29/78) [Record No. 7030].

13. Dr. Vinnik, a plastic surgeon in Las Vegas, wrote, in part: "Physicians have assumed that problems associated with silicone injections were caused by adulterated liquid silicone. This is not the case. In Las Vegas and elsewhere, the injection of sterilized, unadulterated medical-grade fluid has also been implicated in adverse reactions." Vinnik, C.A., "The Hazards of Silicone Injections," JAMA 236(8):959 (8/23/76) [Record No. 0959].

14. Dow Corning report of telephone call from Dr. C.A. Vinnik (11/26/74) [Record No. 7031]; Vinnik, C.A., letter to Robert Rylee, President of Dow Corning Wright (6/23/81) [Record No. 2784].

15. By crosslinking silicone fluid into a gel matrix and surrounding it in a silicone elastomer, Dow Corning was able to call the silicone gel breast implant a medical device, and not a drug or drug delivery device, even though up to 90% of the gel remained liquid silicone and was known to diffuse through the elastomer as "gel bleed."

16. See discussion later in Section III.

17. Crout, J.R., FDA letter to Dow Corning (3/19/76) [Record No. 0623].

18. Lentz, A.J., Chandler, M.L., LeVier, R.R., "Biological Evaluation of an Implantable Silicone Gel: Summary of Acute and Chronic Studies," Dow Corning Report No. 4586 (5/17/78) [Record No. 7017].

19. Peters, S., Memo to Marlar, et al. re: Review of Implantable Gel Concept (4/29/81) [Record No. 0501].

20. It appears that the Cronin study did not even test the same silicone gel used in breast implants but rather used a Silastic R.T.V. See, Cronin, T.D., Gerow, F.J., "Augmentation Mammaplasty: A New 'Natural Feel' Prosthesis," presented at Third International Congress of Plastic Surgery (10/13-18/63) [Record No. 0817].

21. Id.

22. Christopher Batich, 7/22/97, Transcript of Panel Hearing, pp. 147-97. (All subsequent references to the July meeting of the National Science Panel will be as follows: [Witness name] [Date], Transcript of ____Panel Hearing, p. ____].

23. This is a critical fact as different polydimethylsiloxanes have very different biological effects. For example, D4 has different effects than D5. Most, such as D22, have never even been tested for their toxicological properties..

24. Potter, M., Morrison, S., Wiener, F., et al., "Induction of Plasmacytomas with Silicone Gel in Genetically Susceptible Strains of Mice," J. Nat. Canc. Inst. 86(14):1058-1065 (1994) [Record No. 1772].

25. Hayden, J., Barlow, S., "Structure-Activity Relationships of Organosiloxanes and the Female Reproductive System," Tox. & App. Pharm. 21(1):68-79 (1972) [Record No. 2394].

26. Nair, J. H., GE Letter to Dr. Keplinger (Industrial Biotest Labs) GEG 001658-001659 (8/25/75) [Record No. 7032]; Boretos, J.W., Letter from Biomaterials Consultant to B. Liebler (HIMA), HIM 4112 (6/9/93) [Record No. 7023].

27. Duncan , E., Memo to Compton, et al. re: Summation of findings - McGhan mammary prosthesis, MC 7041-7049 (6/28/77) [Record No. 7033].

28. Bennett, D.R., MDL Deposition, Vol. 1, pp. 210-213 (7/18/94) [Record No. 7236].

29. Isquith, A.J., Deposition, Vol. 1, pp. 110-113 (6/13/94) [Record No. 7034].

30. Dow Corning, Exploratory Antigen Modification Research Project Description (5/22/73) [Record No. 0022].

31. Boley, W., Levier, R., Immunological Enhancing Activities of Organosilicon Compounds and Non-functional Fluids, Dow Corning Report No. 4319 (10/2/74) [Record No. 0023].

32. Boley, W., Lake, R., LeVier, R., Dow Corning Patent Memorandum No. 4320 (1/31/75) [Record No. 0024].

33. Lake, R.S., Radonovich, A.F., "Actions of Polydimethylsiloxanes on the Reticuloendothelial System of Mice: Basic Cellular Interactions and Structure - Activity Relationships," Dow Corning Report No. 4509 (10/30/75) [Record No. 0025].

34. Id.

35. Bennett Deposition, Vol. 3, pp. 768, 771 (7/20/94) [Record No. 7035].

36. Dow Corning's legal counsel instructed Arthur Rathjen, who coordinated the data collection from Dr. Ben Gregory not to release the results of the study. Rathjen MDL testimony at p. 138 (11/30/94) [Record No. 7037].

37. A full set of the documents has been previously provided. Attached as Record No. 7036 are the study records from the women who became ill. Also see Rathjen Deposition, Vol. 1, pp. 115-146 (11/30/94) [Record No. 7037].

38. Sparschu, G., Clashman, A., Pathology Report on the Effects of Dow Corning 360 Fluid, TDC 8028 - 8078 (12/2/70) [Record No. 0018].

39. Quast Deposition, pp. 173-192 with Exhibit 7 (12/19/96) [Record No. 7038].

40. Siow, B.S., Memo to Mayhan re: Literature survey of biodegradable polymers, BAX 84228-845 (11/9/75) [Record No. 2589].

41. Pudenz, B., Talcott, T., Heyer-Schulte Memo to Tom Hyans attaching report on gel bolus studies, MD 114595-114598 (5/23/78) [Record No. 7039].

42. Lynch, W., MDL Deposition, pp. 119-120, 1673 [Record No. 7243]. See also, MDL Deposition of William Stith, MEC's Vice President of Scientific Affairs, pp. 224, 277-279 [Record No. 7244].

43. Stith, W., Deposition, Vol. 1., pp. 219-230, 242-249, 260-262, 277-279, 400-403, 407 (12/13/93) [Record No. 7243]; Speed memo from Robert Olsen to Sanders, President of MEC, et al., re: Beagle implant study, autopsy pathology, MED 25034 (4/17/75) [Record No. 7245].

44. Lock, B. (Director of Regulatory Affairs, MEC), MDL Deposition, pp. 106-107 (12/27/93) [Record No. 7246].

45. Yamachika, R., memo to Lynch and Oxley attaching interim report on tissue tolerance of silicone XD material, MEO 66493-503 (8/21/70) [Record No. 2715]; Huntingdon 90-day rabbit test results showing chronic inflammatory reaction, MEI 145252-61 (12/17/71) [Record No. 7247]; Huntingdon Research Center, Toxicology Report to MEC, MEI 149636-148648 (1/10/72) [Record No. 2700] (shows prominent inflammatory response in mammary glands of female animals).

46. Lynch, W., Memo to Sanders, BMS 56502-05 (7/17/79) [Record No. 7248].

47. MEC, Announcement of formation of Scientific Affairs Committee, MEM 281-284 (3/19/77) [Record No. 7249].

48. Helmer, J., Memo to Dave Sanders re: BIMA California meeting, MEM 415-417 (5/16/77) [Record No. 7251].

49. Talcott, T., Memo to Tom Hyans of Heyer-Schulte re: Ann Arbor Meeting, MC 114685-87 (11/23/77) [Record No. 2587]; See also, Lynch W., MiniReport on Ann Arbor Contracture Seminar, Lynch MDL Deposition Exhibit #41 (11/12/77) [Record No. 7252].

50. See, Annelin, R.B., Trace Analysis of Organosilicon in Human Urine and Milk by the ASFT Technique (5/29/80) [Record No. 0034].

51. See, e.g., Spielvogel, D., Robinson, R., Metabolism of Octamethylcyclotetrasiloxane in the Monkey, Dow Corning Report No. 5265 (12/10/80) [Record No. 0033].

52. McCarty, R., Speier, J., Chemical Research Progress Report, Dow Corning Report No. 2964 (10/12/66) [Record No. 2640].

53. Lynch, W., Letter to Stith enclosing reports on transmission electron microscopy and energy dispersive x-ray analysis of tissue samples, MED 26077-26149, Sec. MED 26084 (10/23/78) [Record No. 0031].

54. Lentz, C.W., "It's Safe to Use Silicone Products in the Environment," Industrial Research & Development, pp. 139-143 (4/80) [Record No. 1352].

55. Uretsky, B., O'Brien, J., Courtiss, E., "Augmentation Mammaplasty Associated with a Severe Systemic Illness, "Annals of Plastic Surgery 3(5):445-447 (11/79) [Record No. 1023].

56. Kumagai, Y., Abe, C., and Shiokawa, Y., "Scleroderma After Cosmetic Surgery: Four Cases of Human Adjuvant Disease," Arth. & Rheum. 22(5):532-537 (1979) [Record No. 1015]; Baldwin, C., Kaplan, E., "Silicone-Induced Human Adjuvant Disease," Ann. Plast. Surg.10(4):270-273 (4/83) [Record No. 1088]; Van Nunen, S., Gatenby, P., Busten, A., "Post-Mammoplasty Connective Tissue Disease," Arthr. & Rheum. 25 (6):694-697 (1982) [Record No. 1062]; Kumagai, Y., Shiokawa, Y., Medsger, T., et al., "Clinical Spectrum of Connective Tissue Disease After Cosmetic Surgery," Arthr. & Rheum. 27(1):1-12 (1984) [Record No. 1111]; Okano, Y., Nishikai, M., Sata, A., "Scleroderma, Primary Biliary Cirrhosis, and Sjogren's Syndrome After Cosmetic Breast Augmentation

with Silicone Injection: A Case Report of Possible Human Adjuvant Disease," Ann. Rheum. Dis. 43:520-522 (1984) [Record No. 5262].

57. Heggers, J., Kossovsky, N., Parsons, R., et al., Biocompatability of Silicone Implants," Ann. Plast. Surg. 11(1):38-45 (1983) [Record No. 1093].

58. Heyer-Schulte sold its silicone breast implant line to Mentor Corporation in 1984 and, in the same year, 3M sold its silicone breast implant line to a newly constituted McGhan Medical Corporation.

59. Matherly, J., Memo to Cooper and Ziarno re: Biological testing of gel for implants, M 170037-38 (9/23/83) [Record No. 0471].

60. Veresh, L., Ninety-Day Implant Study of Dow Corning Q7-2218 Silicone Gel System (12/7/84) [Record No. 2758].

61. Bejarano, M.A., Thirty-Day Implant Study of Dow Corning Q7-2218 Silicone Gel System (8/8/85) [Record No. 0475].

62. Id.

63. Id. at T-031532.

64. Boley, W., Malczewski, R.M., Cooper, J.G., "HCB Research Immunotoxicology Program Project Proposal - Investigation of the Effects of Silicone Fluids, Gel & Particles on the Immune System," DCCKMM 386643-659 (2/19/85) [Record No. 0476].

65. Heggers, J.; Kossovsky, N.; Parsons, R.; et al., "Biocompatability of Silicone Implants," Ann. Plast. Surg. 11(1):38-45 (1983) [Record No. 1093].

66. Ben-Hur, N., "Prolonged Allograft Survival by Partial Block of the Reticuloendothelial System with Silicone Fluid," Europ. Surg. Res. 2:73 (1970) [Record No. 7041].

67. Id., p. 4.

68. CUI Corporation, "Characterization of CUI Silicone Elastomer Shells CUI 300317-414 at 359 (10/10/85) [Record No. 0477].

69. Id., at CUI 300379.

70. Id., at CUI 300400.

71. Id., at CUI 300407.

72. Natural Y, Infor-Med re: Smooth Silicone Under Fibrosis, MEI 4230-4233 (10/85) [Record No. 2812].

73. Dow Corning, MedTox Project, DCCKMM 298296-339 (2/23/87) [Record No. 0479] (hereinafter "Medtox").

74. Id., p. 8.

75. Id., p. 9.

76. Id., p. 9.

77. Id.

78. Id.

79. Zimmer, M., Bejarano, M., "Octamethylcyclotetrasiloxane - An Investigation of Hepatic Weight Increases," GEG 32621-32634 (1989) [Record No. 0482].

80. Stump, A., "An Inhalation Range - Finding Reproductive Toxicity Study of Octamethylcyclotetrasiloxane (D4) in Rats," Dow Corning Report No. 1996-I000-41337, DCC 833-610016-6100190 (8/27/96) [Record No. 3096].

81. Mehendale, H. "Evaluation of the Liver Microsomal Enzyme Induction Potential of D5," Dow Corning Report, pp. 15154-15182 (4/17/89) [Record No. 0481].

82. Dow Corning (McKim, J.), "Effects of Octamethylcyclotetrasiloxane on Liver Size and Enzyme Induction: A Pilot Feasibility Study," Dow Corning Report No. 1996-I0000-41772, DIC 835-610001-610039 (9/16/96) [Record No. 5106].

83. J. R. Jenkins Affidavit, ś 4 (7/10/95) [Record No. 0486].

84. Id.

85. Plastic Surgery Education Foundation notes re: Silicone Research Funding Summit Meeting, ASP 22922-28 (7/10/92) [Record No. 7043].

86. Cook, R., Letter to Hollis Coffee, DCC 010001189-010001194 (5/18/92) [Record No. 7256].

87. See generally, Epidemiology Section.

88. Cook, R., Letter to Helen Englert, DCC 279011607-279011609 (9/11/92) [Record No. 7046].

89. Schaefer, C.J., "The Influence of Silicone Implantation Experimental Models of Autoimmunity," Ph.D. dissertation (9/11/97) [Record No. 7204].

90. Naim, J.O., Zhang, J.W., Van Oss, C.J., "In Vitro Activation of Human Monocytes by Various Plasma Proteins Adsorbed onto Silicone Elastomer, Gel and Oils," Surfaces in Biomaterials, pp. 105-106 (1996) [Record No. 7106].

91. Zazgornik, J., Piza, H., Kaiser, W., et al., "Autoimmune Reactions in Patients with Silicone Breast Implants," Wein Klin Wochenschr 108(24):781-787 (1996) [Record No. 7024].

92. Pfleiderer, B., Stanka, M., Bruns, H., et al., "Patients with Silicone Implants: Defect Diagnosis, Exposure to Silicone and Correlation with Symptomatology, "Abstract presented at Fifth Scientific Meeting ISRM, Vancouver (4/97) [Record No. 7168].

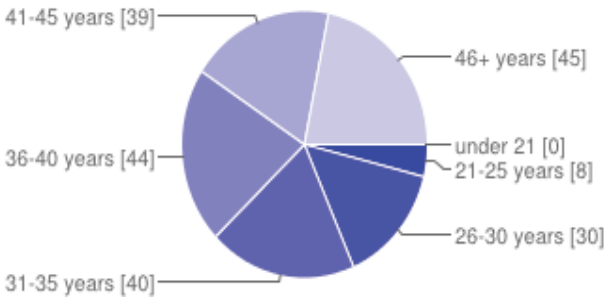
93. Mehihorn, J., Ziegler, V., "Epidemiological Analyses of the Relation Between Scleroderma, Exposure to Quartz and Silicosis for Men in East Germany," Int. Epid. Assoc., p. 76, Abstract (9/5/97) [Record No. 7199].

Members have completed this Health Survey which is available on PIP ACTION CAMPAIGN's webpage and on social networking pages as a Google Document.

Health Survey for Women with PIP Breast Implants

We suspect that behind every ruptured or leaking PIP implant there is a broken heart *

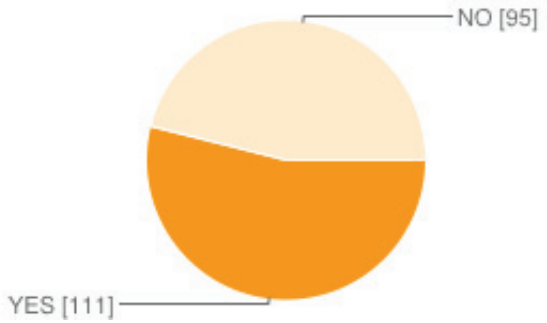
How old are you?



under 21	**0**	0%
21-25 years	**8**	4%
26-30 years	**30**	15%
31-35 years	**40**	19%
36-40 years	**44**	21%
41-45 years	**39**	19%
46+ years	**45**	22%

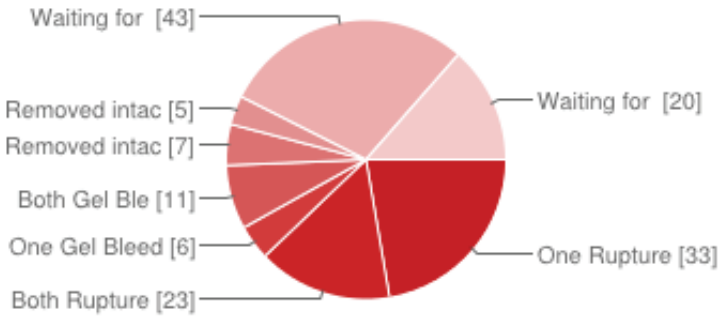
NOTE: Google's Summary of responses, shown in the following pages, is a very basic tool for analysis. A more accurate **Validated Percentages Findings** document is available as well as an EXCEL spreadsheet, which shows detailed responses.

Have you had your PIP implants removed?



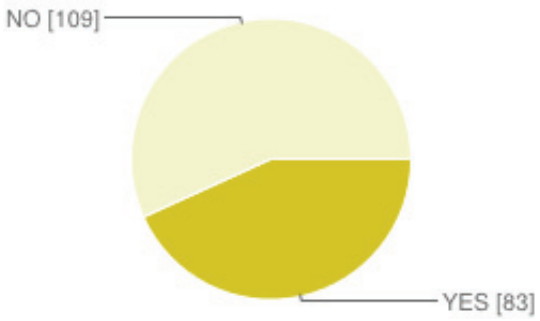
YES	**111**	54%
NO	**95**	46%

About your PIP implants



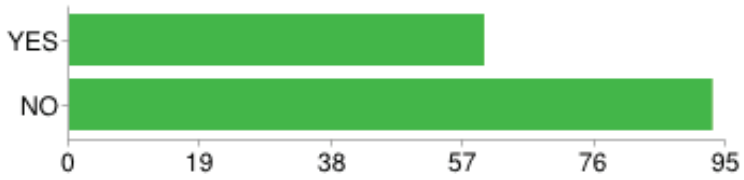
One Rupture	**33**	16%
Both Ruptured	**23**	11%
One Gel Bleed	**6**	3%
Both Gel Bleed	**11**	5%
Removed intact, unsure about gel bleed	**7**	3%
Removed intact, no gel bleed	**5**	2%
Waiting for removal	**43**	21%
Waiting for removal, confirmed rupture	**20**	10%

Have you had your PIP implants REMOVED and REPLACED?



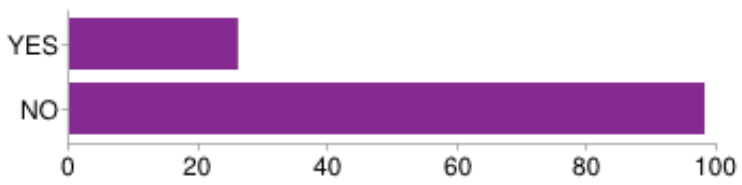
YES	**83**	40%
NO	**109**	53%

Confirmed rupture(s) Ultrasound [Any Indication of PIP rupture or gel bleed BEFORE PIP REMOVAL Surgery?]



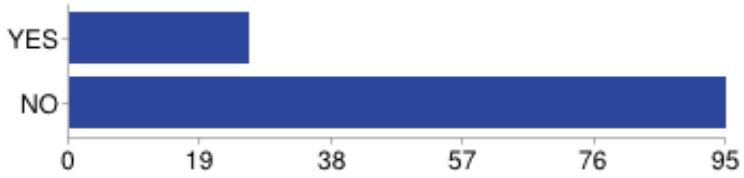
YES	**60**	29%
NO	**93**	45%

Confirmed rupture(s) MRI [Any Indication of PIP rupture or gel bleed BEFORE PIP REMOVAL Surgery?]



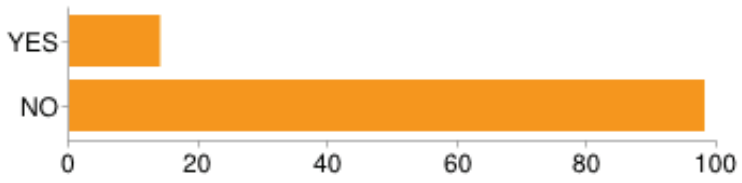
YES	**26**	13%
NO	**98**	48%

Confirmed gel bleed(s) Ultrasound [Any Indication of PIP rupture or gel bleed BEFORE PIP REMOVAL Surgery?]



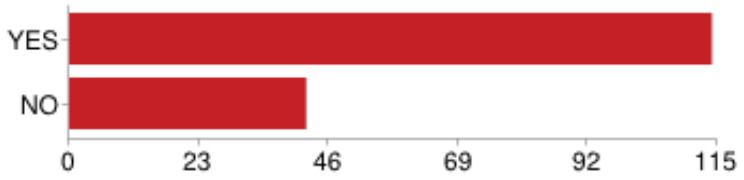
YES	**26**	13%
NO	**95**	46%

Confirmed gel bleed(s) MRI [Any Indication of PIP rupture or gel bleed BEFORE PIP REMOVAL Surgery?]



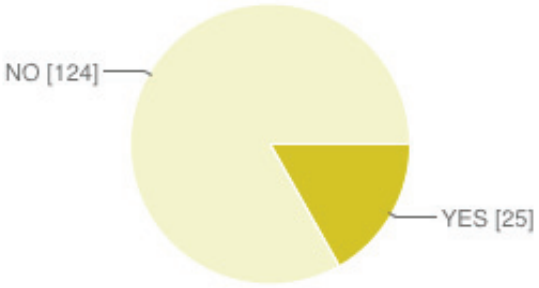
YES	**14**	7%
NO	**98**	48%

Symptoms [Any Indication of PIP rupture or gel bleed BEFORE PIP REMOVAL Surgery?]



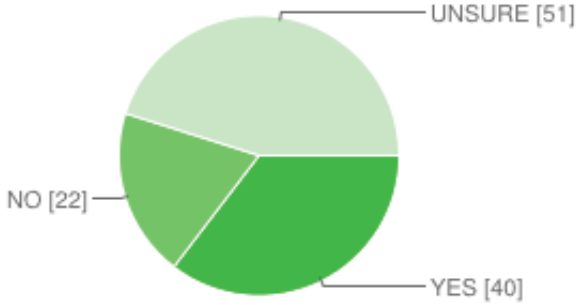
YES	**114**	55%
NO	**42**	20%

Undiagnosed Rupture(s) discovered on REMOVAL surgery?



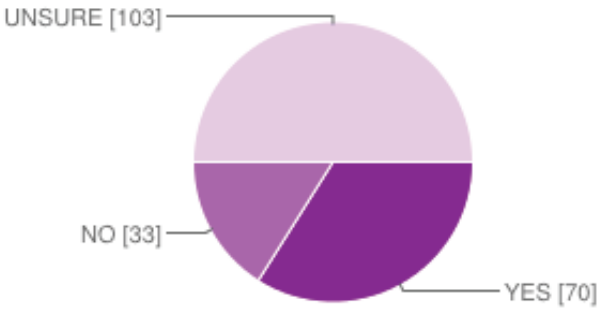
YES	**25**	12%
NO	**124**	60%

If your PIP implants were removed INTACT, did you experience Gel Bleed(s)?



