DES Action® VOICE

We identify, educate, empower and advocate for DES-exposed individuals

Inside

FALL 2022 #173

DES Lawsuits Still Being Filed

It's a common misconception that all lawsuits associated with DES have long ago been settled. There are fewer these days, but we at DES Action have heard of at least half a dozen filed in the past several years.

As an example, here is a new lawsuit that has just been filed in New York against the usual suspects.

Attorney Janice Roven, who is a DES Daughter herself, is representing a DES Daughter, born in 1956 in Massachusetts, though she later lived in New York, where the lawsuit was filed.

The DES Daughter is suing five companies for a total of $10 million in compensatory damages (for the direct harm caused to her) and $10 million for punitive damages (as punishment for the companies' wrongdoing).

The suit names four pharmaceutical companies: Eli Lilly, based in Indiana; E. R. Squibb & Sons, now called Bristol-Myers Squibb and based in New York; The Upjohn Company, based in New York; and Ortho-McNeil Pharmaceutical, based in Pennsylvania and New Jersey.

It also names Dart Industries, based in Florida, which was formerly known as Rexall. Rexall drugstores distributed DES from the 1940s to 1960s.

(Rexall also, incidentally, acquired Tupperware in 1958. The irony here is that Tupperware containers, like most plastic food containers, likely contained the endocrine disruptor BPA up until 2010, when the company made sure it was removed. Even now, however, it may contain BPS, a virtually identical endocrine disruptor, because most BPA in consumer products was replaced with BPS.)

The lawsuit charges five claims against the companies: product liability, company negligence (in how they represented the drug, their lack of testing, and their refusal to warn the public of its risks), two breaches of warranty, and fraudulent misrepresentation.

Although the details of the facts alleged in the lawsuit will be familiar to all DES Daughters, it's validating to read the language in a present-day lawsuit that reminds the country that DES Daughters still exist and are still suffering for how pharmaceutical companies and pharmacies wronged them.

The lawsuit alleges that the defendants "assisted each other to exploit, market and secure permission from the FDA to publicly sell DES for ingestion by women" even though the defendants "were aware, or should have known, that the drug had not been tested and lacked warnings."

And despite this, the companies pushed for FDA approval of DES, "thereby enabling others and them-

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Two Studies on Older DES Daughters' CCA Risk

An estimated 1 in 1,000 to 1 in 750 DES Daughters develop clear cell adenocarcinoma before age 50, but not much research has examined the risk of CCA in older DES Daughters.

In this issue of the VOICE, two separate studies examine risk of DES-related gynecological cancer in DES Daughters over age 50, but they appear — at first blush — to come to different conclusions.

A deeper look from both together, however, suggests that risk of CCA is still higher for DES Daughters over age 50 than those in the general population. The separate findings underscore the importance of continuing to study DES Daughters and other DES-affected populations as they age.

The articles on these studies begin on page 6

Update on Campaign to Restore DES Follow Up Study Funding

The DES Follow Up Study provides valuable and unique information about the health effects of DES-exposure, and it can never be replicated or replaced - it must be restored to continue to benefit DES-exposed individuals across multiple generations, and to help us understand health effects of endocrine disrupting chemicals in general.

In contrast to the fanfare surrounding passage of the DES Education and Research bill in 1992 that created the DES Follow Up Study, there was no announcement from the National Institutes of Health (NIH) about the study's demise in 2020.

When funding ran out the NIH and five research centers participating in the study (University of Massachusetts, University of Chicago, Boston University, Baylor College of Medicine, and Dartmouth Medical School) quietly cut back research related to the multigenerational cohort, with notice this summer to some but not all participants.

Restoring funding for the DES Follow Up Study remains a priority for DES Action USA and our members, building on the many efforts of our members this year and looking forward to next.

- The Appropriations Committee is requiring the NIH to answer a "question for the record" about the study, though it did not include a line item for study funding in the FY 23 federal budget.
- Our partnership with the Endocrine Society continues with drafting report language for the FY 24 federal budget.
- Rep. Jim McGovern stepped up as a champion for the cause, including support for a governmental apology for DES approval and for restoration of funding.
- We submitted a "suggestion" to the Black Maternal Health Caucus for study funding, related to their interest in environmental exposures and endocrine disruption.

As DES Action USA approaches its 45th anniversary, we recognize that if we are to restore study funding it is essential to engage a new generation of elected officials, agency staff, researchers and clinicians as well as DES-exposed individuals and their family and friends.

Thanks to every DES Action USA member who stepped up in 2022 to contact your congressional representatives as every contact increases awareness and likelihood of future support, and also to our colleagues with DES Is It and Descendance Distilbene in France, who sent along letters of support - recognizing the international benefit of the work we are doing. -CC

Renew Your Membership

It's easier than ever to renew your membership. Just log into the site using the email you registered with and your password. If you don't remember your password, you can reset it.

If you no longer use the email you signed up with, send your new address to Cheyenne Chapman at cheyenne@desaction.org. She will set a temporary password for you.

Thank you for supporting DES Action USA with your membership.

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The mission of DES Action USA is to identify, educate, empower and advocate for DES-exposed individuals.