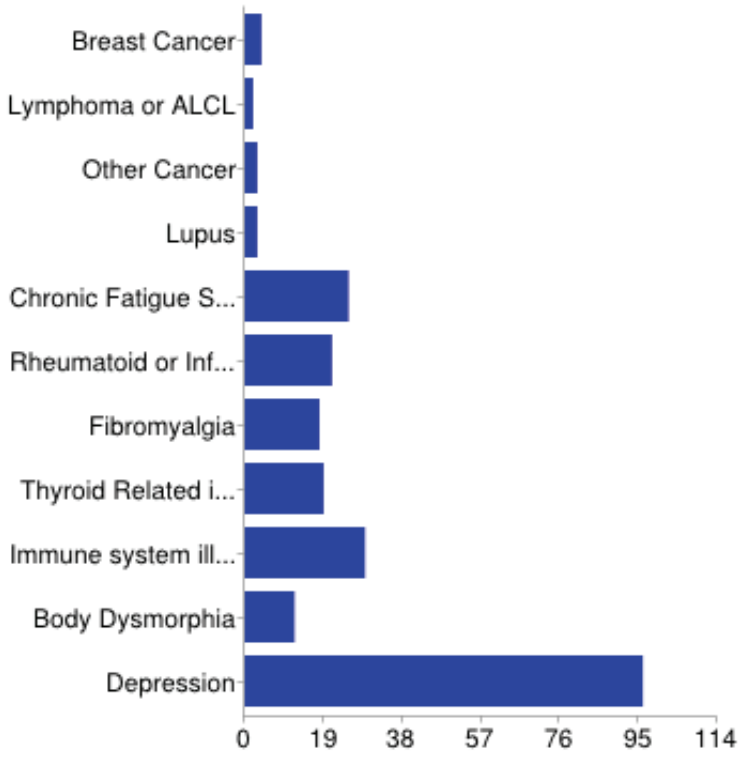
YES	**40**	19%
NO	**22**	11%
UNSURE	**51**	25%

Are your Lymph Nodes affected?



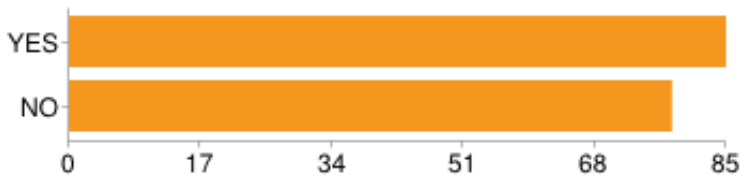
YES	**70**	34%
NO	**33**	16%
UNSURE	**103**	50%

Have you been diagnosed with any of the following?



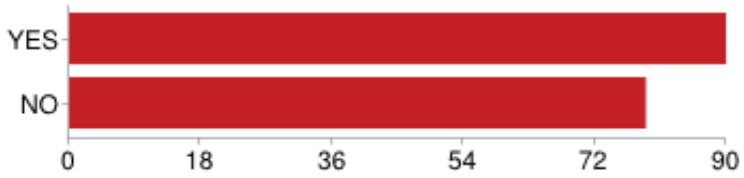
Breast Cancer	**4**	2%
Lymphoma or ALCL	**2**	1%
Other Cancer	**3**	1%
Lupus	**3**	1%
Chronic Fatigue Syndrome	**25**	12%
Rheumatoid or Inflammatory Arthritis	**21**	10%
Fibromyalgia	**18**	9%
Thyroid Related illness	**19**	9%
Immune system illness	**29**	14%
Body Dysmorphia	**12**	6%
Depression	**96**	47%

Blurred Vision [Have you experienced any of the commonly reported general symptoms linked to PIP implants?]



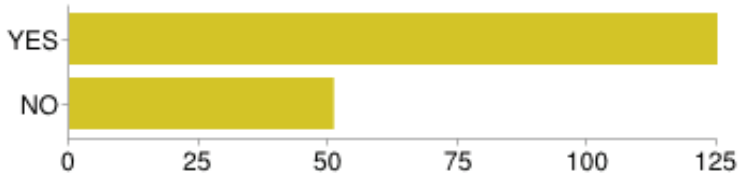
YES	**85**	41%
NO	**78**	38%

Dry or itchy eyes [Have you experienced any of the commonly reported general symptoms linked to PIP implants?]



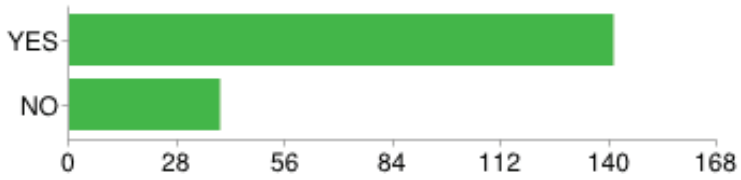
YES	**90**	44%
NO	**79**	38%

Headaches / migraines [Have you experienced any of the commonly reported general symptoms linked to PIP implants?]



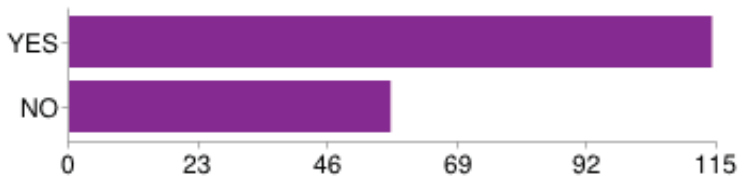
YES	**125**	61%
NO	**51**	25%

Poor concentration [Have you experienced any of the commonly reported general symptoms linked to PIP implants?]



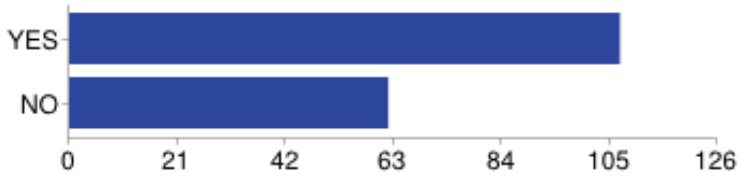
YES	**141**	68%
NO	**39**	19%

Memory loss [Have you experienced any of the commonly reported general symptoms linked to PIP implants?]



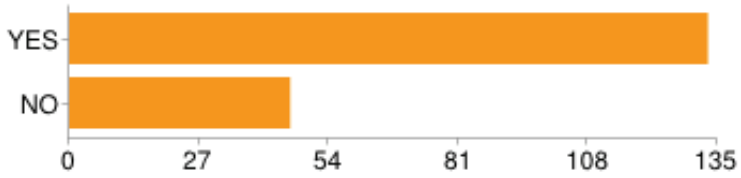
YES	**114**	55%
NO	**57**	28%

Cognitive loss (difficulty finding the right words) [Have you experienced any of the commonly reported general symptoms linked to PIP implants?]



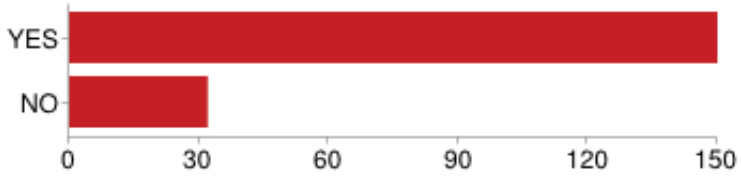
YES	**107**	52%
NO	**62**	30%

Depression [Have you experienced any of the commonly reported general symptoms linked to PIP implants?]



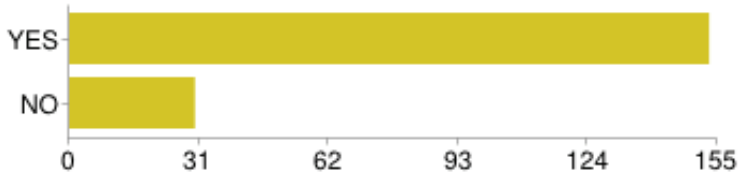
YES	**133**	65%
NO	**46**	22%

Anxiety [Have you experienced any of the commonly reported general symptoms linked to PIP implants?]



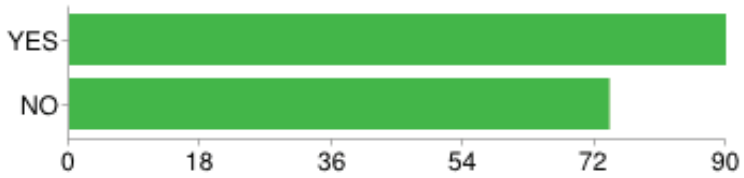
YES	**150**	73%
NO	**32**	16%

Mood swings [Have you experienced any of the commonly reported general symptoms linked to PIP implants?]



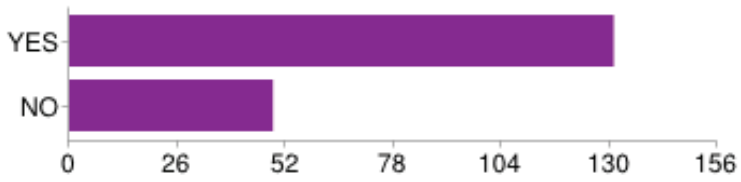
YES	**153**	74%
NO	**30**	15%

Shortness of breath [Have you experienced any of the commonly reported general symptoms linked to PIP implants?]



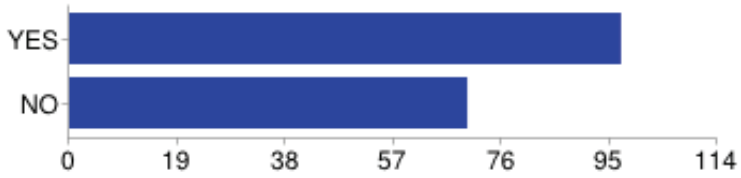
YES	**90**	44%
NO	**74**	36%

Stiffness or pain in joints [Have you experienced any of the commonly reported general symptoms linked to PIP implants?]



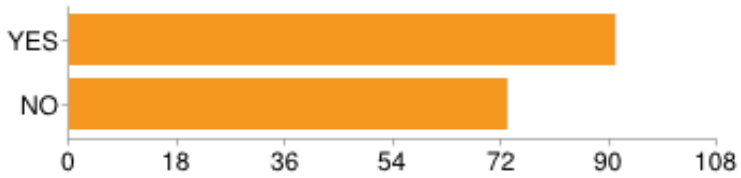
YES	**131**	64%
NO	**49**	24%

Muscle seizures, cramps or spasms [Have you experienced any of the commonly reported general symptoms linked to PIP implants?]



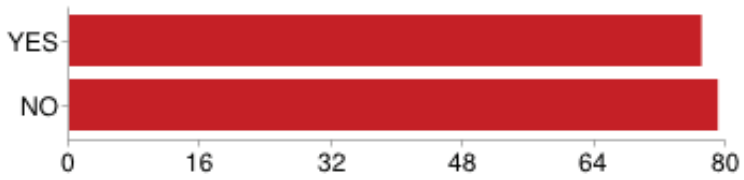
YES	**97**	47%
NO	**70**	34%

Muscle weakness [Have you experienced any of the commonly reported general symptoms linked to PIP implants?]



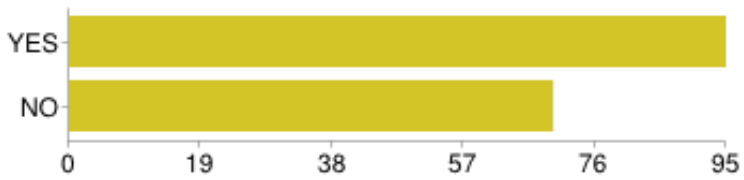
YES	**91**	44%
NO	**73**	35%

Dry mouth [Have you experienced any of the commonly reported general symptoms linked to PIP implants?]



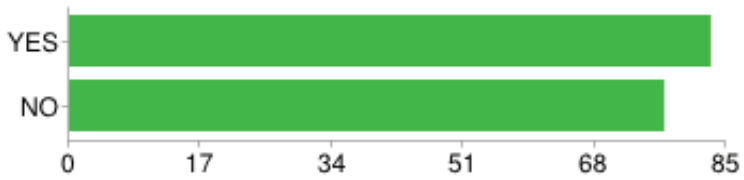
YES	**77**	37%
NO	**79**	38%

Dry skin [Have you experienced any of the commonly reported general symptoms linked to PIP implants?]



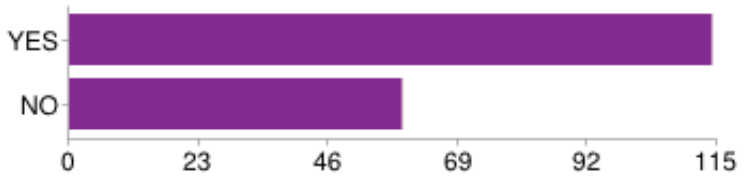
YES	**95**	46%
NO	**70**	34%

Skin rashes [Have you experienced any of the commonly reported general symptoms linked to PIP implants?]



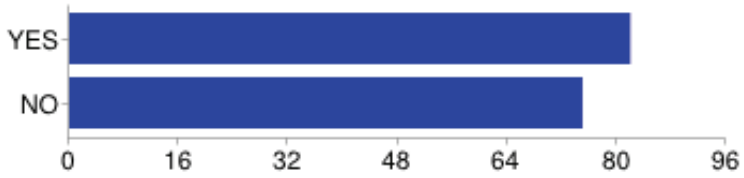
YES	**83**	40%
NO	**77**	37%

Tingling or numbness in hands [Have you experienced any of the commonly reported general symptoms linked to PIP implants?]



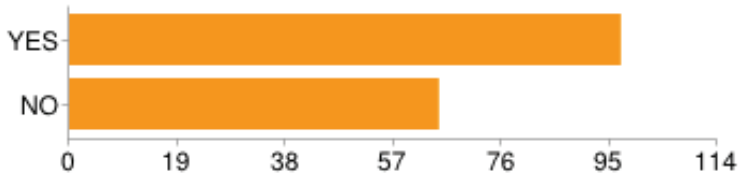
YES	**114**	55%
NO	**59**	29%

Excessive sweating [Have you experienced any of the commonly reported general symptoms linked to PIP implants?]



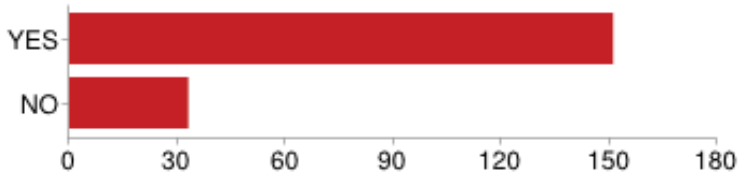
YES	**82**	40%
NO	**75**	36%

Night sweats [Have you experienced any of the commonly reported general symptoms linked to PIP implants?]



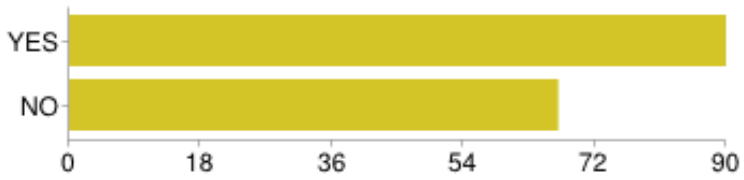
YES	**97**	47%
NO	**65**	32%

Extreme tiredness or fatigue [Have you experienced any of the commonly reported general symptoms linked to PIP implants?]



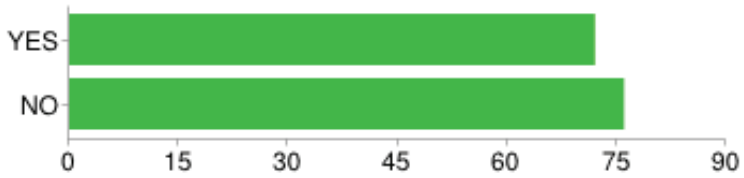
YES	**151**	73%
NO	**33**	16%

Bowel Problems [Have you experienced any of the commonly reported general symptoms linked to PIP implants?]



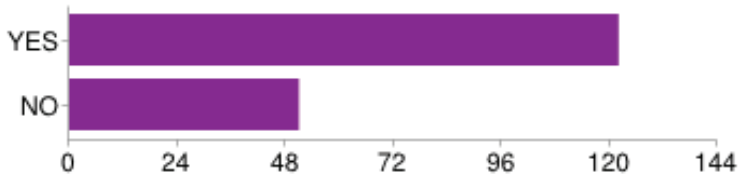
YES	**90**	44%
NO	**67**	33%

Hair thinning or hair loss [Have you experienced any of the commonly reported general symptoms linked to PIP implants?]



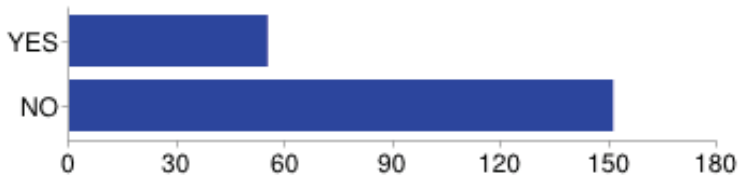
YES	**72**	35%
NO	**76**	37%

Loss or reduction in sex drive [Have you experienced any of the commonly reported general symptoms linked to PIP implants?]



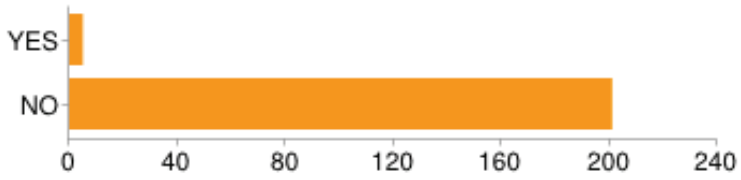
YES	**122**	59%
NO	**51**	25%

Did you have a mammogram while you had PIP implants? [About your PIP Implants]



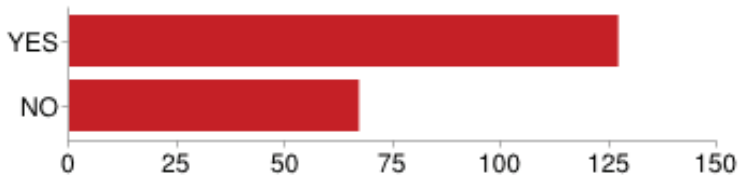
YES	**55**	27%
NO	**151**	73%

Did you have a reconstruction after breast cancer or BRCA with PIP implants ? [About your PIP Implants]



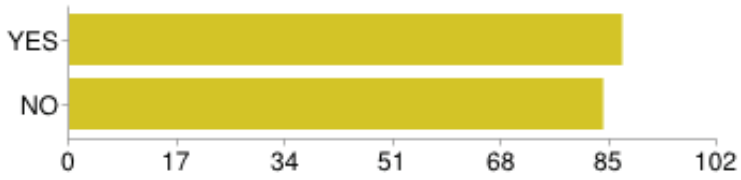
YES	**5**	2%
NO	**201**	98%

Implants changed size or shape [Have you experienced any of the following with PIP implants?]



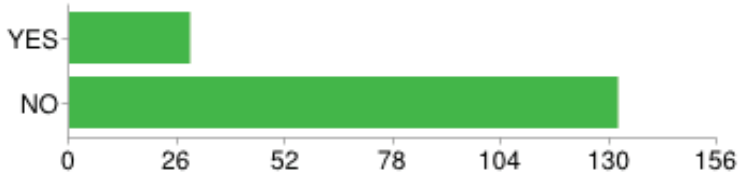
YES	**127**	62%
NO	**67**	33%

Implants Wrinkled [Have you experienced any of the following with PIP implants?]



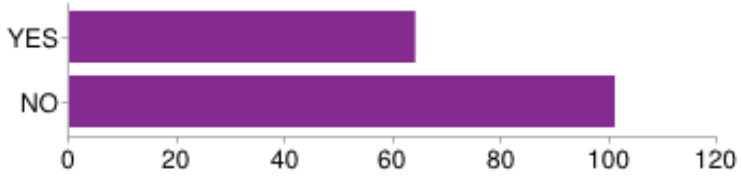
YES	**87**	42%
NO	**84**	41%

Implants Stuck to the chest wall [Have you experienced any of the following with PIP implants?]



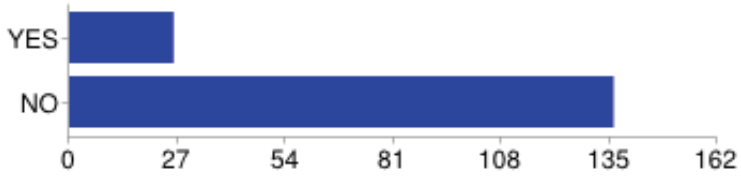
YES	**29**	14%
NO	**132**	64%

Silicone in lymph glands [Have you experienced any of the following with PIP implants?]



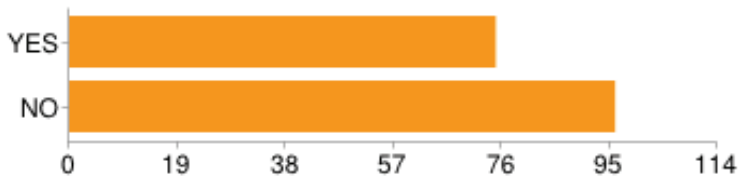
YES	**64**	31%
NO	**101**	49%

Wound infections [Have you experienced any of the following with PIP implants?]



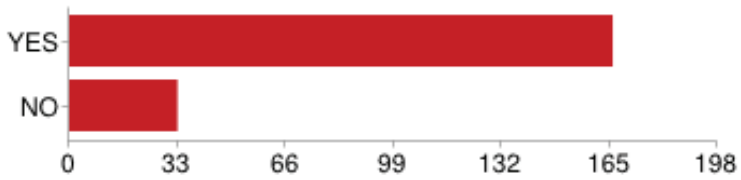
YES	**26**	13%
NO	**136**	66%

Breast inflammation [Have you experienced any of the following with PIP implants?]



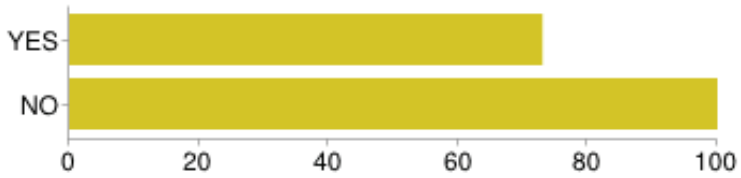
YES	**75**	36%
NO	**96**	47%

Breast pain [Have you experienced any of the following with PIP implants?]



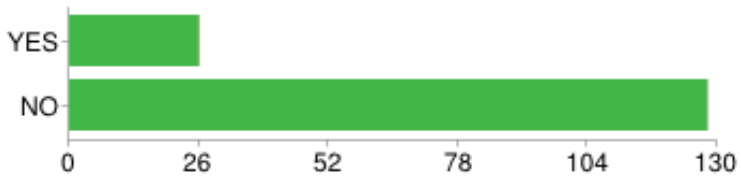
YES	**166**	81%
NO	**33**	16%

Breast lumps or cysts [Have you experienced any of the following with PIP implants?]



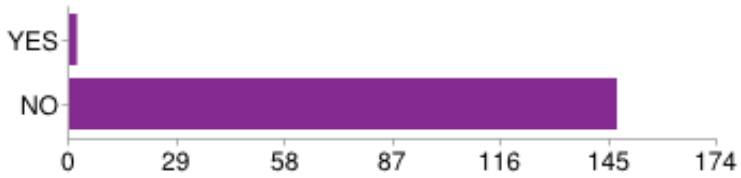
YES	**73**	35%
NO	**100**	49%

Siliconoma(s) or granuloma(s) [Have you experienced any of the following with PIP implants?]



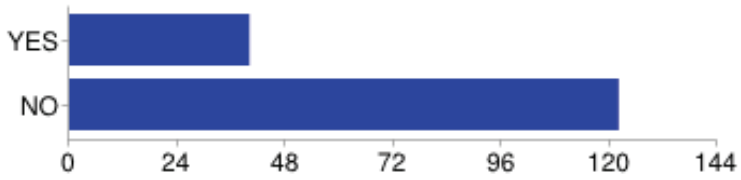
YES	**26**	13%
NO	**128**	62%

Necrosis [Have you experienced any of the following with PIP implants?]



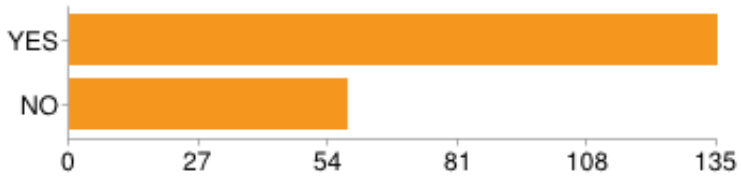
YES	**2**	1%
NO	**147**	71%

Capsular contracture [Have you experienced any of the following with PIP implants?]



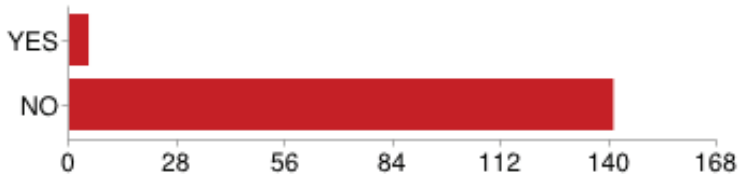
YES	**40**	19%
NO	**122**	59%

Itching, tingling or loss of sensation in your breasts [Have you experienced any of the following with PIP implants?]



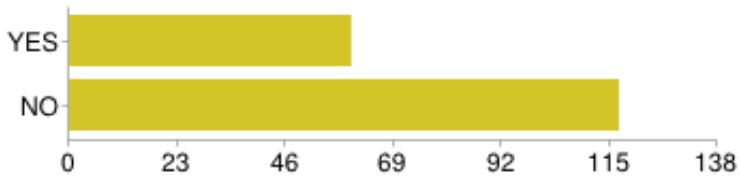
YES	**135**	66%
NO	**58**	28%

Seroma [Have you experienced any of the following with PIP implants?]



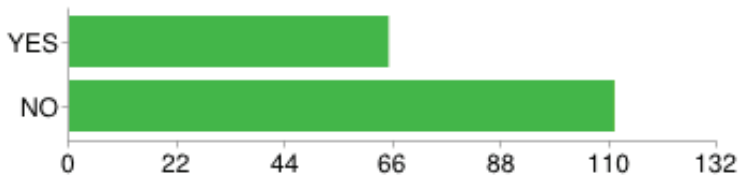
YES	**5**	2%
NO	**141**	68%

Inflammation [Do you frequently suffer from any of the following?]



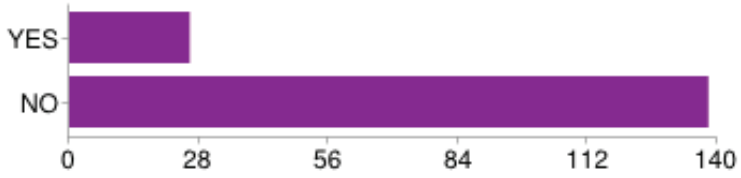
YES	**60**	29%
NO	**117**	57%

Allergies [Do you frequently suffer from any of the following?]



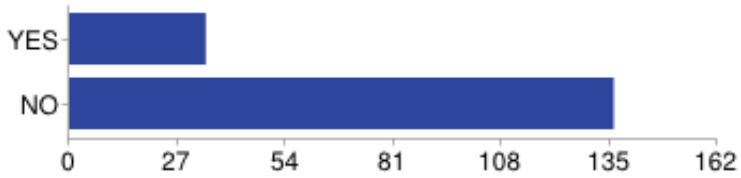
YES	**65**	32%
NO	**111**	54%

Herpes [Do you frequently suffer from any of the following?]



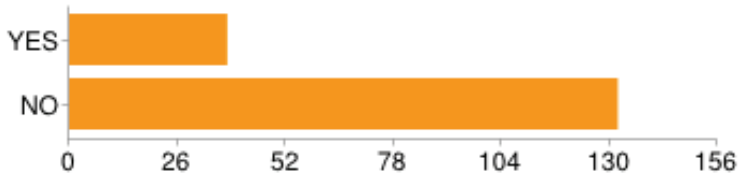
YES	**26**	13%
NO	**138**	67%

Cysts [Do you frequently suffer from any of the following?]



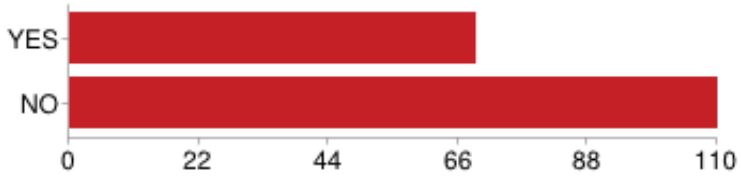
YES	**34**	17%
NO	**136**	66%

Fungal infections [Do you frequently suffer from any of the following?]



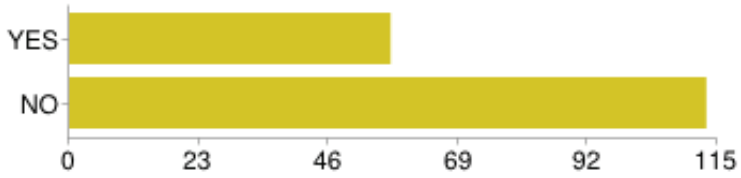
YES	**38**	18%
NO	**132**	64%

Skin Rashes [Do you frequently suffer from any of the following?]



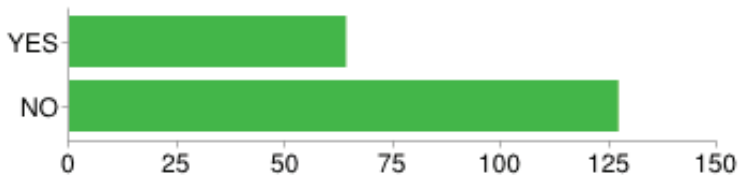
YES	**69**	33%
NO	**110**	53%

Mouth Ulcers [Do you frequently suffer from any of the following?]



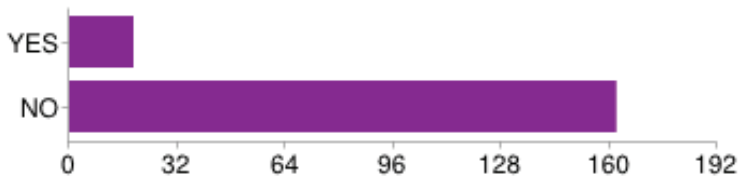
YES	**57**	28%
NO	**113**	55%

Have you been pregnant & given birth with PIP implants? [PIP IMPLANTS Pregnancy & Breast Feeding]



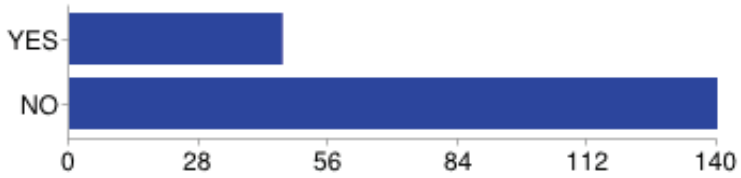
YES	**64**	31%
NO	**127**	62%

Have you experienced any difficulties getting pregnant with PIP implants? [PIP IMPLANTS Pregnancy & Breast Feeding]



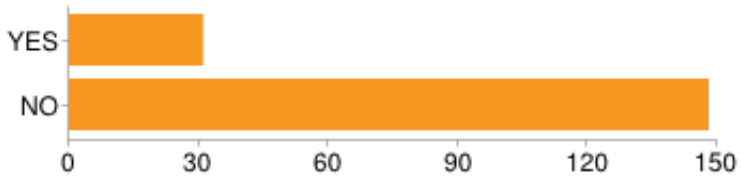
YES	**19**	9%
NO	**162**	79%

Have you breast-fed with PIP implants? [PIP IMPLANTS Pregnancy & Breast Feeding]



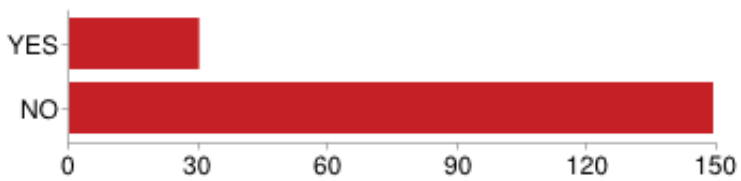
YES	**46**	22%
NO	**140**	68%

Have you experienced breast feeding difficulties with PIP implants? [PIP IMPLANTS Pregnancy & Breast Feeding]



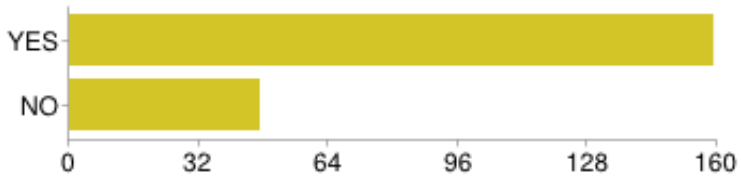
YES	**31**	15%
NO	**148**	72%

Have you experienced any miscarriages with PIP implants? [PIP IMPLANTS Pregnancy & Breast Feeding]



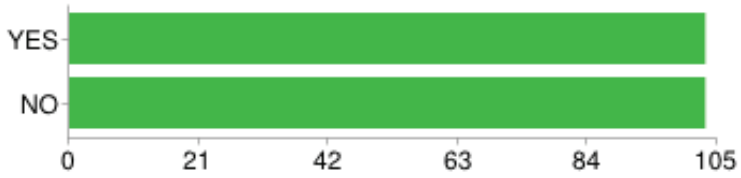
YES	**30**	15%
NO	**149**	72%

Have you visited your GP more than once with health concerns related to PIP implants? [PIP IMPLANTS : the impact on your life]



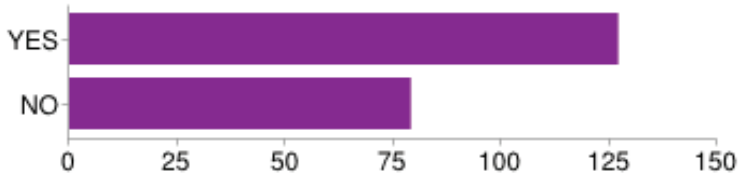
YES	**159**	77%
NO	**47**	23%

Have you delayed seeing your GP to discuss health issues related to your PIP implants? [PIP IMPLANTS : the impact on your life]



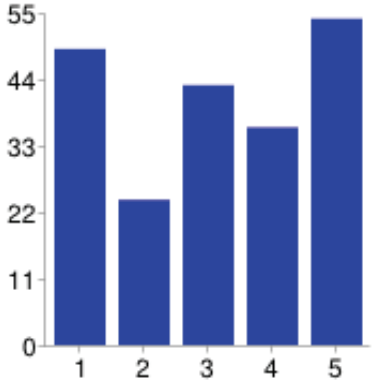
YES	**103**	50%
NO	**103**	50%

Have you taken any time off work due to PIP implants? [PIP IMPLANTS : the impact on your life]



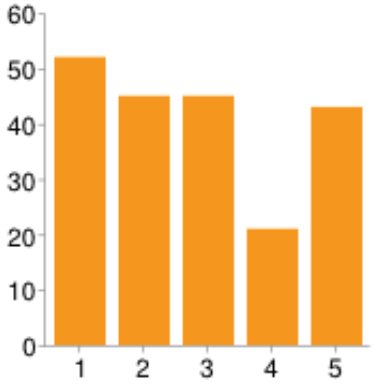
YES	**127**	62%
NO	**79**	38%

Have you experienced relationship problems due to PIP implants or your symptoms?



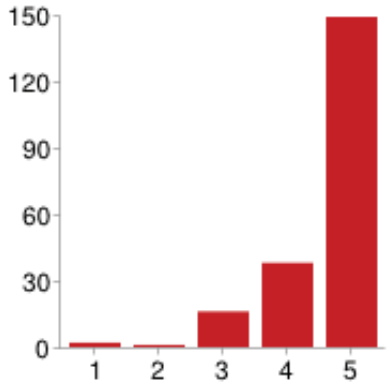
None	1	**49**	24%
	2	**24**	12%
	3	**43**	21%
	4	**36**	17%
Significant	5	**54**	26%

Has your GP been sympathetic & helpful?



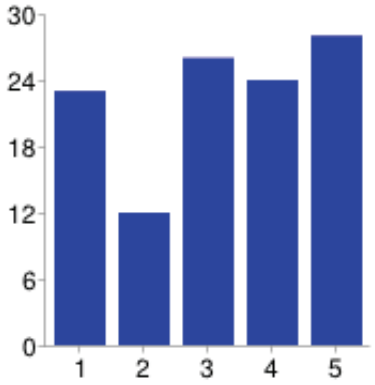
No help	1	**52**	25%
	2	**45**	22%
	3	**45**	22%
	4	**21**	10%
Very sympathetic & helpful	5	**43**	21%

How anxious are you about PIP implants?



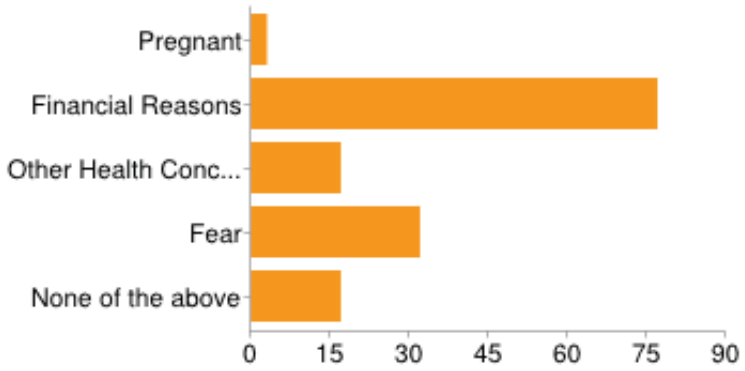
Not at all	1	**2**	1%
	2	**1**	0%
	3	**16**	8%
	4	**38**	18%
Extremely anxious	5	**149**	72%

If you have had your PIP implants removed, are you feeling better?



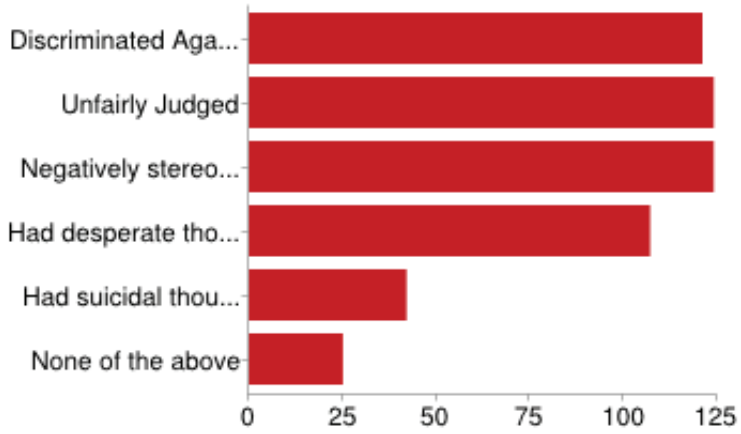
Not at all	1	**23**	11%
	2	**12**	6%
	3	**26**	13%
	4	**24**	12%
Much Better	5	**28**	14%

If you have NOT had your PIP implants removed yet, what is the main reason?



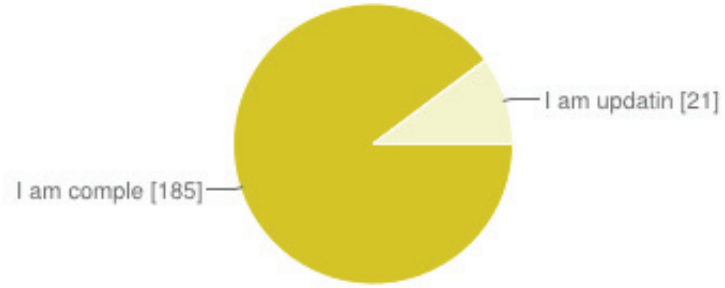
Pregnant	**3**	1%
Financial Reasons	**77**	37%
Other Health Concerns	**17**	8%
Fear	**32**	16%
None of the above	**17**	8%

At any time since finding out about your PIP implants have you felt



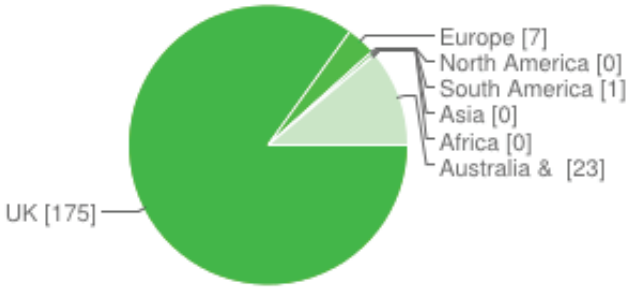
Discriminated Against	**121**	59%
Unfairly Judged	**124**	60%
Negatively stereotyped	**124**	60%
Had desperate thoughts	**107**	52%
Had suicidal thoughts	**42**	20%
None of the above	**25**	12%

This is an anonymous survey.



I am completing this survey for the first time	**185**	90%
I am updating my earlier response	**21**	10%

Where in the world are you?



UK	**175**	85%
Europe	**7**	3%
North America	**0**	0%
South America	**1**	0%
Asia	**0**	0%
Africa	**0**	0%
Australia & New Zealand	**23**	11%

Any Indication of PIP rupture or gel bleed BEFORE PIP REMOVAL Surgery?

confirmedruptureultrasound1

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	YES	28	27.7	37.3	37.3
	NO	47	46.5	62.7	100.0
	Total	75	74.3	100.0	
Missing	System	26	25.7		
Total		101	100.0		

confirmedrupturesMRI1

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	YES	11	10.9	19.0	19.0
	NO	47	46.5	81.0	100.0
	Total	58	57.4	100.0	
Missing	System	43	42.6		
Total		101	100.0		

confirmedgelbleedsultrasound1

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	YES	13	12.9	21.3	21.3
	NO	48	47.5	78.7	100.0
	Total	61	60.4	100.0	
Missing	System	40	39.6		

Total		101	100.0		

confirmedgelbleedsMRI1

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	YES	7	6.9	13.0	13.0
	NO	47	46.5	87.0	100.0
	Total	54	53.5	100.0	
Missing	System	47	46.5		
Total		101	100.0		

rupturegelbleedsymptoms1

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	YES	59	58.4	74.7	74.7
	NO	20	19.8	25.3	100.0
	Total	79	78.2	100.0	
Missing	System	22	21.8		
Total		101	100.0		

TOTAL RESPONSES = (75 + 58 + 61 + 47 + 79) = 320

YES RESPONSES = (28 + 11 + 13 + 7 + 59) = 118

PERCENTAGE ANSWERING YES = 36.88%

Undiagnosed Rupture(s) discovered on REMOVAL surgery?

undiagnosedrupturesonremoval1

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	YES	14	13.9	17.9	17.9
	NO	64	63.4	82.1	100.0
	Total	78	77.2	100.0	
Missing	System	23	22.8		
Total		101	100.0		

If your PIP implants were removed INTACT, did you experience Gel Bleed(s)?

removedintactgelbleeds1

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	YES	20	19.8	32.8	32.8
	NO	12	11.9	19.7	52.5
	UNSURE	29	28.7	47.5	100.0
	Total	61	60.4	100.0	
Missing	System	40	39.6		
Total		101	100.0		

Are your Lymph Nodes affected?

lymphnodesaffected1

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	YES	34	33.7	33.7	33.7
	NO	18	17.8	17.8	51.5
	UNSURE	49	48.5	48.5	100.0
	Total	101	100.0	100.0	

PIP IMPLANTS Pregnancy & Breast Feeding

pregnantbirthPIP1

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	YES	24	23.8	26.7	26.7
	NO	66	65.3	73.3	100.0
	Total	90	89.1	100.0	
Missing	System	11	10.9		
Total		101	100.0		

difficultiesgettingpregnantPIP1

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	YES	11	10.9	12.9	12.9
	NO	74	73.3	87.1	100.0
	Total	85	84.2	100.0	
Missing	System	16	15.8		
Total		101	100.0		

breastfedPIP1

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	YES	17	16.8	19.3	19.3
	NO	71	70.3	80.7	100.0
	Total	88	87.1	100.0	
Missing	System	13	12.9		
Total		101	100.0		

breastfeeddifficulty1

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	YES	14	13.9	16.7	16.7
	NO	70	69.3	83.3	100.0
	Total	84	83.2	100.0	
Missing	System	17	16.8		
Total		101	100.0		

miscarriagePIP1

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	YES	15	14.9	17.6	17.6
	NO	70	69.3	82.4	100.0
	Total	85	84.2	100.0	
Missing	System	16	15.8		
Total		101	100.0		

TOTAL RESPONSES = (90 + 85 + 88 + 84 + 85) = 432

YES RESPONSES = (24 + 11 + 17 + 14 + 15) = 81

PERCENTAGE ANSWERING YES = 18.75%

How many years have you had PIP implants?