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DES Lawsuits Still Being Filed

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selves to market a drug resulting in harm to the offspring of users," the lawsuit states.

The lawsuit states that the companies claimed DES prevented miscarriages and "was a safe and efficacious drug for the treatment of accidents in pregnancy" in its FDA application, in public advertising to the medical community, and in materials given to doctors.

Yet, the companies "knew or should have known that DES had the potential to become harmful to the offspring of users and… that the drug was ineffective for the purpose for which it was marketed and sold," the lawsuit states.

The lawsuit calls the companies' actions "reckless and negligent" since they knew it was a substance that could cross the placenta and harm the fetus.

This misrepresentation of DES's risks to the FDA, doctors and government agencies is the reason the plaintiff's mother was given the drug.

The lawsuit does not list specific effects the DES daughter has experienced but states that she has "sustained severe, serious, permanent and personal injuries… and will be unable to pursue normal means of livelihood."

Because the lawsuit is filed in New York, which allows market share suits, the plaintiff does not necessarily need to prove which companies manufactured the specific DES her mother was given.

Instead, if she wins the suit, she would receive damages from each company based on each one's market share at the time her mother was pregnant. -TH

Patsy Mink, a DES Mother Who Went After Pharma

The late Patsy Mink, who represented Hawaii in the US Congress, is the first woman of color to have her portrait hung in the Capitol Building in Washington, DC. It will be unveiled later this month.

Mink worked hard for passage of Title IX to ban sex discrimination from federally funded programs in education, including sports. She was known for her advocacy on women's rights and social justice issues.

But we in the DES-affected community also know Mink as a DES Mother, although she was publicly quiet about it. She was one of three DES Mothers who filed suit in a case from the early 1950s regarding a University of Chicago DES experiment in which women at the hospital's prenatal clinics were randomly given either DES or placebo pills.

These mothers weren't told they were part of a study, they were simply told the medications were "vitamin pills" and part of routine prenatal care. Of course, those given DES, like Mink, often suffered the terrible effects of the drug.

From that research, now called the Diekmann study, it was determined that DES did not prevent miscarriage — although doing research without informed consent is now recognized as being totally unethical.

The lawsuit asked for $77.7 million in damages on behalf of those who filed the suit and 1,078 other women who were given the drug in the DES experiment without being given an opportunity to provide informed consent.

Yet, even when the *Washington Post* wrote an article about the lawsuit in 1977, the paper noted that doctors at that time "have continued to write thousands of prescriptions for [DES] annually even since Dr. Arthur L. Herbst and his associates at Massachusetts General Hospital reported six years ago their discovery of vaginal cancer in DES daughters."

The newspaper was pointing out how much longer doctors kept prescribing DES even though the Food and Drug Administration had "repeatedly warned doctors about the danger and ineffectiveness of DES."

Unfortunately, the case that Mink filed, alongside DES Mothers Phyllis S. Wetherill and Gladys E. Lang of Stonybrook, was dismissed.

Of note is that drug maker Eli Lilly was named in the lawsuit. Even after the study convincingly proved that DES did not work to prevent miscarriage, the pharmaceutical giant continued promoting its use to doctors for their pregnant patients. That corporate greed is why so many of us DES-exposed individuals remain especially angry at Lilly. - Fran Howell

Q&A: Linda Titus, DES Researcher

Those who have followed DES research for years will recognize the name of Linda Titus, PhD, MA, an adjunct professor in the Muskie School of Public Service and a professor emerita of the Geisel School of Medicine at Dartmouth. Professor Titus shared how she came to study DES and where she thinks the field is headed in the future.

What led you to begin studying DES?

Congress allocated funds to the US National Cancer Institute (NCI) for DES research. The NCI investigators offered this funding to institutions where cohorts had been previously assembled and assessed for DES-related health outcomes. The NCI plan was to combine these existing cohorts to create a larger and more powerful study for further follow-up.

Dartmouth was one of the centers where DES-related health effects had been previously studied. I was offered the opportunity to lead Dartmouth's involvement in the NCI project and, as a cancer epidemiologist with a particular interest in women's health, I gratefully accepted.

What do you find most interesting or fascinating about researching DES?

One of the challenges of studying endocrine disruptors is establishing who was exposed and who wasn't. DES is somewhat unique, because exposure, or lack of exposure, was verified through reviews of medical records. Thus, DES serves as an important model of exposure to an endocrine disrupting chemical.

[Editorial note: Most exposures to endocrine disruptors come from foods, cosmetics or pesticides. Therefore the amount and timing of those endocrine exposures can't be so clearly identified.]

DES is also the only known human carcinogen that passes the placental barrier, and thus affected more than one generation. As you know, the health consequences of DES exposure, including infertility, pregnancy complications, and more rarely, clear cell adenocarcinoma (CCA) of the vagina/cervix, were devastating for a proportion of prenatally exposed women.

Scientifically, what intrigues me most about DES exposure is the possibility, supported by laboratory studies of mice, that the health effects of DES may extend to descendant generations that were not directly exposed to this medication.

Intergenerational DES effects, if shown, would have wide implications for other pharmaceutical, occupational, and environmental exposures, perhaps particularly for endocrine disrupting chemicals.