Statistics

yearswithPIPimplants

N	Valid	101
	Missing	0
Mean		7.03
Minimum		2
Maximum		14

AVERAGE YEARS WITH PIP IMPLANTS = 7 YEARS

Time between original PIP surgery and Removal

Statistics

		datePIPremoval surgery	OriginalPIPsurgery
N	Valid	63	63
	Missing	0	0
Median		2012/08/14	2005.00
Mode		2011/02/26[a]	2006
Percentiles	25	2012/03/20	2004.00
	50	2012/08/14	2005.00
	75	2013/08/02	2006.00

a. Multiple modes exist. The smallest value is shown

MEDIAN YEAR ORIGINAL SURGERY = 2005

MEDIAN YEAR REMOVAL = 2012 (14/08/2012 IS MEDIAN RESPONSE)

Have you experienced any of the commonly reported general symptoms linked to PIP implants?

blurredvision1

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	YES	49	48.5	60.5	60.5
	NO	32	31.7	39.5	100.0
	Total	81	80.2	100.0	
Missing	System	20	19.8		
Total		101	100.0		

dryeyes1

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	YES	48	47.5	57.8	57.8
	NO	35	34.7	42.2	100.0
	Total	83	82.2	100.0	
Missing	System	18	17.8		
Total		101	100.0		

headaches1

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	YES	67	66.3	77.9	77.9

	NO	19	18.8	22.1	100.0
	Total	86	85.1	100.0	
Missing	System	15	14.9		
Total		101	100.0		

poorconcentration1

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	YES	71	70.3	81.6	81.6
	NO	16	15.8	18.4	100.0
	Total	87	86.1	100.0	
Missing	System	14	13.9		
Total		101	100.0		

memoryloss1

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	YES	59	58.4	70.2	70.2
	NO	25	24.8	29.8	100.0
	Total	84	83.2	100.0	
Missing	System	17	16.8		
Total		101	100.0		

cognitiveloss1

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	YES	57	56.4	67.9	67.9
	NO	27	26.7	32.1	100.0
	Total	84	83.2	100.0	

Missing	System	17	16.8		
Total		101	100.0		

depression1

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	YES	70	69.3	82.4	82.4
	NO	15	14.9	17.6	100.0
	Total	85	84.2	100.0	
Missing	System	16	15.8		
Total		101	100.0		

anxiety1

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	YES	77	76.2	88.5	88.5
	NO	10	9.9	11.5	100.0
	Total	87	86.1	100.0	
Missing	System	14	13.9		
Total		101	100.0		

moodswings1

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	YES	76	75.2	88.4	88.4
	NO	10	9.9	11.6	100.0
	Total	86	85.1	100.0	

Missing	System	15	14.9		
Total		101	100.0		

shortbreath1

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	YES	47	46.5	58.8	58.8
	NO	33	32.7	41.3	100.0
	Total	80	79.2	100.0	
Missing	System	21	20.8		
Total		101	100.0		

stiffness1

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	YES	73	72.3	80.2	80.2
	NO	18	17.8	19.8	100.0
	Total	91	90.1	100.0	
Missing	System	10	9.9		
Total		101	100.0		

muscleseizures1

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	YES	53	52.5	66.3	66.3
	NO	27	26.7	33.8	100.0
	Total	80	79.2	100.0	

Missing	System	21	20.8		
Total		101	100.0		

muscleweakness1

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	YES	50	49.5	63.3	63.3
	NO	29	28.7	36.7	100.0
	Total	79	78.2	100.0	
Missing	System	22	21.8		
Total		101	100.0		

drymouth1

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	YES	40	39.6	53.3	53.3
	NO	35	34.7	46.7	100.0
	Total	75	74.3	100.0	
Missing	System	26	25.7		
Total		101	100.0		

dryskin1

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	YES	52	51.5	65.0	65.0
	NO	28	27.7	35.0	100.0
	Total	80	79.2	100.0	

Missing	System	21	20.8		
Total		101	100.0		

skinrashes1

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	YES	43	42.6	55.8	55.8
	NO	34	33.7	44.2	100.0
	Total	77	76.2	100.0	
Missing	System	24	23.8		
Total		101	100.0		

handsnumb1

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	YES	58	57.4	68.2	68.2
	NO	27	26.7	31.8	100.0
	Total	85	84.2	100.0	
Missing	System	16	15.8		
Total		101	100.0		

sweating1

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	YES	41	40.6	56.2	56.2
	NO	32	31.7	43.8	100.0
	Total	73	72.3	100.0	

Missing	System	28	27.7		
Total		101	100.0		

nightsweats1

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	YES	52	51.5	65.8	65.8
	NO	27	26.7	34.2	100.0
	Total	79	78.2	100.0	
Missing	System	22	21.8		
Total		101	100.0		

fatigue1

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	YES	73	72.3	82.0	82.0
	NO	16	15.8	18.0	100.0
	Total	89	88.1	100.0	
Missing	System	12	11.9		
Total		101	100.0		

bowelproblems1

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	YES	42	41.6	57.5	57.5
	NO	31	30.7	42.5	100.0
	Total	73	72.3	100.0	

Missing	System	28	27.7		
Total		101	100.0		

hairloss1

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	YES	38	37.6	52.1	52.1
	NO	35	34.7	47.9	100.0
	Total	73	72.3	100.0	
Missing	System	28	27.7		
Total		101	100.0		

losssexdrive1

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	YES	62	61.4	72.9	72.9
	NO	23	22.8	27.1	100.0
	Total	85	84.2	100.0	
Missing	System	16	15.8		
Total		101	100.0		

TOTAL RESPONSES = (81 + 83 + 86 +87 + 84 + 85 + 87 + 86 + 80 + 91 + 80 + 79 + 75 + 80 + 77 + 85 + 73 + 79 + 89 + 73 + 73 + 85) = 1882

YES RESPONSES = (49 + 48 + 67 + 71 + 59 + 57 + 70 + 77 + 76 + 47 + 73 + 53 + 50 + 40 + 52 + 43 + 58 + 41 + 52 + 73 + 42 + 73 + 42 + 38 + 62) = 1298

PERCENTAGE YES = 68.97%

M E M O R A N D U M

TO: Robert Barham, Ph.D.
Assistant Chief, Stationary Source Division
Air Resources Board

FROM: George Alexeeff, Ph.D.
Deputy Director for Scientific Affairs

DATE: September 13, 2007

SUBJECT: REVIEW OF TOXICITY INFORMATION ON D5

We are forwarding our review of available information on the toxicity and persistence of decamethylcyclopentasiloxane (D5), a proposed alternative for perchloroethylene in dry cleaning. The review was conducted to provide ARB with information on which to base a determination of whether D5 could be considered a non-toxic alternative to perchloroethylene for dry cleaning under AB 998 (Lowenthal, Chapter 821, Statutes of 2003), pursuant to contract number 05-414. In response to your request to evaluate available information on the toxicity of D5 under the statutory mandate, OEHHA staff have reviewed information submitted by the Silicones Environmental Health and Safety Council (SEHSC), including studies evaluating acute and subchronic toxicity, neuroendocrine activity, estrogenicity, genotoxicity, chronic toxicity and carcinogenicity and related mode of action studies, and pharmacokinetics. In addition, we evaluated an SEHSC white paper summarizing the toxicity of D5, and an exposure assessment conducted by Environ Corporation for SEHSC. We also searched the open literature for additional information, including government documents from other countries, and identified additional information on human exposure, environmental persistence and accumulation in biota. As requested by ARB, we focused on evaluating the applicability of the SEHSC-proposed mechanism of action of tumor formation in rodents to human health risk assessment. Our review of the available information is attached.

In the process of reviewing the information, we met three times with the SEHSC representatives, including their toxicologists. We sought outside expertise from the University of California, Davis, regarding the merits of the proposed mode of action of D5 induced tumors in rodents. We also spoke with U.S.EPA scientists, who reviewed materials on D5 toxicity under

their own regulatory program, particularly with regard to the proposed mode of action of D5 induced rodent tumors.

OEHHA has several concerns about the toxicity and persistence of D5. In evaluating the information on the mode of action of D5 tumorigenesis in rodents, we used similar criteria to those laid out by U.S. EPA for determining whether a mode of carcinogenic action in animals is applicable to humans. The materials presented by SEHSC argue that D5 mode of action involves a pathway not applicable to humans – in acting as a dopamine agonist in the brain, the hormonal milieu of the rodent becomes estrogen-dominated, thus stimulating uterine tumors. Although the argument that the uterine tumors in rats due to D5 exposure occur by a mechanism not applicable to humans appears plausible, OEHHA has determined that the data presently in hand are insufficient to conclude definitively that this is the MOA for tumorigenesis and that the information is irrelevant to human risk assessment. In making this determination, OEHHA is consistent with the judgment of U.S. EPA's scientists, who reported a similar conclusion to SEHSC in December 2006. Furthermore, additional non-carcinogenic effects, associated with altered dopamine and prolactin levels, have been reported in humans and animals. Systems affected include the nervous system, fat tissue, the liver (bile formation), and the immune system. Thus, more widespread exposure to D5, a dopamine agonist, has potential public health impacts. Further, D5 appears to have significant bioaccumulative potential, has been measured in several aquatic species at ppm concentrations, and appears to have a long half-life in humans. Thus, D5 persistence in the environment and in animal and human tissues is a concern. OEHHA cannot conclude at this time that D5 is non-toxic.

We hope the review of this material is useful in your implementation of AB 998. Should you have any questions or concerns, please call me at (916) 322-2067, or Dr. Melanie Marty at (510) 622-3150.

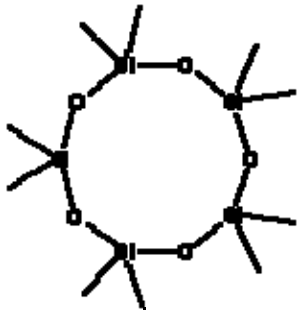
Attachment

cc: Robert Krieger, ARB
Melanie A. Marty, Ph.D.
Andrew Salmon, Ph.D.

D5 Data Review
September 13, 2007

TOXICITY DATA REVIEW

Decamethylcyclopentasiloxane (D5)



CAS Registry Number: 541-02-6

Summary

Decamethylcyclopentasiloxane (D5) is a low molecular weight cyclic siloxane used for industrial (silicone fluids and elastomers) and consumer product (cosmetics and toiletries) applications. It is also being developed as an alternative to perchloroethylene in dry cleaning and is currently in use in California under the Green Earth trademark. Under the Non-toxic Dry Cleaning Program established by AB 998 (Lowenthal, Chapter 821, Statutes of 2003), dry cleaners who currently use perchloroethylene are eligible to apply for $10,000 demonstration grants to assist them in switching to non-toxic and non-smog forming cleaning technologies. This evaluation discusses whether there is a scientific basis for considering D5 to be non-toxic. Concerns for possible toxic effects of D5 were raised following the discovery that D5 exposure causes uterine cancer in female rats. At the request of the California Air Resources Board, staff of the Office of Environmental Health Hazard Assessment (OEHHA) evaluated information on D5 toxicity, including a proposed mode of action for the formation of rodent tumors, and the relevance of this mechanism to cancer in humans. This review includes data in the open literature or made available by the Silicones Environmental Health and Safety Council (SEHSC) through June 2007.

D5 is an oily liquid that boils at 210°C. It has low solubility in water and high lipid solubility; the logarithm of its octanol water partition coefficient (log K_{ow}) is between 5 and 6 (Table 1). Thus it has a 100,000 times greater preference for lipids than water. Based on this log K_{ow}, OEHHA concludes that D5 could accumulate in the environment and may bioconcentrate. Estimations of the bioconcentration factor (BCF) for D5 range from 2000 (HSDB, 2007) to 46,774 (Environment Canada, 2007). (For comparison, the range of BCF for perchloroethylene, for which D5 is a proposed substitute, is 26-76 (HSDB, 2007).) A chemical with a BCF of > 1000 is considered by U.S. EPA (1998) to be a potentially persistent pollutant, while a BCF > 5000 is characteristic of highly persistent substances such as DDT and polychlorinated biphenyls. D5 has been detected in human adipose tissue and breast milk, and in fish. Animal experiments have also shown that siloxane residues, including unchanged D5, are persistent in a

variety of tissues for extended periods after exposure. Based on the log K_{ow}, BCF, detection in biota and experimental data showing residues, OEHHA considers D5 to be a persistent substance.

Table 1. Chemical and physical properties (HSDB[a], 2007; Environment Canada[b], 2007)

Description	oily liquid
Molecular formula	$C_{10}H_{30}O_5Si_5$
Molecular weight	370.8 daltons
Boiling point	210°C
Melting point	-38°C
Density/Specific gravity	0.9593 at 20°C/4°C
Vapor pressure	0.2 torr (mm Hg) at 25°C
Solubility	0.017^a – 0.05^b mg/L at 25°C
Log Kow	5.2^a – 5.71^b
Log Koc (organic carbon/water partition coefficient)	5.16
Henry's law constant	0.306 atm-m^3/mole at 25°C
Hydroxyl radical reaction rate constant	1.55 x 10^{-12} cm^3/molec-sec at 25°C
Conversion factor	1 ppm = 15.1 mg/m^3

Inhalation of 160 ppm D5 for 12 or 24 months by female rats led to uterine endometrial adenocarcinomas (Dow Corning, 2005a). The structural analog octamethylcyclotetrasiloxane (D4) is estrogenic in rats, but D5 is not positive in the assays conducted to date for estrogenicity. The SEHSC has proposed that the mode of action for rodent carcinogenicity, involving action as a dopamine agonist causing suppression of prolactin (and thus of progesterone) that leads to tumor formation in the female rat, is not relevant to humans. Although the proposed mode of action is plausible, additional study is necessary to make a definitive conclusion that this is the mode of action for tumorigenesis and that it has no relevance to human risk assessment. OEHHA also has concerns about other health implications of the effects of D5, including impacts on the various human physiological systems that are regulated or influenced by prolactin (e.g., reproductive system, adipose tissue, bile production, immune system), and the potential for effects on the nervous system subsequent to disruption of normal dopaminergic neurotransmission (e.g., possible psychological imbalance). Based on these health concerns, and the evident potential for bioaccumulation, OEHHA is not prepared to recommend that D5 be considered non-toxic.

D5 Environmental Effects

Environmental Fate and Transport

D5 exhibits high vapor pressure, Henry's law constant, log Kow (octanol:water partition coefficient) and log Koc (organic carbon:water partition coefficient) values. These data indicate that D5 will partition into air, soil and sediments. Fugacity modeling indicates that if this substance is released equally to the three major environmental compartments (air, water, and soil), it will partition into all compartments including air, water, soil, and sediments, with the

latter two compartments being predominant (Environment Canada, 2007). D5 released only to air will generally remain in air, with little partitioning to other compartments. D5 released to water will adsorb to suspended solids and sediment because of its high log Koc value, which will reduce the potential for volatilization. Therefore, D5 can be expected to remain mainly in water and primarily partition into sediments. D5 released to soil is expected to remain mostly in soil, since it will adsorb to and be relatively immobile in soil, thus reducing its potential for volatilization.

Environmental Occurrences

Air

US EPA (1992) reported detecting D5 in 29 indoor air samples (0.3-12.4 µg/m3) from office buildings located in 7 cities and in three outdoor air samples (0.21-0.9 µg/m3).

Indoor air measurements of siloxanes were performed in children's bedrooms in 400 Swedish households as part of a siloxanes screening study performed for the Swedish Environmental Protection Agency by the IVL Swedish Environmental Research Institute (IVL SERI). D5 was detected in 250 homes at concentrations of 0.5 - 79.4 µg/m^3, with a mean concentration of 9.7 µg/m^3 (personal communication, Norbert Schmidbauer, Norwegian Institute for Air Research, 2005, as cited in Kaj et al. 2005).

An environmental monitoring study of volatile methylated siloxanes in the Nordic countries was sponsored by the Council of Nordic Ministers (Norden, 2005). This study found D5 in air, water, sediment, sewage sludge and biota samples, and D5 was noted to be the dominating siloxane in most samples. The average air concentration of siloxanes [D4 (Octamethylcyclotetrasiloxane), D5 and D6 (dodecamethylcyclohexasiloxane)] was in the\range of 0.01 - 5 µg/m^3 in urban areas, landfills, and other point sources. Samples taken inside sewage treatment plants (STPs) were significantly higher (up to approximately 20 µg/m^3).

Water

D5 has been detected in drinking water concentrates obtained from water supplies in new Orleans, LA and Cincinnati, OH (Lucas, 1984).

In wastewater treatment plants in Canada, levels of organosiloxanes, principally D4 and D5, have been reported to be up to 710 µg/L and up to 13 µg/L in the influent and effluent, respectively (Maguire, 2001; as cited in Hydromantis et al., 2005).

D5 was not detected in any of six water samples analyzed in the Swedish siloxane screening study (Kaj *et al*., 2005). D5 was also not detected in background or urban water in the Nordic screening study (Norden, 2005), but was detected in substantial amounts in sewage treatment plant (STP) intakes (approximate concentrations 1 – 25 µg/L), and in sewage treatment plant outfalls (approximately < 1 – 5 µg/L) and landfill leachates (approximately 0 - 5 µg/L).

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Sediments

The Swedish siloxane screening study (Kaj et al. 2005) did not find D5 in analyzed lake or marine sediments. However, D5 was the predominant cyclosiloxane detected in sediments in the Nordic screening study (Norden, 2005). Concentrations ranged from <5 - 130 ng/g dry weight (dw), with one Danish sample having a concentration of 2,000 ng/g dw.

Aquatic Organisms

The Swedish siloxane screening study (Kaj *et al*., 2005) did not find D5 in analyzed fish muscle. However, in the Rhine River in Germany, D5 has been detected in fish up to 1 mg/kg (1 ppm) and in eels up to 2.6 mg/kg (Mait, 2005).

D5 was also detected in aquatic organisms in the Nordic siloxane screening study (Norden, 2005). D5 was the predominant cyclosiloxane found in both fish livers and marine mammals. D5 concentrations in freshwater and marine fish from urban areas and near STPs ranged from < 5 - 84 ng/g wet weight (ww). One sample of cod liver (9 pooled livers) collected near a Norwegian city center had a D5 concentration of 2,200 ng/g ww. D5 was also detected in the blubber of seals and pilot whales at concentrations ranging from <5 - 24 ng/g ww. Environment Canada (2007) concluded that since concentrations of D5 in Nordic waters were <5 µg/L, except for STP influents, the detection of D5 in biota indicated that D5 has the potential to bioaccumulate.

<u>Environmental Persistence</u>

D5 appears to be relatively persistent in air, water, soil and sediments. The fugacity modeling done by Environment Canada (2007) indicates that D5 will partition to air, where it will be oxidized by photochemically produced hydroxyl radicals. The half-life for D5 in this reaction is 6.9 days (Atkinson, 1989), indicating that this substance is persistent in air (half-life > 2 days). This reaction is expected to be the most important fate process in the atmosphere for D5, as it is not expected to degrade via direct photolysis or react appreciably with other photo oxidative species in the atmosphere (Atkinson, 1991).

Environment Canada (2007) noted that no D5 empirical persistence data for water, sediment and soil were available, and therefore proceeded to make an environmental persistence evaluation based on comparisons with other cyclic siloxanes and persistence modeling data. D5 is structurally similar to D3 (hexamethylcyclotrisiloxane) and D4 (octamethylcyclotetrasiloxane); Environment Canada considered it to be likely that D5 would have a biodegradation potential similar to that of D3 and D4. D3 did not undergo biodegradation over 28 days in a ready-biodegradation test (SEHSC 2005b), suggesting that it is persistent in water, sediment and soil. Additionally, D4 did not biodegrade in an aerobic water/sediment system (Silicones Health Council 1991, as cited in Environment Canada, 2007). Environment Canada (2007) modeled D5 biopersistence using BIOWIN v4.02 and found that the probability of biodegradation of D5 occurring in water or soils was essentially zero.

Based on the above data, Environment Canada (2007) categorized D5 as persistent in air based on empirical data, and also likely to be persistent in soil, sediment and water based on the weight-of-evidence from the behavior of similar chemicals and modeled data. Environment Canada (2007) concluded that D5 meets the persistence criteria for soils, sediments and water (half-lives in soil and water > 182 days; in sediments > 365 days) as set out in the *Persistence and Bioaccumulation Regulations* (Government of Canada, 2000).

Potential for Bioaccumulation

Empirical bioaccumulation data is not available for D5. Bioaccumulation can be estimated from the octanol:water partition coefficient K_{ow}. The higher the Kow (or its logarithm), the more likely a chemical will bioaccumulate in fatty tissue. The empirical and modeled log K_{ow} values for D5 (Table 1) suggest that this substance has the potential to bioaccumulate in the environment (log K_{ow} > 5). D5 has been reported to have the potential to be taken up by fish in a laboratory bioconcentration study where particles were not present to which D5 could bind and where D5 was not allowed to evaporate (SEHSC 2004). The Nordic siloxane environmental screening data also indicates that D5 has the potential to accumulate in fish livers and marine mammals (Norden, 2005). Environment Canada (2007) used D4 exposure data in fathead minnows (*Pimephales promelas*) (Annelin and Frye, 1989) to generate an experimental bioconcentration (BCF) factor for D4 of 12,400 L/kg.

Environment Canada (2007) also generated modeled fish BCF and bioaccumulation factor (BAF) data for D5. A BAF of 34,670 L/kg was derived using a Gobas BAF T2MTL model (Arnot and Gobas, 2003) and BCF values of 1995, 7244 and 46,774 L/kg were derived using BCFWIN v2.15, OASIS 2005 and Gobas BCF T2MTL (Arnot and Gobas, 2003) models, respectively. Environment Canada noted that the BCFWIN model may underestimate the BCF value for cyclosiloxanes, since the BCFWIN modeled D4 BCF (1,698 L/kg) was much lower than an experimentally derived D4 BCF (12,400 L/kg). These modeled bioaccumulation values do not take into account any potential metabolism of D5 to other compounds. However, an experimental BCF study with D4 (Fackler *et al*., 1995) suggests that metabolism of D4 in fish is probably not significant, and therefore D5 may also not be significantly metabolized in fish. Environment Canada (2007) found the weight of evidence indicated that D5 meets the bioaccumulation criterion (BCF, BAF > 5,000) as set out in the *Persistence and Bioaccumulation Regulations* (Government of Canada 2000).

Environmental Toxicity

D5 environmental toxicity study data are not available. However, D4 is both acutely and chronically toxic to fish and daphnia (crustaceans) (Hobson *et al*., 1997). Acute No Observable Effect Levels (NOELs) for fish and daphnia were 4.4 and 15 µg/L, respectively. A chronic NOEL for daphnia was 7.9 µg/L. Based on their similarity in structure and physical-chemical properties, the modes of action and toxicities to aquatic organisms of D5 would be expected to resemble those of D4. Environment Canada (2007) developed modeled data (ECOSAR v.0.99h) suggesting that D5 would be capable of causing harm to aquatic organisms at relatively low concentrations. Concentrations causing a 50% effect (EC50) in green algae and daphnia were

96 µg/L (96 hour exposure) and 32 µg/L (16 day exposure), respectively. Environment Canada (2007) noted that these values were close to or below the D5 solubility limit, and concluded that D5 has the potential to cause ecological harm in Canada.

D5 Human Exposure

In addition to detection in the breathing space of people working with D5, this compound has been detected in the fat of members of the general population, in human breast milk and in women with breast implants.

A national survey of human adipose tissue in 1982 found D5 in 28 of 46 people sampled (US EPA, 1987). Kaj *et al*. (2005) reported levels of D5 as high as 4.5 µg/L in samples of human breast milk in Sweden. Neither D5 nor any other siloxane was measured for the recent Second National Report on Human Exposure to Environmental Chemicals released in January 2003 by the National Center for Environmental Health. D5 and its structural analog D4, which has one less dimethylsiloxane group than D5, occur together in breast implants and are often investigated together because of their structural similarities. However, D4 has some activity mimicking the female hormone estrogen, so any contamination of D5 by D4 is cause for concern.

Flassbeck *et al*. (2001) analyzed plasma and blood of women exposed to silicone gel-filled implants (n = 14) and of control subjects (n = 2) for low molecular weight silicones. D5 and its structural analogs D3, D4, and D6 were not detectable in control plasma or blood. The numbers of patient samples were limited, but the data showed an increase in the amount of low molecular weight cyclic siloxanes in the bodies of women with silicone implants. Many years after the removal of ruptured silicone implants, siloxanes were still in blood samples from several women. D3 varied from 6 to 12 ng/mL in plasma and from 20 to 28 ng/mL in blood. The range of D4 was 14-50 ng/mL in plasma and 79-92 ng/mL in blood. D5 (28 ng/mL) and D6 (17 ng/mL) were detected in the plasma of one patient. Possible shortcomings in the data, which were noted by Smith (2002), included only two controls, possible inadvertent contamination, and some values near or at the limit of detection.

Flassbeck *et al*. (2003) used a sophisticated combination of mass spectrometry and gas chromatography to analyze siloxanes (D4, D5, D6) in prosthesis capsule, muscle, and fat of 3 women who had silicone gel-filled breast implants and in breast tissue of 3 control women. In all tissues of women with breast implants, D4, D5 and D6 were identified. Depending on the siloxane species and type of tissue analyzed, siloxane levels in the range of 10-1,400 ng/g were detected. The highest level of D5 was 637±100 ng/g (637 ppb) in the fat tissue of one woman. This investigation shows that siloxanes leak from prostheses and accumulate in surrounding tissues.

In addition to its presence in cosmetics and toiletries, D5 is emitted from some furnishings, such as urethane cushions (Schaeffer *et al*. (1996). Otson and Fellin (1992) [cited in HSDB (2007)] report that the average value for 25 different locations in the United States was 0.206 ppb in air. No site exceeded 1 ppb.

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Environ (2006) reported several measurements of occupational exposure to D5 in workplace air. Mean values included 0.0587 ppm for silicone workers, 2.21 ppm for antiperspirant products workers, 1.06 ppm for skin care products workers, 0.002 ppm for hair care product workers, and 0.143 ppm for dry cleaners.

D5 Health Effects Information

OEHHA staff reviewed published literature on D5 toxicity, and information submitted by the Silicones Environmental Health and Safety Council (SEHSC). These materials included studies evaluating acute and subchronic toxicity, neuroendocrine activity, estrogenicity, genotoxicity, chronic toxicity and carcinogenicity and related mode of action studies, and pharmacokinetics. In addition, we evaluated an SEHSC white paper summarizing the toxicity of D5.

Metabolism/pharmacokinetics/pharmacodynamics

Varaprath *et al*. (2003) reported that Fischer 344 rats metabolize D5 to at least ten metabolites identifiable by GC-MS analysis. The metabolites of D5 were: $(CH_3)_2Si(OH)_2$, $CH_3Si(OH)_3$, $CH_3Si(OH)_2OSi(OH)_3$, $CH_3Si(OH)_2OSi(OH)_2CH_3$, $CH_3Si(OH)_2OSi(OH)(CH_3)_2$, $(CH_3)_2Si(OH)OSi(OH)(CH_3)_2$, $(CH_3)_2Si(OH)OSi(CH_3)_2OSi(OH)(CH_3)_2$, nonamethyl-cyclopentasiloxanol, and hydroxymethylnonamethylcyclopentasiloxane. No parent D5 was detected in the urine. Thus metabolism of D5 in the rat is extensive, and it is likely that the distribution, excretion, and toxic effects reported after D5 exposure are influenced by the properties of its metabolites.

McKim *et al*. (1999) investigated the effects of exposure to 160 ppm D5 for 28 days on the expression and activity of selected rat hepatic phase I and phase II enzymes. Exposure to D5 resulted in a 1.4-fold increased activity of hepatic NADPH-cytochrome c reductase, a 1.8-fold increase in 7-ethoxyresorufin O-deethylase (EROD) activity (CYP1A1 and CYP1B1 activity), a 4.2-fold increase in both 7-pentoxyresorufin O-dependentylase (PROD) activity and immunoreactive CYP2B1/2 protein (3.3-fold), a 2.4-fold increase in testosterone 6-beta-hydroxylase activity and in CYP3A1/2 immunoreactive protein, a small increase in 11- and 12-hydroxylation of lauric acid (CYP4A activity), no change in immunoreactive CYP4A levels, and increases of 1.7- and 1.4-fold, respectively, in liver microsomal epoxide hydrolase activity and immunoreactive protein. The authors suggested that the profile for enzyme induction following inhalation exposure of female Fischer-344 rats to D5 vapors is similar to that reported for phenobarbital, and therefore described D5 as a weak "phenobarbital-like" inducer. D5 also induced some of these activities in male and female Sprague-Dawley rats administered 1, 5, 20, or 100 mg/kg D5 in corn oil daily by gavage for 4 days (Zhang *et al*., 2000). Thus D5 exposure alters the activity of several liver enzymes involved in metabolism of other foreign compounds (xenobiotics) and of endogenous chemicals that have hormone activity (see also Table 3 below).

In experiments in CD-1 female mice, a mixture of cyclosiloxanes (i.e., breast implant distillate), which included D5, was shown after a single subcutaneous injection of 250 mg to be widely distributed in the ten organs examined and to persist for at least a year, with highest levels in mesenteric lymph nodes, abdominal fat, ovaries and uterus (Kala *et al*., 1998). In

mesenteric lymph nodes, D5 levels at one year (~5.4 ppm) were similar to those 9 weeks after injection. In the ovaries and uterus, D5 levels at one year were half or less of those at 9 weeks after injection. D5 was selectively retained in tissues compared to D4. According to these animal experiments, siloxane residues, including unchanged D5, are persistent in a variety of tissues for extended periods after exposure.

The physical properties of D4 and D5 are unusual in combining both moderate volatility and very high lipophilicity (solubility in fats), which necessarily impacts the pharmacokinetic properties. D4 and D5 are cleared from the circulation by exhalation and methyl-group oxidation. High lipophilicity, i.e., fat:blood partition coefficients of 1000-2000, usually leads to bioaccumulation. Andersen and colleagues have developed a multi-dose route (including inhalation), multi-species physiologically based pharmacokinetic (PBPK) model for D4 and integrated physical chemical, metabolic and partitioning information to provide an understanding of the expected time course of D4 concentrations in tissues, including fat, during various scenarios (Andersen *et al*., 2001; Sarangapani *et al*., 2002).

PBPK models for D5 dermal absorption and inhalation have been under development for several years but have not been fully published (Reddy *et al*., 2005a, b, submitted). Reddy *et al*. (2004) used extensive data on D5 distribution in the rat following inhalation to develop a PBPK model, similar to that for D4. The rat D5 model incorporated deep compartments in lung and liver and had two fat compartments and an unusual combination of low blood:air and high fat:blood partitioning. For D5 in humans, a PBPK model was based on the rat model but was simplified since less human data are available. In spite of this, a similar model structure described D5 pharmacokinetics in both rats and humans. An important component of both models was a sequestered pool of D5, presumably in lipoproteins. This bound D5 was released from the liver, distributed by the blood, and "cleared" into fat. D5 metabolism is essentially flow-limited, due to its low blood:air partition coefficient (0.2 in rats and 0.5 in humans in vivo). However, the primary mechanism of D5 elimination was exhalation.

Andersen *et al*. (2005) simplified the model(s) for D4 and D5 to evaluate the time course of their concentrations in plasma and fat during periodic daily exposures. The model(s) was calibrated with blood and tissue levels in rats due to 6 hr/day exposures for 1 day, 14 days, and 6 months. The model had a central compartment with first-order metabolic clearance and either one or two fat compartments with variable limitations for uptake by diffusion. At steady state, D5 levels were equal to those expected for a continuous exposure multiplied by the ratio of the daily exposure duration/24 hours. As stated by the authors, the approach to steady state and persistence after cessation for all exposure scenarios depended on the characteristic clearance by diffusion from the deeper fat compartment.

The authors of these PBPK modeling studies (Reddy *et al*., 2005a; 2005b; Andersen *et al*., 2005) stated that, despite high fat:blood partitioning, they did not expect D5 to accumulate due to rapid clearance by exhalation and metabolism. However, this expectation is not consistent with the reported occurrence of measurable levels of siloxanes (including D5 and metabolites) in plasma and tissues of women who had received implanted silicone prostheses, including those where the prostheses had been later removed (Flassbeck *et al.,* 2001; 2003). It

is also difficult to reconcile with reportedly substantial levels of D5 in breast milk (Kaj et al., 2005). The percentage of inhaled D5 which is retained in fat may be small under the conditions examined by Reddy *et al.* and Andersen *et al*. (which may actually imply that the model in question is not suited to examining the question of long-term persistence). However, that portion retained in fat seems to be persistent, both in animal studies (Kala *et al*., 1998), and in humans in the case of D5 leaking from silicone breast implants. Thus, OEHHA remains concerned about the empirical data indicating a long half-life in humans and animals, and the chronic effects of this persistent compound.

Hormonal effects

Hormonal effects are of interest and concern because of the finding of malignant tumors (adenocarcinomas) due to chronic D5 exposure in a hormone sensitive organ, the rat uterus (Dow Corning, 2005a). A similar exposure study of D4 in rats found benign uterine tumors (adenomas) at the highest concentration tested (700 ppm) (Plotzke *et al*., 2005). D4, a structural analog of D5, has one less dimethylsiloxane group, and has been shown to have direct (estrogenic) hormonal effects on the uterus. Such direct estrogenic effects would be relevant to humans. The indirect hormonal effect on the rat uterus by D5 via prolactin would not be relevant to humans, because prolactin affect the corpus luteum in rats, but not in humans..

Hayden and Barlow (1972) reported that several siloxanes are estrogenic in animals and that the cyclic compounds are more active than the linear compounds. Hayden and Barlow (1972) did not examine D5 but did find weak (not statistically significant) estrogenic activity in its structural analog D4 in the ovariectomized (to reduce endogenous estrogen), immature female rat uterus following oral administration. Some cyclic siloxanes with phenyl groups (rather than methyl groups as in D5) had stronger estrogenic activity in the assay.

In mice dosed orally for 3 days He *et al*. (2003) reported that D4 at 250, 500 and 1000 mg/kg body weight was estrogenic using the uterine wet weight test in ovariectomized animals but that D5 was not estrogenic using the assay.

In a recent peer-reviewed paper, Quinn *et al*. (2007) used receptor-binding experiments and a luciferase reporter gene assay to determine if D5 was able to bind and activate either the estrogen receptors (ERs) or the progesterone receptors (PRs). They used the rat uterotrophic assay (RUA) for estrogenic activity and the Hershberger assay for androgenic activity as in vivo assays. In the ER-binding studies, D5 did not bind to either ER- α or ER- ß. D5 was also negative in the estrogen reporter gene assay and was not a ligand for the progesterone receptors. Both the RUA and Hershberger assays were conducted using whole-body inhalation of 160 ppm D5 for 16 h/day for 3 and 10 days, respectively. D5 was negative in both rat strains (Sprague-Dawley and Fischer-344), indicating that D5 does not possess estrogenic activity. D5 also did not possess any significant antiestrogenic activity. D5 was negative in the Hershberger assay indicating that it did not have any significant androgenic activity. The structural analog D4 had a low affinity for ER- α *in vitro* and was weakly estrogenic in vivo. D4 had no androgenic activity. As noted later in the section on developmental toxicity, Siddiqui *et al.* (2007) observed

a significant increase in male pup anogenital distance. This may indicate an anti-estrogenic or androgenic effect.

Neuroendocrine activity

Dopamine acts both as a hormone in regulating prolactin release from the pituitary gland and as a transmitter of nerve impulses. Thus it can affect both the endocrine and nervous systems. Jean *et al*. (2005) evaluated the potential for D5 (and D4) to modulate pituitary prolactin secretion as dopamine D2-receptor agonists. In an *in vitro* cell line, derived from a rat pituitary tumor (MMQ, American Type Culture Collection #: CRL-10609), 10 μM (3.7 μg/mL), D5 decreased maitotoxin-induced prolactin release by 55% without affecting cell viability. An *in vivo* model was used to assess serum prolactin levels in reserpine-treated female Fischer 344 rats following 6-h vapor inhalation exposure to 160 ppm D5. In this model, serum prolactin levels were decreased 50% by 160 ppm D5 relative to the reserpine control. Pretreatment with sulpiride, an antagonist of the dopamine receptor, blocked the effect of D5 suggesting that D5 is a dopamine D2-receptor agonist on pituitary cells (Table 2). However, as discussed further below (D5 Cancer risk evaluation, section 2), some desirable controls were missing and no attempt to determine a dose-response relationship was reported.

Table 2. Effect of D5 on dopamine receptor regulation of serum prolactin (Dow Corning, 2005b)

	Serum prolactin (ng/ml)	
	Experiment 1	Experiment 2
Untreated control Fischer 344 rats	Not reported	Not reported
Ovariectomized control rats	11 ± 6 (10)	5 ± 3 (9)
Reserpine (2 mg/kg) controls	72 ± 36 (9)	58 ± 34 (7)
Reserpine + 160 ppm D5 exposure	37 ± 20 (7)	38 ± 37 (8)
Reserpine + 160 ppm D5 + 6 mg/kg sulpiride	Not done	395 ± 200 (8)

* mean ± SD (number of rats)

Acute and subchronic toxicity

There are few published reports evaluating D5 toxicity. OEHHA staff obtained a copy of the "Siloxane Product Stewardship Program" 2002 Annual Progress Report of Dow Corning Corporation to the U.S. EPA. Dow Corning tested D5 for various effects, including organ effects and reproductive effects, by the inhalation, oral, and dermal routes of exposure for up to 13 weeks, and for potential genetic activity. The acute inhalation LC_{50} in rats was calculated to be 8.67 mg/liter (8670 mg/m^3), *i.e*., relatively nontoxic. The results of other tests are presented in publications reviewed in this report.

Burns-Naas *et al*. (1998a) assessed potential toxic consequences and immune system modulation of inhalation exposure to D5 in male and female Fischer 344 rats exposed by whole body inhalation to 0, 10, 25, 75, or 160 ppm D5 6 h/day, 7 days/week for 28 days. D5 inhalation exposure did not alter humoral immunity (as measured by an anti-sRBC (sheep red blood cell)

antibody-forming cell response) and caused only minor, transient changes in hematological, serum chemistry, and organ weight values. Histopathological changes were confined to the respiratory tract and appeared to be reversible. The no-observed-adverse-effect-level (NOAEL) for systemic toxicity, based primarily on the liver weight changes, was 75 ppm for this 28 day study.

Burns-Naas *et al*. (1998b) evaluated the subchronic toxicity of D5 using a 3-month, nose-only inhalation exposure. Control and high dose groups were also allowed a 4-week recovery period to observe reversibility, persistence, or delayed occurrence of any potential adverse effects. Male and female Fischer 344 rats were exposed for 6 h/day, 5 days/week for 3 months to target concentrations of 0, 26, 46, 86, and 224 ppm D5. There were several minor changes observed in clinical biochemistry parameters; the most notable was an increase in gamma glutamyl transferase (gamma-GT) in both sexes at the high dose (Table 3). In females, this effect was dose-related between 46 and 224 ppm and did not return to control levels upon cessation of exposure. Additionally, there was a decrease in serum lactate dehydrogenase (LDH) observed in females at 86 and 224 ppm, which did not resolve during recovery. There was an increase in absolute and/or relative liver weight in rats of both sexes. Taken together, these data suggest that the female rat is more sensitive to the actions of D5 on the liver. Exposure-related increases in absolute and relative lung weights were observed in both sexes at terminal necropsy. This observation was not noted in males in the recovery phase, but was still present in females. Histopathology indicated that the lung is a target organ following D5 inhalation, with an increase in focal macrophage accumulation and interstitial inflammation in the lungs of male and female rats exposed to 224 ppm D5. This observation did not appear to resolve at the end of a 1-month period of non-exposure. The incidence of these changes was also slightly increased in rats of both sexes exposed to 86 ppm D5. The authors however characterized the changes in the lung following nose-only D5 vapor inhalation as minimal. The authors report no histopathological findings noted in the livers, despite the observed changes in organ weight and serum chemistry parameters shown in Table 3.

Table 3. Effects of inhalation of D5 for 3 months in female rats

D5 level	*Liver wt (g)*	*Serum triglycerides (mg/dL)*	*Serum γ-glutamyl tranferase (U/L)*	*Serum LDH (U/L)*
0 ppm	3.71±0.46[#]	42.88±7.88	0.70±0.15	229.2 ± 29.4
26 ppm	3.94±0.26	39.38±4.38	1.10±0.34	206.4 ± 83.4
46 ppm	4.26±0.60**	33.25±3.5**	1.49±0.37**	171.6 ± 84.6
86 ppm	4.02±0.50	31.50±3.5**	1.56±0.53**	147.0 ± 33.6*
224 ppm	4.31±0.59**	35.00±3.5	3.35±0.51**	97.8 ± 22.8**
Recovery	3.74±0.29	35.00±3.5	1.80±0.26**	181.8 ±30.0**

[#] mean ± standard deviation ($n \geq 10$); * $p<0.05$; ** $p<0.01$ compared to controls

Lieberman *et al*. (1999a) injected female CD-1 mice intraperitoneally with different doses (3.5-35 g/kg body weight) of breast implant distillate containing D3, D4, D5, and D6. The distillate was lethal at high doses and all the mice injected with 35 g/kg died within 5-8 days. The median lethal dose (LD_{50}) for distillate was approximately 28 g/kg. The mice developed inflammatory lesions of the lung and liver as well as liver cell necrosis with elevated serum

levels of alanine aminotransferase, aspartate aminotransferase, and lactic acid dehydrogenase. Administration of D4 alone produced lethality with an LD_{50} of 6-7 g/kg. D4-treated mice exhibited pulmonary and hepatic lesions and elevated serum enzymes. The authors stated that analysis of LD_{50} data indicated that D4 is about as acutely toxic as carbon tetrachloride or trichloroethylene. The authors measured hydroxyl radical formation in D4-treated mice and found increases of approximately 20-fold in liver and approximately 7-fold in lung on day 4 following injection. They believe that the findings are significant because experiments *in vitro* have demonstrated that cyclosiloxanes can migrate out of breast implants. However, chemicals requiring a dose of greater than 15 g/kg to exert lethality are generally considered to be of low toxicity. Five commenters (Carlton, 1999; Meeks, 1999; Witschi, 1999; Burin, 1999; and Dost, 1999) noted this point and were critical of the author's conclusions. They pointed out (1) the low toxicity classification of the chemicals based on the LD_{50}s reported by Lieberman *et al*., (2) the likelihood that the distillation pretreatment of the chemicals by the investigators altered the chemicals including opening of the cyclosiloxane ring structure, and (3) the lack of mass balance calculation in the study of distribution of the chemical. On the other hand, Lukasiak et al. (1999) were complimentary and pointed out that related chemicals were used to treat intestinal gas in humans. Lieberman *et al*. (1999b) defended their study and said that it was the first time an LD_{50} had been reported for cyclic siloxanes. In addition, they reported effects at doses below the LD_{50}. They state that effects similar to those obtained with the distillate were seen with commercial D4; thus heat treatment of the distillate did not cause the effects.

Developmental/reproductive toxicity

Siddiqui *et al*. (2007) carried out a two-generation reproduction study of D5. Sprague-Dawley rats (30/sex/group) were exposed by whole-body inhalation to 30, 70, or 160 ppm D5 or filtered air for 6 h/day. Exposures for the F0 and F1 generations started at least 70 days prior to mating and lasted through weaning of the pups on postnatal day 21. Female exposures were interrupted from gestation day 21 through postnatal day 4 to allow for parturition and continuous maternal care for the pups. F2 pups were not directly exposed to D5. The authors found no exposure-related mortalities, no clinical signs of toxicity, no effects on body weight or food consumption, and no treatment-related gross findings or organ weight effects at the F0 and F1 necropsies. However, in F0 females the 10% increase in liver weight at 160 ppm was significantly different from controls. The only noteworthy microscopic finding to the authors was minimal alveolar histiocytosis in all exposed groups (Table 4).

Table 4. Alveolar histiocytosis (minimal) in F_0 and F_1 rats

	Control	30 ppm	70 ppm	160 ppm
F_0 males	5/30	5/29	7/30	6/28
F_0 females	0/30	5/29	4/29	10/29*
F_1 males	2/30	4/30	6/30	7/30
F_1 females	3/30	10/30	8/30	13/30*

$p < 0.05$ vs. controls by the Kolmogorov-Smirnov test, one-tailed

No significant changes between D5-treated and control groups were noted in reproductive parameters (specifically number of days between pairing and mating, mating and

fertility indices, gestation length, and parturition), spermatogenic parameters (sperm number, production rate, motility, morphology), ovarian primordial follicle counts, and numbers of corpora lutea in the F_0 and F_1 parental animals. Mean live litter sizes, number of pups born, sex ratios, pup body weights, postnatal pup survival, and the general physical condition of offspring in each generation were not affected. There was a slight, but statistically significant, increase in the mean F_1 male pup anogenital distance (AGD; the distance between the anus and the male genitalia) at the highest concentration (5.5 ± 0.50 mm in the controls versus 6.1 ± 0.77 mm at 160 ppm; the AGD was not measured in F_1 male pups exposed to 30 and 70 ppm D5). The authors did not consider this effect to be related to treatment, but did not explain why they reached this conclusion. Vaginal patency and balanopreputial separation were unchanged compared to controls. The authors suggested a NOAEL of 160 ppm D5 for parental and reproductive toxicity. However, OEHHA considers the statistically significant increase in AGD at 160 ppm an effect of concern, possibly reflecting an anti-estrogenic (female hormone) or androgenic (male hormone) property of D5.

Genotoxicity

Isquith *et al*. (1988) evaluated D5 and 11 other organosilicon compounds for genotoxic potential in vitro. Microbial assays included the Ames test (reverse mutation assay in five *Salmonella typhimurium* his^- tester strains), mitotic gene conversion in *Saccharomyces cerevisiae* strain D4, and DNA repair in *E. coli* pol A +/-. The assays were conducted with and without an S-9 metabolic activation system that contains the soluble fraction of Aroclor 1254-induced rat-liver homogenate. The range of D5 tested in the microbial assays was 0.001 to 5 microliters (1 microgram to 5 mg) D5 per plate. Forward gene mutation, sister-chromatid exchange, DNA alkaline elution, and chromosome aberration potential were evaluated in mouse lymphoma L5178Y tissue culture cells. The tissue culture assays were performed with and without metabolic activation mixture utilizing uninduced mouse-liver S-9. D5 was tested in the range of 0.8 to 25 microliters D5 per milliliter of culture medium (2 to 65 mM). D5 showed no activity in gene mutation. D5 also did not have in vitro clastogenic activity. Although the existing data do not suggest that D5 is genotoxic, no studies evaluating oxidative DNA damage have been reported.

Chronic toxicity/carcinogenicity

A 24 month combined chronic toxicity and carcinogenicity study was conducted in male and female Fischer 344 rats exposed to 0, 10, 40, or 160 ppm D5 6 hr/day, 5 days per week (96 rats/sex/dose). The concentration of 160 ppm is the highest that can be maintained as a vapor. Above 160 ppm some D5 aerosol is formed. Dow Corning's Environment, Health and Safety Office reported preliminary results to the U.S. EPA's Office of Pollution Prevention and Toxics in a letter dated February 4, 2003 (Dow Corning, 2003) and a final report was later released (Dow Corning, 2005a; Crofoot *et al*., 2005). The experiment was conducted with 4 groups (Table 5):

Table 5. Scheme of chronic toxicity and oncogenicity study

Group	*Rats*	*Exposure*	*Recovery*	*Analysis*
A	6/sex/dose	6 months	None	D5 levels in liver, fat, plasma
B	10/sex/dose	12 months	None	Necropsy and organ/tissue analysis
C	20/sex/dose	12 months	12 months	Necropsy and organ/tissue analysis
D	60/sex/dose	24 months	None	Necropsy and organ/tissue analysis

All animals were monitored for mortality, clinical signs, food consumption, and body weights. Laboratory tests included hematology, clinical biochemistry, and urinalysis.

D5 was measured in rats in Group A at necropsy. D5 levels in fat and plasma increased with increasing levels of exposure (Table 6). D5 levels in the fat of females were three to six times higher than in male rats.

Table 6. D5 levels in plasma and fat of Group A animals (µg/g or ppm).

D5 exposure (ppm)	Plasma	Abdominal fat	Perirenal fat	Brown fat
Males				
0	0.122	0.205	0.091	0.177
10	0.189	2.09	2.04	0.970
40	0.471	5.93	9.36	7.42
160	2.20	23.0	54.5	32.0
Females				
0	0.048	0.128	0.081	0.192
10	0.169	7.83	7.26	5.83
40	0.625	27.3	40.2	42.8
160	3.19	115	176	141

Crofoot *et al*. (2005) found no mortality, clinical signs or palpable masses related to D5 exposure. They reported slight increases in female body weights of 0.7 to 9.2% at 40 and 160 ppm after 24 months of exposure and in the recovery group, and in all males exposed to D5 for 24 months (1.4 to 4.3%) but they did not find a dose-response relationship. Increased liver weights in males after 24 months at 160 ppm and females after 6 and 12 months at 10 and 160 ppm showed no dose-response. Crofoot *et al*. (2005) also reported histological changes in the nasal cavity at 160 ppm in both males and females. They considered the changes to be consistent with changes due to the chronic inhalation of a mild irritant.

After both 12 and 24 months of exposure, female rats showed an increase in tumors of the uterine endometrium. No uterine tumors were seen in groups A and B. Results in group C females (12 months exposure plus 12 months recovery in air) were (Table 7):

Table 7. Uterine tumors after 12 months exposure to D5 plus 12 months recovery in air

Tumor	*0 ppm*	*10 ppm*	*40 ppm*	*160 ppm*
Endometrial adenocarcinoma	1	1	0	2
Endometrial adenomatous polyp	0	0	0	1
Total tumors	*1*	*1*	*0*	*3*
Number rats in group	20	20	20	20

In group D, after 24 months of exposure to D5, the results in female rats were (Table 8):

Table 8. Uterine tumors after 24 months exposure to D5

Tumor	*0 ppm*	*10 ppm*	*40 ppm*	*160 ppm*
Endometrial adenocarcinoma	0	1	0	5
Endometrial adenoma	0	1	0	0
Endometrial adenomatous polyps	1	0	1	0
Total tumors	*1*	*2*	*1*	*5*
Number of rats in group	60	60	60	60

The authors note that the progression of hyperplasia (abnormal increase in the number of cells) to adenoma to adenocarcinoma was not observed in the experiments, but some hyperplasia was found in a later analysis of the pathology slides (Environ, 2006). For adenocarcinomas alone, the authors reported a p value for trend < 0.05. The authors found a statistically significant increase in adenocarcinomas alone using the Peto test ($p < 0.05$). OEHHA staff also found a significant increase in adeno-carcinomas in the 160 ppm D5 group using the Fisher exact test (one-sided) ($p = 0.029$).

Interim D5 Reference Exposure Level Determination

In experiments with rats, D5 has shown adverse effects on the liver, the lung, and the uterus. The most sensitive non-cancer effects were seen in the liver in a three month study (Table 3). The No Observed Adverse Effect Level (NOAEL) was 26 ppm and the Lowest Observed Adverse Effect level (LOAEL) was 46 ppm (Burns-Naas et al., 1998b). Dose response effects included increases in liver weight and serum gamma-glutamyl transferase, and decreases in serum triglycerides and lactate dehydrogenase. An interim chronic Reference Exposure Level (cREL) is estimated below based mainly on the liver effects. The cancer effects in the uterus and the noncancer effects on the lung were reported in a lifetime study but were significant only at the highest concentration of 160 ppm. The experiments on hormonal effects which bear on the uterine tumors were only studied at 160 ppm. Because there is still uncertainty about whether the uterine tumors are or are not relevant to humans, it was considered premature to calculate a cancer potency for D5.

Interim D5 inhalation chronic REL estimate

A chronic REL is a level at or below which adverse noncancer health effects would not be expected to occur even in sensitive subpopulations. An interim chronic REL for D5 can be estimated from the spleen and liver changes reported by Burns-Naas *et al*. (1998a).

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Study	Burns-Naas *et al*. (1998a)
Study population	Male and female Fischer 344 rats
Exposure method	Discontinuous whole-body inhalation to 0, 26, 46, 86, and 224 ppm
Critical effects	Spleen and liver changes
LOAEL	46 ppm
NOAEL	26 ppm
Exposure continuity	6 hours/day, 5 days/week
Exposure duration	3 months
Average experimental exposure	4.6 ppm for NOAEL group (26 x 6/24 x 5/7)
Human equivalent concentration	4.6 ppm for NOAEL group
LOAEL uncertainty factor	1
Subchronic uncertainty factor	3 (NOAEL is based on a 3 month study in rats)
Interspecies uncertainty factor	3 (see below)
Intraspecies uncertainty factor	10
Cumulative uncertainty factor	100
Interim Reference Exposure Level	46 ppb; 700 $\mu g/m^3$

The NOAEL from the 3 month (subchronic) study of Burns-Naas *et al*. (1998a) was 26 ppm. The NOAEL was time adjusted to an equivalent continuous exposure of 4.64 ppm. OEHHA's methodology for developing a chronic Reference Exposure Level (REL) entails division of the NOAEL by a series of uncertainty factors (UFs). A subchronic UF of 3 was used since the study lasted only 3 months. An interspecies UF of 3 was used to account for residual susceptibility differences in rats not accounted for by U.S. EPA Human Equivalent Concentration (HEC) approach. Finally, an intraspecies UF of 10 was used to account for variability in susceptibility in the human population). This results in a chronic inhalation REL of 46 ppb (700 $\mu g/m^3$). This value is an estimate based on our approved procedure (OEHHA, 2000), but it has not been reviewed by the state's Scientific Review Panel for Toxic Air Contaminants. Thus, OEHHA considers this to be an interim guidance value.

Margin-of-safety (MOS) calculations were made by Environ for the SEHSC based on a NOAEL of 160 ppm (Environ, 2006). However, there are several statistically significant effects seen at 160 ppm that OEHHA considers adverse including:

- At the end of the two year study a "statistically significant increase of hyaline inclusions in the respiratory/olfactory epithelium was noted in high dose (160 ppm) males and females" when all levels of the nasal cavity were considered. At 40 ppm, females exposed for 24 months and males exposed for 12 months with 12 months recovery showed significantly increased hyaline inclusions.
- In the two year study a statistically significant effect was increased lung foci, presumably sites of macrophage accumulation, in 13% of the females (8/60) at 160 ppm after 24 months (controls = 0%).

- In a two-generation reproduction study of D5 by inhalation, Siddiqui *et al*. (2007) reported increased alveolar histiocytosis (minimal) in the F_0 and F_1 rats (Table 7). The increase was statistically significant in F_0 and F_1 females exposed to 160 ppm D5.
- In newborn rats the external genitalia are undeveloped, but both sexes have a genital tubercle. The AGD is the distance from the anus to the insertion of this tubercle. The AGD is androgen dependent and is about twice as long in males as in females (Swan *et al*., 2005). Siddiqui *et al*. (2007) reported a small, but statistically significant, increase in the mean F_1 male pup anogenital distance (AGD) at 160 ppm (6.1 ± 0.77 mm vs. 5.5 ± 0.50 mm in the controls; the AGD was not measured in the 30 and 70 ppm D5 pups.
- Finally, as discussed above, the proposed mode of action of D5 involves central dopamine agonism. Thus production of tumors at 160 ppm indicates dopamine agonism at this dose level.

These data indicate that selection of 160 ppm as a NOAEL is inappropriate.

D5 cancer risk evaluation

A statistically significant increase in a malignant tumor (uterine adenocarcinoma) due to D5, a chemical that may be bioconcentrated and is a candidate to replace perchloroethylene in dry cleaning, indicates a potential hazard for workers in the dry cleaning industry and perhaps for the general public. Dow Corning has proposed that the tumors in rats are due to a mechanism not applicable to humans (Environ, 2006). Dow Corning postulates that D5 acts as a dopamine agonist, i.e., D5 mimics the effects of dopamine by binding to dopamine receptors in the body and causing effects like dopamine. Dow Corning has done a variety of experiments to test this hypothesis. In the human female the release of luteinizing hormone (LH) from the pituitary gland results in an increase in progesterone which favors maturation of the corpus luteum. In female rats, however, the LH mechanism does not operate; instead, prolactin (PRL) acts as the luteotrophic hormone. In rats, dopamine (or a dopamine agonist such as bromocriptine) binds to dopamine D2 receptors in the pituitary and causes inhibition of pituitary prolactin release. It has been suggested that the lower prolactin levels cause an increased estrogen/progesterone (E/P) ratio, leading to estrogen dominance over progesterone in the rat ovary. Estrogen dominance would then result in endometrial stimulation followed by endometrial hyperplasia and finally uterine endometrial adenomas and adenocarcinomas in the rat. In aged rats experiencing lower levels of dopamine, prolactin is released which leads to progesterone dominance (pseudopregnancy) which does not cause endometrial stimulation. This mode of action would indicate that the uterine adenocarcinomas observed in the rat after D5 exposure would not be relevant to human cancer risk assessment.

This hypothesized mode of action for D5 rat uterine carcinogenicity is plausible, but a substantial amount of uncertainty remains due to contradictions and information gaps in the available data. The main points of concern regarding the proposed mode of action for D5 carcinogenicity are listed below:

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1. The proposed mode of action for D5 carcinogenicity involves an increase in the estrogen/progesterone (E/P) ratio (estrogen dominance). However, no direct data, such as estrogen and progesterone blood, plasma or uterine levels, have been provided to indicate that this action is actually happening.

2. Some experimental design deficiencies are apparent in the studies used to characterize the dopamine agonist activity of D5 (Dow Corning, 2005b):

   First, it is not clear if all the experiments were performed in an animal from which the ovaries had been removed (ovariectomized, OVX). The comparison of prolactin (PRL) levels between intact animals treated with reserpine (a dopamine antagonist) and OVX control animals is inappropriate (the comparison should be to levels in OVX + reserpine animals or in untreated intact control animals).

   Second, the authors in the experiment that uses reserpine interpreted the result of D5 inhibiting the action of reserpine as an effect on the dopamine receptor (DR). There was no analysis of other possible mechanisms than a direct action of D5 on reserpine (e.g., changes in metabolism, or D5 blocking the reserpine effect by other means than at the DR). In summary, these experiments showed only that D5 decreased the action of reserpine but do not provide evidence for a possible MOA.

   Third, the experiments with sulpiride (DR antagonist) also lack the appropriate control groups. If sulpiride were to directly increase PRL, then the D5 effect (lower PRL) would not necessarily demonstrate an interaction with the DR but could simply be an inhibition of sulpiride action by any mechanism (including, but not limited to, an effect at the DR). In summary, this experiment only demonstrated that sulpiride increases PRL and does not demonstrate the interaction of D5 and DR that the author suggests.

3. Studies that have been cited in support of the proposed mode of action for D5 carcinogenicity include studies that compare spontaneous uterine endometrial tumor incidences and E/P ratios in Donyru and F344 rats. The Donryu rats experienced substantially greater E/P ratios, endometrial hyperplasia and spontaneous uterine endometrial tumor incidences compared to the F344 rats (Nagaoka *et al*., 1990, 1994; Ando-Lu *et al*., 1998). These studies have been cited as evidence for the proposed D5 carcinogenicity mode of action; that is, D5 dopamine agonist activity causes a decrease in PRL release, leading to an increased E/P ratio which results in increased endometrial hyperplasia, and thence endometrial tumors. However, the D5-exposed rats in the 2-year carcinogenicity study did not demonstrate increased endometrial hyperplasia (Dow Corning, 2005a). An increase in endometrial hyperplasia would be expected if D5 was causing an increased E/P ratio. The lack of endometrial hyperplasia exposed in the D5-exposed rats calls into question how well the D5 carcinogenicity data fit the Donyru rat estrogen dominance endometrial cancer model. Also, dopamine agonists such as cabergoline which induce uterine tumors in rats also tend to induce endometrial hyperplasia (FDA, 1996).

   Additionally, Environmental Pathology Laboratories, Inc. (EPL) performed a review and comparison of uterine adenomas, adenocarcinomas, and carcinomas from

untreated control animals (107 studies) in the National Toxicology Program (NTP) database at the request of Dow Corning Corporation (EPL, 2003). EPL did not find a substantial amount of endometrial hyperplasia in the untreated control rats, either with or without tumors. EPL also found fewer non-neoplastic changes (cystic endometrial hyperplasia, epithelial hypertrophy) in the uteri of the rats with adenomas or adenocarcinomas after treatment with D5 compared to the NTP study animals. It has been suggested that spontaneous tumors in untreated animals may result from factors such as errors in DNA replication and repair, and accumulation of DNA damage from endogenous generation of reactive oxygen species (Jackson and Loeb, 2001). The lack of rat endometrial hyperplasia seen after D5 treatment, and the similarity of uterine tumor and non-tumor histopathology to that in untreated control animals that develop spontaneous tumors, suggest that D5 may have an adverse effect on the processes that are involved in the generation of spontaneous tumors.

4. Cytochrome P450 CYP1B1 enzyme converts 17β−estradiol to the carcinogenic 4−hydroxyestradiol, which forms adducts with DNA and undergoes redox cycling to generate reactive oxygen species that can damage DNA, protein and lipids (Husbeck and Powis 2002). Cytochrome P450 CYP1B1 mRNA is expressed in rat uterine tissue (Desaulniers *et al*., 2005). D5 has been observed to induce a variety of cytochrome P450 isozymes (McKim *et al*., 1999; Zhang *et al*., 2000), and was present in the uteri of rats exposed to 160 ppm D5 at levels 3-4-fold greater than the levels observed in blood. This suggests the possibility that D5 might induce uterine cytochrome P450 which then could metabolize estrogen to the carcinogenic metabolite 4−hydroxyestradiol.

5. According to the SEHC submission, D5 is a dopamine agonist, and the proposed mode of action for the induction of the rat uterine tumors seen after D5 exposure depends on the indirect effects of dopamine receptor activation. Dopamine agonists such as cabergoline and mesulergine have been observed to have adverse effects on male and female reproductive function in rats (FDA, 1996; Dirami and Cooke, 1998). These effects include inhibition of female fertility (prolactin is essential in rats for maintaining corporea lutea formation and progesterone production, which are necessary for conception), and induction of Leydig cell hyperplasia and adenomas. However, female fertility was unaffected by D5 treatment, and D5 did not induce Leydig cell hyperplasia or adenomas in male rats. It would be anticipated that these effects would occur if D5 was a dopamine agonist.

6. D5 has not been adequately tested for genotoxicity. As described above, D5 has been tested and generally found to not cause gene mutations resulting from bulky DNA adduct formation, or chromosomal damage (Environ, 2006). However, D5 has not been adequately tested for oxidative DNA damage. It has been claimed that the negative results which occurred when D5 was tested for mutagenicity using *E. coli* strain WP2 uvrA indicate that D5 does not cause mutations due to oxidative DNA damage. However, the parent *E. coli* strain WP2 uvrA has been demonstrated to be relatively insensitive to oxidative DNA damage (Blanco *et al*., 1998; Martinez *et al*., 2000). This suggests the need for further testing to determine if D5 is capable of causing oxidative DNA damage. Such testing could include bacterial mutagenicity

testing using *Salmonella* strains TA102 and TA104, and the OxyR deficient strain of *E. coli* WP2 uvrA, as well as the COMET single-cell gel electrophoresis DNA damage assay using a suitable cell type.

Other human health concerns

Even if the uterine adenocarcinomas seen at 160 ppm in the 2-year study are due to a carcinogenic mechanism which is rodent specific, there is still concern that D5 could be a dopamine agonist and result in other adverse effects in humans.

- Dopamine is a major neurotransmitter, involved in many brain functions and downstream physiological processes. Dopamine has been demonstrated to affect brain neural architecture during development (Todd, 1992; Swarzenski *et al*., 1994; Song *et al*., 2002). Data described above indicate that brain levels of D5 in rats exposed to 160 ppm D5 were approximately twice as high as corresponding blood levels. This raises the possibility that *in utero* exposure to D5 could result in adverse effects on brain neural development. Dopamine D2 receptors, with which D5 interacts, have a role in neurological disorders and mental illness (Ben-Jonathan and Hnasko, 2001; Seeman *et al*., 2006). For example, administration of the dopamine agonist bromocriptine may exacerbate schizophrenia (Ben-Jonathan and Hnasko, 2001) or it may produce improvements in negative symptoms (Lindenmayer, 1995).
- Dopamine acts on the endocrine system by inhibiting prolactin release (Ben-Jonathan and Hnasko, 2001). In humans prolactin induces and maintains the secretion of milk (lactation) and during lactation decreases reproductive function and suppresses sexual drive in the mother. Drugs used to treat hyper-prolactinemia, such as cabergoline and bromocriptine, are dopamine receptor agonists (Melmed and Jameson, 2005).
- Dopamine can activate dopaminergic receptors in normal human T-cells, and trigger the selective secretion of IL-10 and/or TNFα (Besser *et al*., 2005). Assuming D5 has dopamine agonist properties, this could have detrimental consequences in various immunological diseases, injuries and cancers.
- Prolactin has been reported to affect a variety of other cells including human adipocytes (Asai-Sato *et al.*, 2006; Nilsson *et al.*, 2005), mouse adipocytes (Flint *et al.*, 2006) rat cholangiocytes (Bogorad *et al.*, 2006a, b), rat chondrocytes (Zermeno *et al.*, 2006), human natural killer (NK) cells (Sun *et al.*, 2004), developing human thymocytes (Carreno *et al.*, 2005), and rat pancreatic islet cells (Amaral *et al.*, 2004).
- *In vivo*, in rodents, prolactin has a synergistic relationship with the glucocorticoids and adrenal function, possibly acting to determine adrenal size and function (Silva *et al.*, 2004). A recent report that alactogenesis resulting from an inherited defect in prolactin secretion also has an adrenal component in humans (Saito *et al.*, 2006) raises the possibility that adrenal function and carbohydrate metabolism could be adversely affected by chronic suppression of prolactin in humans.

Thus, even if D5 does not induce uterine or other tumors in humans, if D5 acts as a dopamine agonist it may therefore have other adverse health impacts.

Finally, there are several data gaps:

- Although there is information that D5 does not adversely effect reproduction, developmental toxicity data are limited; in one study a possible effect (on anogenital distance) was identified but was dismissed as not being treatment related without sufficient justification. There also is no information on toxicity due to exposure in very young animals. OEHHA has a mandate to protect infants and children in its risk assessments.
- The PBPK model for D5 is not final. Results from the model might address some of OEHHA's concerns about possible D5 bioaccumulation in humans. However, data indicate that D5 bioaccumulates in fish, a negative ecological effect and a source of additional exposure to humans via fish consumption. Detailed analysis by Environment Canada indicates potential for bioaccumulation in biota. Further, biomonitoring data indicate a long half-life of D5 in humans.

Conclusions

(1) The MOA for tumor induction in rodents is plausible, but there are at present insufficient data to conclusively determine the relevance or otherwise of these tumors to humans. Measurement of a sustained, dose-dependent increase in the ratio of estrogen to progesterone levels in chronically D5-treated animals would strengthen the evidence supporting the proposed MOA. Clarity on whether or not D5 induces sustained uterine endometrial hyperplasia would also strengthen the proposed MOA.

(2) D5 might have effects other than cancer in humans due to dopaminergic activity. For example, although prolactin is not the luteinizing hormone in humans, it has important roles in human reproduction. Thus, there is substantial concern that D5 would produce other toxicities by virtue of its impacts on prolactin via the dopamine agonist properties (e.g., on adipose tissue, bile production, and the immune system). Further, dopamine is a major neurotransmitter in the central nervous system. Disruption of dopaminergic pathways by D5 could have adverse health impacts on the nervous system (e.g., possible psychological imbalance).

(3) Several data gaps are present both for the cancer mode of action analysis and for the general toxicity of D5, including limited data on developmental toxicity, lack of toxicity data in young animals, and incomplete genotoxicity data.

(4) Concerns exist for the environmental persistence of D5, which is highly lipophilic, has been measured in aquatic species in a number of environments, and has a long half-life in human tissues.

For these reasons, OEHHA cannot make a finding at this time that D5 is non-toxic.

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Bioavailability of D_4 after Inhalation and Implantation Exposure to Silicones

In the November 2001 issue of *EHP*, Luu and Hutter (*1*) described a physiologically based pharmacokinetic (PBPK) model for the bioavailability of octamethylcyclotetrasiloxane (D_4) following exposure to D_4 by inhalation and implantation. In this paper the authors developed a PBPK model that used a very limited data set obtained after either single or repeated intravenous (iv) administration of D_4 as a microemulsion (*2*). The intravenous pharmacokinetic data reported by Kirkpatrick (*2*) were obtained from a study I helped design and conduct; I am familiar with the data and with the limitations of the study design for this type of assessment. Kirkpatrick (*2*) obtained blood and tissue samples at various time intervals after administration of radiolabeled D_4 and determined total radioactivity in these samples, but did not attempt to distinguish between parent D_4 and D_4 metabolites. Although the data obtained by Kirkpatrick were for iv dosing, Luu and Hutter (*1*) actually used intra-arterial dosing in their PBPK model. They validated their model by predicting inhalation kinetics in rats and comparing their prediction with a data set published by Plotzke et al. (*3*); they assumed that the radioactivity measured by Plotzke et al. (*3*) was parent D_4, with no contribution from metabolites. Luu and Hutter (*1*) plan to use their PBPK model to assess risk after exposure to D_4 resulting from migration from silicone gel breast implants. In addition to specific issues about their PBPK model, I also have several concerns about the manner in which this model will ultimately influence any risk assessment performed for D_4. These concerns relate to *a*) the assumptions of the level of D_4 in a silicone gel breast implant, *b*) the actual level of exposure to D_4 arising from a silicone gel breast implant, *c*) the limited understanding of the metabolism of D_4 reported by Luu and Hutter (*1*), and *d*) the prediction from their PBPK model that D_4 will bioaccumulate with repeated exposures.

The level of low molecular weight siloxanes (LMWS), both cyclic and linear, that persist in the polydimethylsiloxane (PDMS) used to make the silicone gel and elastomer shell of a breast implant is in the range of ≤ 0.1%. In a recent comprehensive pharmacokinetic study on PDMS, Jovanovic (*4*) measured the actual concentration of D_4 to be 0.03% of the PDMS by weight. Our own analysis of D_4 in silicone gel breast implants shows that D_4 levels rarely exceed 700–1,000 ppm (0.07–0.1%) (*5*). This higher level of D_4 in the silicone gel could result during the manufacturing process. If one conservatively assumes that a silicone gel breast implant could contain up to 0.1% D_4 and that the average size of a breast implant is 250 g, then the total D_4 content in two breast implants is 500 mg, or 8.7 mg D_4/kg body weight based on the U.S. Environmental Protection Agency's default body weight of 57 kg for a woman (*6*).

The migration of silicone from a silicone gel breast implant ranges up to 820 µg/day (*7*), with the migration of D_4 occurring at a rate of about 0.58 µg/day (*5*). For a woman who weighs 57 kg, this migration equates to a relatively small exposure of 0.01 µg/kg/day. Luu and Hutter (*1*) estimated that the extra dose of D_4 received from a silicone gel breast implant is 5.7 µg/kg/day, an overestimate by over 500-fold. The estimate of daily intake reported by Shipp et al. (*8*) resulting from exposure to D_4 in a wide variety of personal care products was 158 µg/kg/day. If we assume the value reported by Luu and Hutter (5.7 µg/kg/day) is correct, then the exposure to D_4 resulting from migration from a gel-filled implant would account for a proportionately small increase in total exposure to D_4 (from 158 µg/kg/day to 164 µg/kg/day). This small increase has little effect on the initial risk assessment for D_4 (*8*).

Two of the references (*9,10*) cited by Luu and Hutter (*1*) to support "migration of significant amounts of silicone out of gel implants into surrounding tissue and to the liver" have been retracted by the authors (*11*). Further, Hull (*12*), a member of the *Magnetic Resonance in Medicine*'s Editorial board, wrote that "as a referee, none of Garrido's papers should have been published in their current form," and in a summary statement concluded that

> the inadequacies, omissions, inconsistencies, and unresolved questions that are apparent in the work of Garrido et al. allow only one possible conclusion: there is no convincing and reproducible evidence of millimolar concentrations of silicon in tissue or blood.

The work of Garrido and colleagues (*9,10*) certainly does not support the contention of Luu and Hutter (*1*) in the introduction of their paper that

> the migration of significant amounts of LMWS from silicone gel breast implants … would add to the dermal or inhalation exposures from personal care products in a typical woman.

Luu and Hutter (*1*) postulated that D_4 saturates the elimination process, thereby potentially increasing the delivered dose to the target tissue and causing accumulation of D_4 in fat, liver, and kidneys. This conclusion is based on their analysis of the iv data (but they actually used intra-arterial administration). Several studies show that D_4 induces cytochrome P450 2B1/2B2 in a time, dose-dependent, and phenobarbital-like manner (*13,14*). Studies conducted by Plotzke and colleagues (*3,15,16*) and Varaprath et al. (*17,18*) provide evidence that rats extensively metabolize D_4. Metabolism and subsequent elimination of hydrophilic metabolites in urine and feces are important elimination mechanisms for D_4 in mammalian species. In addition, the elimination of D_4 occurs not only by this high metabolic clearance from liver but also by exhalation of parent D_4 via the lung. If Luu and Hutter (*1*) were correct and D_4 did saturate the enzymes responsible for metabolism, proportionately more D_4 would be eliminated through exhalation. As shown by Plotzke et al. (*3,15,16*), in fact, the rates of metabolism and clearance of D_4 and its metabolites support the conclusions reached with a more comprehensive PBPK model developed by Andersen et al. (*19*); that is, D_4 will not be unusually persistent in mammalian species.

In their discussion, Luu and Hutter (*1*) focused much of their attention on the potential bioaccumulation of D_4. The PBPK model developed by Andersen et al. (*19*) was based on an extremely robust inhalation pharmacokinetic data set for D_4 developed by Plotzke et al. (*3*) that included exposure to three concentrations, single and repeated exposures, and separate measurement of parent D_4 and metabolites (*15–18*). This model showed that D_4 is not expected to accumulate with repeated exposures. This lack of accumulation, despite high fat:blood partitioning, is due to rapid metabolism and the low blood:air partition coefficient that allows for ready exhalation of D_4. Metabolism does not saturate until the inhalation exposure concentration exceeds 500 ppm (v/v). To assess the validity of the prediction that D_4 would not accumulate, we recently collected blood and fat samples from female rats after 6 months of exposure to D_4. As part of a 2-year bioassay, these female rats were exposed by inhalation for 6 hr/day, 5 days/week to 700 ppm (v/v) D_4. We measured parent D_4 concentrations in both the blood and fat and compared the concentrations at 6 months of exposure with those obtained at 15 days in the inhalation pharmacokinetic study by Plotzke et al. (*3*). The concentrations in blood and fat, respectively, at 15 days were 7.2 µg/g and 1,079 µg/g tissue. At 6 months, the D_4 concentrations in blood and fat, respectively, were 13 µg/g and 1,200 µg/g tissue. These results confirm that D_4 does not accumulate in the body.

As with any risk assessment, it is essential to understand both the exposure to target

populations and the dose response for toxicity in experimental animals. The development of a PBPK model plays an important role in calculating the dose delivered to target tissue from specific exposure conditions. These PBPK models also can play a role in understanding the dynamic processes that occur while the D_4 is in the organism. Recently, D_4 was shown to have an effect on the reproductive system of female rats following inhalation exposure to 500 and 700 ppm (v/v) (*20*). This effect consisted of a reduction in mean live litter size and implantation sites. In the F_1 generation, there also was a reduction in mating at 500 and 700 ppm (*20*). The mode-of-action for these reproductive effects is the ability of D_4 to block or shift the preovulatory surge of luteinizing hormone (*21*). The highest exposure concentration that does not cause a significant reproductive effect [i.e., the no-observed-adverse-effect level (NOAEL)] appears to be around 300 ppm. The estimate of daily intake reported by Shipp et al. (*8*) for D_4 exposure from a variety of sources including personal care products is influenced by two characteristics or assumptions. First, at the time we completed our initial exposure assessment, roll-on antiperspirants (AP) contained up to 60% D_4 and accounted for about 50% (70 µg/kg/day) of the estimated daily intake. In the last few years, there has been a shift away from D_4 in roll-on APs such that the estimate of daily intake today should be about 40–50% lower than the original value. Second, the primary exposure to D_4 in personal care products is dermal application. After absorption into the venous blood, D_4 goes to the lung before reaching other tissues. As D_4 passes through the lung, some is eliminated in the expired air before entering the arterial circulation. Based on its partition coefficient, one-half of the free D_4 in the venous blood will be exhaled during passage through the lung. This first pass effect, predicted by the PBPK model developed by Andersen et al. (*19*) is consistent with the physical properties of D_4 and therefore further lowers the estimated daily intake. Luu and Hutton (*1*) estimated a daily intake or exposure resulting from migration of D_4 from a silicone gel breast implant to be 5.7 µg/kg/day, which is likely to significantly overestimate the actual daily intake. However, if we conservatively estimate the daily intake from personal care products to be 78 µg/kg/day (based on the reduced use of D_4 in roll-on APs as discussed above) and add the estimated daily intake or exposure by Luu and Hutter, then the estimated total daily intake for D_4 becomes 85 µg/kg/day. Exposure of rats to 300 ppm (v/v) of D_4 for 6 hr/day equates to an inhaled dose of 45,000 µg/kg/day using an absorption value of 5%, as determined in our inhalation pharmacokinetic studies (*3*). These values give a margin of safety (or exposure), as determined by dividing the NOAEL by the estimated daily intake, of over 500. A margin of exposure (MOE) of a specified magnitude indicates that exposure at or below the corresponding estimated intake level is not expected to result in adverse effects in the exposed populations. An MOE of 100 is typically considered large enough to be health protective when the NOAEL is based on animal data. The components of the MOE can be thought of as the typical factors of 10 for interspecies extrapolation (from animals to humans) and a factor of 10 for intrahuman variability, resulting in an MOE of 100.

In summary, Luu and Hutter (*1*) reported that they have developed a PBPK model for exposure to D_4 via two routes: *a*) inhalation in association with daily use of multiple personal care products, and *b*) migration of small amounts of silicone fluid from silicone gel breast implants. Their PBPK model is built from data generated by intravenous administration of D_4 as a microemulsion (*2*) and then modeled for intra-arterial dosing. They assumed that all radioactivity was parent D_4, even though there is significant conversion of D_4 to hydrophilic metabolites. A more complete PBPK model (*3*) was developed from an extensive inhalation data set on D_4, including evaluation of metabolism of D_4. This more comprehensive model and the actual data from our 6-month inhalation study show that there are only modest increases of D_4 concentration in fat on repeated exposures to D_4 compared to concentrations achieved after single exposures. Luu and Hutter (*1*) also overestimated the contributions to the daily intake resulting from the migration of D_4 from a breast implant. However, this overestimation of the daily intake by Luu and Hutter does not significantly change the MOE for D_4. The conservative MOE of > 500 indicates that current use practices with D_4 have adequate safety margins

Robert G. Meeks
Dow Corning
Midland, Michigan
E-mail: robert.meeks@dowcorning.com

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Further Comments on the Bioavailability of D_4

We would like to comment on a paper by Luu and Hutter (*1*) published in the November 2001 issue of *EHP*. We have developed multidose route, multi-species PBPK models for D_4 over the past several years. Our PBPK models have been presented in abstract form at several national meetings, and the complete inhalation model for D_4 in the rat was published earlier this year (*2*). In their paper, Luu and Hutter (*1*) incorrectly attribute several conclusions to our earlier abstracts, including the comment that our model did not describe blood concentrations during and after exposure. Surprisingly, they did not cite conclusions from our complete, peer-reviewed documentation of our model. We would like to point out some important differences between their model and our D_4 model. We would like to address several issues: *a*) the unconventional model structure and inappropriate use of available pharmacokinetic data to estimate the blood:air partition coefficient by Luu and Hutter (*1*); *b*) the process by which all available pharmacokinetic data should have been used to ensure adequate validation of their PBPK model; and *c*) the unusual kinetic behavior of D_4 compared to other volatile organic compounds that needs to be captured in any kinetic model for this compound.

A major difference in Luu and Hutter's model (*1*) and our published model (*2*) is the value used for the blood:air partition coefficient ($P_{b:a}$). Our estimate of $P_{b:a}$ derived from the measured concentrations of parent D_4 in blood at the end of a 6-hr exposure was 0.8; our direct measurements of the $P_{b:a}$ by equilibration of D_4 between blood and air *in vitro* gave a value near 4.0. Luu and Hutter used a much higher value of 20 and reported that they were able to describe both the rat and human inhalation results. It is of interest to determine why there would be such a large discrepancy in a critical parameter between the two models.

Luu and Hutter's model for D_4 in the rat (*1*) is based on studies in which total radioactivity was measured in blood after exposure of rats to ^{14}C-D_4. Luu and Hutter (*1*) used the radioactivity data from Plotzke et al. (*3*) and assumed that the radioactivity in blood was parent compound. In our work, we modeled parent D_4 and metabolites separately. By the end of the 6-hr inhalation exposure in rats, the majority of radioactivity in blood is metabolite (about a 3- to 4-fold greater concentration of metabolite vs. parent D_4 at the end of the exposure). After the 6-hr exposure, D_4 is rapidly eliminated by exhalation compared to the metabolites, and the discrepancy between total radioactivity and parent D_4 only increases. To predict these artificially high blood levels and retain these high concentrations for long periods of time, Luu and Hutter's model requires an artificially high estimate of the partition coefficient, thus the use of 20 in their model versus 1.0 in our model in which parent D_4 and metabolites were described separately.

Luu and Hutter (*1*) then scaled the model with the high partition coefficient to humans. In this case the data in their paper was for parent D_4; nonetheless, they still showed good correspondence between data and model predictions. We believe that this agreement is quite misleading and related to differences between their human modeling approach and conventional approaches used with other volatiles. Their ability to fit the human D_4 was based on an artificial constraint added to limit retention of inhaled D_4.

Based on the equations of Ramsey and Andersen (*4*), a paper cited as the basis of Luu and Hutter's work, the concentration of styrene in the arterial air (C_{art}) could be approximated from a steady-state formula published by Andersen (*5*):

$$C_{art} = \frac{P_{b:a} \times Q_{alv} \times C_{inh}}{Q_{alv} + P_{b:a} \times E_H \times Q_H}, \qquad [1]$$

where Q_{alv} is the alveolar ventilation, E_H is hepatic extraction, Q_H is the hepatic blood flow, and C_{inh} is the inhaled concentration of compound. In PBPK models, inputs include partition coefficients, inhaled concentrations, and the suite of physiologic factors, including blood flows, breathing rates, and characteristics of metabolizing tissues. Using all of these factors together, it is possible to predict the amount of inhaled compound that is retained during respiration. For modeling exposures in rats, Luu and Hutter (*1*) correctly used the ventilation × the inhaled concentration as the input term to the arterial blood in the rats. In contrast, for the human modeling Luu and Hutter (*1*) cited the differences (input – output) measured in a human study from the University of Rochester (*6*) and applied them as a constraint on the model. Thus, their input is (Q_{alv} × C_{inh} × proportion retained). Because the proportion retained was only 0.1, the model required an anomalously high blood:air partition coefficient to achieve blood concentrations equal to the inhaled air concentrations. (This behavior follows from Equation 1 if the proportion retained is included empirically.) Our PBPK model for D_4, following previous approaches with volatile compounds such as styrene, describes parent D_4 concentrations in rat and humans without artificial constraints on uptake. The proportion retained is an output of the model, not a constraint. In this fashion, both rat and human uptake curves are adequately described in our modeling efforts with $P_{b:a}$ = 1.0.

The novel kinetic behavior referenced in the title of our paper (*2*) is the persistence of nonexchangeable D_4 in blood at long times after exposure. We only identified the necessity to include this bound form in blood because of our efforts to fit blood and exhaled D_4 during both the exposure and the postexposure periods. Luu and Hutter's model (*1*) also included blood sequestration from the plasma pool of D_4. (The equation in their paper for the weakly bound compartment appears to be incorrect. The last term in their paper for this equation should be $k_{si} \times C_{wk}$ rather than $k_{si} \times C_{str}$. According to the author's description

$$V_{weak}\frac{dC_{wk}}{dt} = k_{wi}C_{ai} + k_{so}C_{str} - k_{wo}C_{wk} - k_{si}C_{str},$$

where C_{ai} is the concentration of D_4 dissolved in plasma; C_{wk} is the concentration of D_4 weakly protein bound in plasma; C_{str} is the concentration of D_4 strongly protein bound in plasma; k_{wi} is forward rate constant for weak protein binding of D_4 in plasma; k_{si} is forward rate constant for strong protein binding of D_4 in plasma; k_{so} is reverse rate constant for strong protein binding of D_4 in plasma; k_{wo} is reverse rate constant for weak protein binding of D_4 in plasma; V_{weak} is the volume of weakly bound plasma.

Another similarity in structure of the two models is the use of multiple fat compartments. Luu and Hutter (*1*) used a diffusional movement from a single fat compartment into a sequestered compartment within the main fat compartment. In our model, we described different fat compartments within the body with different time constants for equilibration. Luu and Hutter (*1*) referred to blood flow to deep fat, although the description and equations indicate a diffusional movement from weakly bound fat to the deep fat compartment. Their equation for the deep fat compartment is also inaccurate as written; it should show a term for movement from the weakly bound fat compartment. In its present form in their paper (*1*), the rate of change of mass for the deep fat would always be zero. [The equation for the lung compartment in Luu and Hutter's paper (*1*) also has an error, with C_{lung} appearing twice in the second term of the mass balance equation.]

The model structure used by Luu and Hutter (*1*) for intravenous dosing actually is for intra-arterial dosing, in which the compound is placed in the arterial blood and

infused into tissues rather than introduced into the venous blood, where it must traverse the lung with opportunity for exhalation before passing to the arterial blood. For a compound with a low $P_{b:a}$ such as D_4, it is important to have physiologic realism in the dosing route in order to estimate exhaled D_4 accurately after intravenous dosing.

Another issue is that Luu and Hutter (*1*) should have used all available pharmacokinetic data to insure adequate validation of their PBPK model. After configuring the model for intravenous dosing, a practice common to many pharmacokinetic studies, Luu and Hutter (*1*) predicted plasma and fat concentrations for a single inhalation exposure of rats to D_4. The model overestimated the early time points in fat. In addition, the overall time course in plasma was underestimated for this one attempt at extrapolation and validation. Surprisingly, this validation exercise used a single study from an extremely rich data set on the inhalation pharmacokinetics of D_4 in rats. The data used for dose route extrapolation and validation once again were for radioactivity rather than for parent D_4 in blood and fat, whereas their pharmacokinetic model was purportedly for parent D_4 alone.

Plotzke et al. (*3*) performed pharmacokinetic studies of inhaled D_4 in male and female rats at three exposure concentrations for both single and multiple exposures. These inhalation studies generated important data on tissue time courses of D_4 in a large set of tissues, as well as in exhaled breath concentrations. Similarly, the available human data for interspecies extrapolation include exhaled breath concentrations and blood concentrations from volunteers (*6*). Any model validation exercise should consider all available kinetic information and not rely on a limited selection of these results. Luu and Hutter's (*1*) conclusions regarding validation should be regarded as preliminary until their PBPK model is rigorously tested against more complete data sets. For Luu and Hutter to assert that prediction of a limited set of available human data from an unconventional model for inhalation constitutes dose–route and interspecies validation of their PBPK model is an overinterpretation of available information.

A third area of concern in Luu and Hutter's study (*1*) involves the unusual kinetic characteristics of D_4. There is little doubt that the defining characteristic of D_4 is its lipophilicity, including a high fat:blood partition coefficient (P_f). We determined by vial equilibration methods that P_f was 500–600 in rats (*2*). The overall kinetic behavior of D_4, however, is related to several important characteristics: lipophilicity, high metabolic clearance from liver, and high exhalation clearance due to its relatively low $P_{b:a}$. This suite of characteristics insures that D_4 does not bioaccumulate excessively with repeated dosing. Although both Luu and Hutter's model (*1*) and our PBPK model agree that the fat–time constant is of the order of several weeks, D_4 behaves much differently from poorly metabolized, nonvolatile compounds that bioaccumulate extensively with multiple exposures. The blood levels of D_4 do not increase with daily exposures and the fat concentration increases only slightly, as noted in the multiple exposure studies reported by Dow Corning scientists and analyzed with our more complete PBPK model (*2*). On a fairly minor note, the pharmacokinetic models developed by both groups are linear, low-dose models. Luu and Hutter (*1*) called the kinetics of the intravenous administration nonlinear. The appropriate terminology would be polyexponential, not nonlinear.

We are pleased to see PBPK modeling approaches for evaluating interspecies differences in disposition appear in *EHP;* however, Luu and Hutter's statements regarding our inability to model postexposure D_4 levels are inaccurate. The postexposure kinetic behavior of D_4 is determined by a combination of free D_4 and D_4 in a nonexchangeable compartment. These time-course curves have been accurately described at various concentrations after both single and multiple exposures in male and female rats with our PBPK model structure (*2*). As Luu and Hutter noted, we did not report extrapolation to humans. The reason for this was that we were in the process of completing a more definitive examination of human inhalation kinetics from two complete human data sets on a total of 18 exposures. These analyses have now been completed (*7,8*).

To summarize our human modeling, we found that the structure of the rat PBPK model for D_4 with a $P_{b:a}$ of near 1.0, when scaled appropriately, was entirely adequate for describing all available data from human volunteers. We are concerned about the inaccurate attribution of conclusions of our modeling efforts by Luu and Hutter (*1*) and appreciate the opportunity to provide clarification on these points. We emphasize that the kinetics of D_4 are well described with $P_{b:a}$ = 1.0 in both rats and humans, when sequestration in blood lipids is included in the model structure. Because of the high rate of metabolism and exhalation of poorly soluble D_4 from blood, there should be little tendency for D_4 to bioaccumulate in any tissues upon repeated exposures.

Melvin E. Andersen
Ivan D. Dobrev
Micaela B. Reddy
Colorado State University
Foothills Campus
Fort Collins, Colorado
E-mail: mela@colostate.edu

Ramesh Sarangapani
ICF Consulting
Research Triangle Park, North Carolina

Richard H. Reitz
RHR Toxicology Consulting Services
Midland, Michigan

Kathleen P. Plotzke
Dow Corning Corporation
Midland, Michigan

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Rebuttal and Critical Review of Andersen et al.'s D_4 PBPK Model

The letters of Meeks and Andersen et al. regarding our paper in *EHP* (*1*) included inaccurate statements and misconceptions about our pharmacokinetic model of D_4.

After reviewing Andersen et al.'s recent paper (*2*), we found several shortcomings. First, Anderson et al. (*2*) used an unconventional experimental method to underestimate the affinity of D_4 for blood and fat; these partition coefficients were not comparable to those obtained for other lipid soluble organic chemicals. They further reduced

these experimental measurements in order to "fit" a 10-compartment model, which included 3 deep compartments in the lungs, fat, and liver. Andersen et al. used these low values to underestimate potential D_4 accumulation in fat and increase its clearance.

Second, Andersen et al. (*2*) did not validate and verify their PBPK model using independent data from intravenously (iv) treated rats. When we used Andersen et al.'s parameters for D_4 [blood:air partition coefficient ($P_{b:a}$), fat:blood partition coefficient (P_{fat}), and metabolism rate (V_{max})] in our own model, our results did not fit the iv experimental rat data, especially regarding D_4 tissue distribution in fatty tissues. Andersen et al.'s conclusions about the disposition and fate of D_4 also were not substantiated by the experimental rat inhalation data because high lipid solubility and slow desorption would favor accumulation in fatty tissues, as in the case with styrene.

Third, in their letter, Andersen et al.'s criticism about the dose rate of D_4 from a breast implant was incorrect; the dose rate reported was for D_4 leaching from the saline-filled breast implants and not from the silicone gel-filled breast implants.

We question the validity of Andersen et al.'s model (*2*) and believe that their predictions about the safety assessment of D_4, a component in silicone personal products and breast implants, may be misleading.

Andersen et al. (*2*) used a low $P_{b:a}$ (0.88) in their model, despite reporting a measured experimental value of 4.3. They also used an unconventional method to measure the $P_{b:a}$ and blood:tissue partition coefficient ($P_{b:t}$).

To measure the $P_{b:a}$ and $P_{b:t}$ of D_4, Andersen et al. (*2*) placed liquid D_4 and matrices such as blood, fat, lung, and liver in separate glass scintillation vials. All of the vials were subsequently placed in an enclosed 500-mL beaker. The D_4 was not in physical contact with the blood or any other matrices throughout the experiment. Using this method, a low volatility compound like D_4 would have to vaporize, diffuse through a gas space, and diffuse into a stagnant blood or tissue phase with liquid mass transfer resistance. This process would take time to reach equilibrium, but did Andersen et al. allow enough time for equilibrium to occur? Shields et al. (*3*), who measured D_4 concentrations in indoor air using a state-of-the-art analytic method, indicated that the sampling intervals for D_4 should be in weeks, not hours, in order to reach equilibrium. Andersen et al. (*2*) reported that they agitated for 24 or 48 hr and measured $P_{b:a}$ at two unknown time points. In fact, if the samples were allowed to reach equilibrium, their measurement of the $P_{b:a}$ of D_4 (4.3) might reach our estimated value of 20. The measured concentrations of D_4 in blood based on molecular diffusion between the vapor phase of D_4 and blood are not reliable unless they used long sampling intervals (*3*). Because Andersen et al. (*2*) did not describe internal standards for the experiment, it is likely that the percentage recovery was low after 24–48 hr. The same method was also used to underestimate other partition coefficients for fat, lungs, and kidneys.

A more accurate and direct measurement of $P_{b:a}$ (or $P_{tissues}$) would be to place several milliliters of the viscous D_4 liquid in direct contact with the tested matrix (e.g., whole blood, fat, liver, etc.) in a closed scintillation vial (*4*). The headspace (air) concentration and matrix concentration of D_4 should then be quantified during several time intervals following agitation. This minimizes the equilibrium problems not addressed by Andersen et al. (*2*).

The physical properties of D_4 (Table 1) play an important role in its tissue distribution and excretion; thus it is important that the use of arbitrary "fitted" parameters be avoided. This arbitrary low value of $P_{b:a}$ used by Andersen et al. (*2*) differed by a factor of 5 from the *in vitro* evaluation. Similarly, the partition coefficients used for fat and other tissues also varied widely from their experimental data (*2*). For example, Andersen et al. used a P_{fat} of 550.6 for instead of their experimentally determined value of 2,089 so their model would fit the data.

The low $P_{b:a}$ value is not comparable to those of other organic chemicals with properties similar to those of D_4. As shown in Table 1, the higher the volatility, the smaller the value of $P_{b:a}$ of an organic compound. For example, because benzene is more volatile than styrene, it has a smaller $P_{b:a}$ (75% smaller) than styrene (Table 1). According to Andersen et al.'s results (*2*), D_4 would be more volatile than benzene in blood. This is inconsistent with the observed volatility because benzene has a boiling point of 80.1°C, whereas D_4 has a boiling point of 175°C (Table 1). Because D_4 has a lower volatility than both styrene and benzene, its $P_{b:a}$ would be expected to be at least as large as the values reported for these two chemicals, and not smaller (Table 2). The D_4 $P_{b:a}$ would not be expected to have a value as low as 0.88, which is outside the range of all of the chemicals listed in Table 2. Ramsey and Andersen (*16*) reported a $P_{b:a}$ for styrene of 40.2 (Table 1).

Under the scenario of Andersen et al. (*2*), if both 1 µg D_4 and 1 µg of a much more volatile component such as benzene or another chemicals in Table 2 were added to blood, the D_4 would vaporize more readily. This is due to its partition coefficient, which favors transfer to the gas phase. Thus, D_4, which boils at 175°C, would be more volatile than benzene, which boils at 80.1°C, a situation which makes no sense.

As we discussed in our paper (*1*), the physical properties of D_4 favored its absorption into fat. High absorption of D_4 (100%) by the iv route and slow desorption, as well as a long half-life in fat ($t_{1/2}$ = 18 days), were attributable to the high $P_{b:a}$, P_{fat}, and high lipid solubility of D_4 [log octanol/water partition coefficient (K_{ow}) = 5.1]. For similar reasons, other highly lipid soluble organic compounds such as styrene, with high $P_{b:a}$ and P_{fat}, tend to accumulate in the fat tissue of rats and humans (*5–7*).

To compensate for this estimate of a thermodynamic property in blood and to "fit" the rat data for inhalation exposure, Andersen et al. (*2*) modified their basic model with 6 compartments to a refined model with 10 compartments, including deep compartments (deep lung, deep liver,

Table 1. Comparison of physical properties of D_4, styrene, and benzene.

Property	D_4	Styrene	Benzene
Melting point (°C)	17.5	–30.6	5.5
Boiling point (°C)	175.4	145–146	80.1
Vapor pressure (mmHg)	1 (25°C)	4.5 (20°C)	2.3 (3°C)
$P_{b:a}$	0.88[a]	40–52	17.8
Solubility in water	56 ppb	300 ppm	—
Log K_{ow}	5.1	2.95	2.14

[a]We used a value of 20 for $P_{b:a}$.

Table 2. Blood:air ($P_{b:a}$) and blood:fat partition coefficients (P_{fat}) of some known VOCs.

Compound	Log K_{ow}	P_{fat}	$P_{b:a}$
Hexane	3.87	69.43	2.29
Isoprene	2.42	38.5	1.87
1,1,1-Trichloroethane	2.48	45.66	5.76
Tetrachloroethene	3.40	86.67	18.9
Benzene	2.14	28.03	17.8
Toluene	2.64	56.72	18
p-Xylene	3.15	42.32	41.3
Styrene	2.95	86.47	40.2
Chlorobenzene	2.86	21.5	59.4

deep fat). But any scenario can be fitted by simply adding more compartments. However, adding more mass balance equations requires more biochemical parameters, which may not be available or accurately measured.

In our study, we derived the $P_{b:a}$ as the reciprocal of the D_4 Henry's Law Constant, which is its published water:air partition coefficient (a value ranging from 3 to 32) (*8–11*). The value we used in our model was within the range reported by these independent investigators (*8–11*). Still, we included in our paper (*1*) a discussion of the discrepancy caused by blood to the aqueous Henry's Law Constant of D_4, and we also cited the paper that supported these observations (*4*). We believe that Andersen et al. (*2*) did not take into account the $P_{b:a}$ of lipophilic organic compounds described by Beliveau and Krishnan (*4*).

Even though our $P_{b:a}$ is significantly larger than that reported by Andersen et al. (*2*) we predicted that the absorbed D_4 would be mostly exhaled [range, 42–59% in humans; see Table 6 of our paper (*1*)]. We do not understand Andersen et al.'s comment in their letter that we did not predict significant exhaled D_4. Recalculating the exhaled air amount using the following material balance on the exhaled air may clarify our concerns to Andersen et al.

$$\text{Exhaled} = \int_0^t Q_{air} C_{air}\, dt \qquad [1]$$

In preparing this response, we ran our PBPK model again using Andersen et al.'s fitted values (*2*) for $P_{b:a}$, P_{fat}, and V_{max} for metabolism rate (8 times higher than our V_{max} value). The results in Figure 1 show that the model using parameters employed by Andersen et al. (*2*) predicted poorly the D_4 levels in fat while predicting reasonable plasma D_4 levels following a single, low-dose iv injection. Using Andersen et al.'s parameters (*2*), we found that > 80% of D_4 is exhaled after iv exposure. Therefore, this would cause underprediction of D_4 accumulation in fat, experimentally found to be 16% of the iv dose. As shown in Figure 5 in our paper (*1*), our model gave excellent simulations of the rat iv (*12*) and rat inhalation data (*13*).

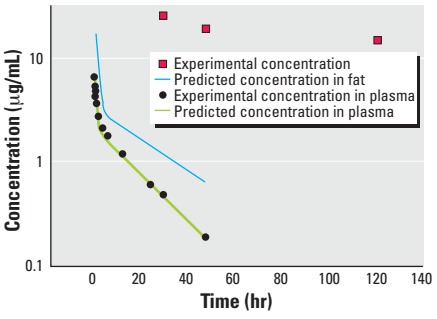

Figure 1. Comparison of predicted and experimental D_4 concentrations in fat and plasma. The experimental concentration in fat is from our model (*1*), and other values are from Andersen et al. (*2*). Andersen et al.'s model underpredicts the accumulation of D_4 in fat.

Two structurally different PBPK models could not both be correct, and both models fit the rat inhalation reasonably well. This leads us to believe that there are other shortcomings in Andersen et al.'s study (*2*):

- Andersen et al. (*2*) based their model on a rat inhalation study in which the absorption and elimination rates are compromised. Only 10% of the exposed D_4 in the air is absorbed, compared to 100% absorption of D_4 with iv exposure. The dose absorption is limited from the mass transfer resistance in the lungs. Using a low $P_{b:a}$, Andersen et al. reported that > 50% of the D_4 absorbed is eliminated in the expired air, whereas they assumed the metabolism rate of D_4 to be 8 times higher in their model than in ours. The unusual kinetics could not be confirmed by other published studies.
- Andersen et al.'s model lacks validation and verification using independent data such as included in the rat iv study (*12*), so their conclusions about the disposition of D_4 are best described as preliminary.
- Andersen et al.'s model is not accurate because they failed to measure partition coefficients for both parent compounds and metabolites for the 10 compartments including 3 deep compartments (lungs, liver, and fat). Instead, they have to curve fit, leading to errors and uncertainty regarding D_4 distribution in fatty tissues especially.
- Andersen et al.'s conclusions on D_4 kinetics even contradicted what others (*13,14*) reported regarding D_4 kinetics. In fact, they reported that D_4 plasma and tissue distributions resemble other volatile organic compounds such as styrene, which were found to accumulate in fat tissues of both experimental animals and exposed workers (*5–7*).
- Andersen et al. (*2*) failed to determine accurate D_4 pharmacokinetic data which show that D_4 is retained in fat. Because 8–10% of D_4 dose was found in fat 7 days postexposure and because rats were to be exposed daily for 14 days, it is hard to believe that D_4 would not retain and accumulate in the body.

In our paper (*1*), we estimated the maximum dose rate of residual D_4 that could migrate from the silicone envelope of a breast implant to be 5.7 μg/kg/day based on Fick's Law of Diffusion. We estimated a leaching rate of 95% in 30 days for the thin shell of a saline-filled breast implant surrounded by fatty tissues. The diffusivity of 5.4×10^{-8} cm^2/sec was consistent with published values for other chemicals (*15*). Our reported dose rate was the dose rate of D_4 leaching from saline-filled breast implants. The dose rate of D_4 leaching out of implanted silicone gel-filled breast implants could be easily determined, if needed.

In their letter, Andersen et al. correctly identified a typographical error in the Appendix regarding the material balance on the lung. The correct equation is as follows:

$$V_{lung}\frac{dC_{lung}}{dt} = Q_t C_{ai} - Q_t C_{lung} H_{air} - Q_{air} C_{lung}$$

In this equation, C_{ai} is a venous blood concentration as defined by the equation at the mix point [Appendix of our paper (*1*)]. It is not an arterial concentration, as suggested by Andersen et al. In this nomenclature, a = average. Thus, unlike the claims of Andersen et al. in their letter, this model does not artificially limit the exhalation of D_4. Any introduced D_4 will flow through the lung in a physiologically realistic manner, despite claims to the contrary. The above equation is equivalent to the tubular equilibrium lung used in the styrene model (*16*). The capture efficiency we used in both the rat and human models was similar and was only used to determine the delivered dose to the rat or human body as described in the Appendix of our paper (*1*). In the reference (*14*) cited in our paper, the delivered dose was experimentally determined by measuring the gas flow and inlet and outlet concentrations of D_4 at the rebreathing tube connections. We used the same model structure for both the rat and the human. Andersen et al. agreed that our rat inhalation model was correct because the human model had an identical structure.

In their letter, Andersen et al. also claimed that the "accumulation in the strongly bound fat compartment would always be zero." Figure 2 shows the accumulation in this compartment for F344 rats after low-dose inhalation (*13*).

It is informative to use animal data in a PBPK model to predict D_4 dose metrics in an animal body. This approach also allows the determination of the internal dose in target tissues, which can then be extrapolated to humans and correlated with the toxicity. However, models should be physiologically realistic and should not be used to predict phenomena beyond the reasonable bounds of the data by "fitting" highly restrictive cases. In an accurate model, the following problems should be avoided:

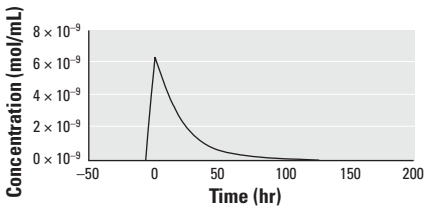

Figure 2. Accumulation of D_4 in strongly bound fat of F344 rats after low-dose inhalation.

- Artificially high pulmonary clearance of D_4 resulting from use of a $P_{b:a}$ that is not comparable to one obtained experimentally.
- Use of unconventional methods to reduce the potential of accumulation in target organs.
- Overestimation of the rate of metabolism, which is caused by a reduced absorbed dose resulting from inhalation exposure.
- Inappropriate use of the inhalation model for D_4 to examine the disposition and fate of D_4 leached from silicone breast implants.

Because of these problems with Andersen et al.'s model (*2*), the authors underestimated the potential bioavailability of D_4 and were unable to predict its bioaccumulation after repeated exposures or long-term exposure that occurs when D_4 leaches from silicone breast implants.

Hoan-My Do Luu
Joseph C. Hutter
Office of Science and Technology
Center for Devices & Radiological Health
U.S. Food and Drug Administration
Rockville, Maryland
E-mail: hml@cdrh.fda.gov

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four infections may cause death by some specific mechanism in the subsequent 12 months? If so, can they suggest what it is?

Philip P Mortimer *director*
Sexually Transmitted and Blood Borne Virus Laboratory, Central Public Health Laboratory, London NW5 5HT

Competing interests: None declared.

1 Helms M, Vastrup P, Gerner-Smidt P, Mølbak K. Short and long term mortality associated with foodborne bacterial gastrointestinal infections: registry based study. *BMJ* 2003;326:357. (15 February.)

Authors' reply

Editor—Our study was unique because it included patients with infectious gastroenteritis, by and large people who sought care from their family doctor and had no severe underlying illness. The concerns that O'Brien and Feldman raise about bias introduced by case selection is likely to be less relevant in Denmark as the Danish counties reimburse laboratory costs, and for epidemiological reasons doctors often request stool specimens. Our study was the first to determine mortality while adjusting for background mortality. This was pivotal because gastrointestinal infections often affect elderly people. Furthermore, we adjusted for comorbidity by using data from the national discharge registry. We applied the principles described by Charlson et al,[1] but calculated new empirical weights based on the actual survival rates of the large background population. This approach was used to ensure that the weights were valid and appropriate in the given context. This approach takes care of most of the concerns expressed by Cox. We also found excess mortality in the subanalysis, when all individuals with underlying illness had been excluded.

Many acute infections, including foodborne bacterial infections, are associated with short term and long term complications. These include acute complications such as severe dehydration, misdiagnosis of abdominal cramps, leading to surgery, or spread of the pathogens into the bloodstream. Salmonellas are a well known cause of focal and vascular infections.[2 3] The Guillain-Barré syndrome is a severe reactive complication to a campylobacter infection.[4] Although each of these events is uncommon, taken together they may account for our findings.

We agree with O'Brien and Feldman that both the infecting dose and subtype of bacterial species are of importance. In the analyses we looked at the effect of specific zoonotic salmonella serotypes. Beyond *Salmonella enteritidis*, *S typhimurium*, and *S dublin*, we could not see any differences, probably because the number of each of the exotic serotypes was too small to see this. Finally, antimicrobial drug resistance may be associated with adverse public health effects.[5]

The biological plausibility is supported by the fact that our estimates are in line with common knowledge of the different agents. For example, mortality after salmonella infection was higher than after campylobacter infection, and in the group of *Salmonella* infections, serotype *dublin*, known to be invasive, was associated with a marked excess mortality. Although long term mortality was observed for *Salmonella*, *Campylobacter* and *Yersinia enterocolitica*, the proportion of deaths attributable to the infection was highest in the acute phase. The table was prepared based on the figures in our table 2. The relative mortality has been converted to the attributable proportion of deaths among exposed, that is, a measure of the probability of a death being related to the gastrointestinal infection. In our opinion, the pattern presented in the table makes sense from a clinical point of view, and supports the notion that our findings are more than artefacts.

Morten Helms *research fellow*
Pernille Vastrup *statistician*
Kåre Mølbak *staff specialist*
Statens Serum Institut, DK-2300 Copenhagen, Denmark

Competing interests: KM reviewed data relating to *Campylobacter* on behalf of US Food and Drug Administration's centre for veterinary medicine for an administrative hearing concerning a proposed withdrawal of the fluoroquinolone enrofloxacin (Baytril, Bayer) for use in poultry. Please note: Dr Feldman and Cox Associates reviewed similar data on behalf of Bayer.

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2 Cohen JI, Bartlett JA, Corey GR. Extra-intestinal manifestations of salmonella infections. Medicine (Baltimore) 1987;66:349-88.
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4 Allos BM. Campylobacter jejuni infection as a cause of the Guillain-Barré syndrome. *Infect Dis Clin North Am* 1998;12:173-84.
5 Travers K, Barza M. Morbidity of infections caused by antimicrobial-resistant bacteria. *Clin Infect Dis* 2002; 34(suppl 3):S131-4.

Mortality data among 48 857 patients infected with salmonella, campylobacter, shigella, and *Yersinia enterocolitica*. Mortality is expressed as the cumulative mortality risk in a time interval after infection and the proportion of these deaths attributable to the gastrointestinal infection

	Time since infection (days)					
	0-30		31-180		181-365	
Species	Mortality risk per 1000	Attributable proportion (%)	Mortality risk per 1000	Attributable proportion (%)	Mortality risk per 1000	Attributable proportion (%)
Salmonella	12.3	92	10.8	55	8.1	35
Campylobacter	2.7	80	5.0	46	4.1	26
Shigella	3.0	95	—	NS	—	NS
Yersinia	1.7	72	3.5	60	—	NS

NS=no significant excess mortality.

Mortality in Swedish women with cosmetic breast implants

Study found increased risk of suicides and cancer deaths

Editor—The increased suicides and lung cancers among implant patients reported by Koot et al is consistent with a study by Brinton et al at the US National Cancer Institute.[1 2] However, Brinton et al found an increased risk of suicides and cancer deaths compared with other patients having plastic surgery.

If plastic surgery patients have more psychological problems than the general population, as Koot suggests, that would not explain the difference between suicide rates of breast augmentation patients compared with other plastic surgery patients. There are other, more likely explanations. Notably, unlike most other plastic surgery patients, implant patients suffer from well documented complications such as chronic pain and implant breakage that increase in likelihood every year. Our centre receives letters every week from women whose implants are broken and who cannot afford explant surgery. Many of these women are quite desperate, especially when silicone is migrating to other organs or causing pain or deformities. Even in countries with national health care, these problems can be difficult to remedy and could potentially cause an increase in suicides.

A flaw of the Koot et al study is that it included women who had breast implants for less than one year, which weakens the statistical power. In contrast, the Brinton et al study included women who had breast implants for at least eight years and found increases in deaths from suicide, lung cancer, and brain cancer compared with plastic surgery patients who reported similar smoking and lifestyle habits.

Diana Zuckerman *president*
National Center for Policy Research for Women and Families, 1901 Pennsylvania Avenue, NW Suite 901, Washington, DC 20006, 202 223-4000, USA
dz@center4policy.org

Competing interests: None declared.

1 Koot VCM, Peters PHM, Granath F, Grobbee DE, Nyren O. Total and cause specific mortality among Swedish women with cosmetic breast implants: prospective study. *BMJ* 2003;326:527-8. (8 March.)
2 Brinton LA, Lubin JH, Burich MC, Colton T, Hoover RN. Mortality among augmentation mammoplasty patients. *Epidemiology* 2001;12:321-6.

Body dysmorphic disorder should be considered

Editor—Koot et al reported an increased risk of suicide among patients who had received cosmetic breast implants.[1] The somatoform disorder known as body dysmorphic disorder entails a preoccupation with a defect in appearance, and the defect is either imagined, or, if a slight physical defect is present, the patient's concern is markedly excessive with subsequent impairment of social or occupational functioning.[2] The patient's distress may lead to suicidal ideation, suicide attempts, and

Sientra Silicone Gel Breast Implants

Date of FDA Notice of Approval: March 9, 2012

Cyclic Siloxane	**Shell µg/g**	**Gel Filler µg/g**
D_3 (Average)	0.87	ND
D_4	0.60	73
D_5	3.92	510
D_6	25.39	2119
D_7	20.64	2153
D_8	14.01	1560

Cyclic Siloxane	Shell µg/g	Gel Filler µg/g
D9	8.29	952
D10	6.11	964
D11	5.05	1107
D12	5.76	1111
D13	6.94	1276
D14	9.0	1808
D15	10.93	2180
D16	14.08	2539
D17	18.0	2563
D18	14.84	2471
D19	15.75	2402
D20	21.79	1447
D21	15..24	ND
Sum D	**219.45**	**Sum D**
ND = Not Detected		

3-D21

4-20: **27234**

MENTOR MEMORY GEL

Table 3. Volatile Results Compound	Shell Not Exposed to Gel (ppm)	Shell Exposed to Gel (ppm)	Gel Filler (ppm)	Whole Device (ppm)
D3	ND	0.19	0.18	0.18
D4	<0.06	0.23	0.49	0.46
D5	0.28	0.79	1.60	1.47
Methoxytrimethylsilane	3.13	3.34	ND	0.43
Dimethoxydimethylsilane	ND	0.20	ND	0.03
Methoxytriethoxysilane	0.04	ND	ND	ND
Tetramethyldiethyldisiloxane	ND	ND	0.05	0.04
Acetone	1.02	1.38	ND	0.18
Isopropanol	<1.06	2.03	ND	0.26
2-Pentanone	0.05	ND	ND	ND
Methyl Butanoate	0.04	ND	0.09	0.01
Ethylbenzene	<0.01	ND	ND	ND
m- & p-xylene	0.06	ND	<0.09	0.08
4-Methyl-3-penten-2-one	0.07	0.08	ND	0.01
o-xylene	<0.02	ND	ND	ND
Alpha-Pinene	<0.02	ND	ND	ND
Cyclohexanone	<0.56	ND	ND	ND
1-Ethyl-2-methylbenzene	0.02	0.06	ND	0.01
Decane	0.09	ND	ND	ND
Benzaldehyde	0.04	0.08	ND	0.01

Date of Panel Recommendation: April 13, 2005

Date of Notice of Approval to

Inamed® Silicone-Filled Breast Implants Allergan*

Dates of Panel Recommendation: October 15, 2003 and April 12, 2005

Date of Notice of Approval to Applicant: November 17, 2006

Table 3: Concentrations of Low Molecular Weight Components Detected (in ppm by component weight). Identification	Gel (ppm)	Implant Shell & Patch (ppm)	Virgin Shell & Patch (ppm)
D3	ND (<146)	ND (<17)	ND (<7)
D4	ND (<69)	ND (<8)	ND (<3)
D5	ND (<6)	ND (<1)	ND (<1)
D6	ND (<6)	ND (<1)	ND (<1)
D7	ND (<6)	ND (<1)	ND (<1)
D8	ND (<8)	ND (<1)	ND (<1)
D9	ND (<8)	6	ND (<1)
D10	ND (<8)	12	2
D11	11	21	9
D12	32	94	26
D13	64	62	65
D14	237	186	209
D15	366	278	285
D16	491	351	317
D17	593	432	328
D18	729	527	342
D19	678	601	0
D20	735	605	212
D21	668	474	129

ND (<X) = Not detected at less than X, the concentration in parts per million.

Concentrations of Low Molecular Weight Components (amu ≤ 1500)

Identification	Molecular Weight (amu)	Siloxane Silicones (µg/g)
D3	222	0.97
D4	296	6.36
D5	370	12.35
D6	444	<6.3*
D10	740	90.4*
D15	1110	347.3*
D20	1480	62.3*
Isopropanol	60.09	1.88
Toluene	92.13	0.03
Xylenes	106.2	3.89
Metals		
Tin	118.7	0.5
Platinum	195.1	0.78
Arsenic	74.9	ND
Lead	207.2	ND
Zinc	65.4	0.26
Total Extractables (methylene chloride)		2.11%

* Methylene Chloride extraction

For cyclic-octamethyltetrasiloxane (D4), the amount per gram of implant was 6.36 µg. The total D4 in the largest device (Siltex Spectrum, weighing 48.3 g) would be 307 µg. The exposure level for a 60kg woman with two of the largest implant would be 614 µg total or 10.2µg/kg, if all the D4 were released at once.

In rat studies conducted by Dow, the no adverse effect level for D4 for a reversible increase in liver weight was 12 mg/kg. Using safety factors of 10 for the species difference and a safety factor of 10 for the route of entry difference, the no observed adverse effect level (NOAEL) would be 0.12 mg per kg, well above the level of 10.2 µg/kg. Reproductive effects were not seen below 80mg/kg. Because of the diffusion limitation, far less than 10.2 µg/kg could be released immediately. The diffusion estimate is that only 0.44 µg/kg could be released over a 30-day period. The expected exposure to D4 is well below toxic levels.

Smooth and Textured Saline-Filled Mammary Prostheses

Saline-Filled and Spectrum® Mammary Prostheses

Mentor Corporation
201 Mentor Drive
Santa Barbara, California 93111

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