What are some of the most interesting things you've discovered through your research into DES and/or other endocrine disruptors or environmental contaminants?

The most disturbing finding was the apparent excess of ovarian cancers in the DES-exposed granddaughter generation. Our study was small, identifying only three cases, so the association may be a fluke.

Still, it's worrisome, particularly as the cases occurred in very young women, which is consistent with a prenatal mechanism and with CCA occurring at early ages in the prenatally exposed women.

The most intriguing finding is the potential implications for the third generation women, but I was also surprised by previously unknown health effects — moderate/severe cervical intraepithelial neoplasia (the development of abnormal cells in the cervix which can lead to cancer) and early menopause in the prenatally exposed women.

Despite the funding from NCI being halted for the long-term DES study, are you continuing to study DES with other funding?

I'm very fortunate to be working closely with NCI investigators on analyses of data collected in our past studies, and to be involved in a new phase of the DES project involving passive follow-up of our cohorts.

What is most surprising to you, if anything, about the story of DES?

The widespread use of DES in pregnant women — despite an absence of evidence supporting its efficacy — and the near-miss of discovering its connection with CCA are, for me, riveting. In reality, because of the long delay between DES exposure and health outcomes, toxicity trials (which weren't conducted) wouldn't have shown the adverse consequences of DES exposure.

But clinical trials conducted in the early 1950s showed that DES was not effective for its intended purpose — reducing risk of pregnancy complications and losses. Despite the lack of evidence supporting the use of DES, it continued to be prescribed to pregnant women for two more decades.

Equally horrifying, for me, is that the link between prenatal exposure to DES and CCA in young women was nearly overlooked. Boston doctors had noticed and launched an investigation of an "epidemic" of CCA in girls and young women.

However, they did not consider pregnancy exposure to DES in their investigation. Consequently, the mothers of 8 CCA cases and 32 non-cases who were participating in the Boston study were not queried for DES exposure during pregnancy.

The connection between prenatal DES exposure and CCA was discovered only because a mother in New York was convinced the drug she'd been prescribed during pregnancy was responsible for her daughter's cancer, and persuaded her daughter's oncologist to communicate her suspicions to the Boston doctors investigating CCA.

As a consequence of this communication, the Boston doctors queried the mothers about pregnancy exposure to DES, and the link between DES and CCA was discovered. Several months after the Boston study connecting prenatal DES exposure to CCA was published, the US Food and Drug Administration (FDA) issued a bulletin warning against the use of DES in pregnancy.

However, the use of DES in pregnancy was not banned, and obviously, it should have been. It's possible the FDA response was conservative because the published study was small and there was no corroborating evidence. Nevertheless, despite the warning, some physicians continued to prescribe DES to pregnant women.

Has knowing the history of DES influenced the way you feel about the medical industry, physicians, the pharmaceutical industry, government regulation, or any other "industries" or groups?

Yes, it has. Although clinical trial evidence of efficacy is now required before a drug can be FDA-approved for a specific purpose, the DES story strongly illustrates that long-term effects, which won't be seen in clinical trials, may be serious.

Personally, I'm wary of all new pharmaceutical products, particularly those used to treat conditions that are not dangerous. I also think we need to be extremely careful about prescribing drugs to pregnant women; in that scenario, we may harm two generations.

Although this statement is politically charged, I'm particularly wary of obstetric prescriptions. Women have suffered hard lessons twice in the past 70 years — those arising from DES exposure, and the increased risks of endometrial cancer and breast cancer, respectively, associated with estrogens and estrogen-progesterone regimens prescribed to relieve the symptoms of menopause.

My feelings toward "Big Pharma" are mixed. On the whole, we owe a great deal to research and development of new and sometimes life-saving drugs. Are these companies motivated by financial gain? No doubt. But, ultimately, physicians are the interface between pharmaceutical firms and everyday people and are responsible for prescribing safely.

Do you think it's possible for "another DES" to occur in some form in the future with a different drug? Or do you think we've learned the lesons necessary to prevent such a tragedy in the future?

In all likelihood, it has already happened and will continue to happen without being noticed. An investigation into the cause of CCA was launched only because of the striking rareness of this disease in young women.

If a pharmaceutical, occupational or environmental agent [substance] contributes to a health condition that's already common in certain age groups, we may not notice an uptick of that condition; consequently a possible cause will not be investigated. Similarly, if there's a long period of time between exposure to an agent and a related health outcome, it may be challenging to identify the responsible agent.

How do you feel about the funding being cut off for the long-term DES study? What will be lost from the absence of that funding stream?

It was sad to lose the opportunity to continue our long-term follow-up of the second generation (prenatally exposed), and even more so, of the third generation (granddaughters). On the other hand, we accomplished a great deal over 28 years of funding, and for that, I am grateful.

What is your hope for the future as it relates to DES?

I have broad-based hopes for the future relating to DES and other exposures. Within the context of DES, I hope there are no further health effects in the second and third generations, and that the apparent excess of ovarian cancer in the third generation was a fluke.

I also hope we will be more mindful, moving forward, about the risks of introducing new exposures to the public, particularly to pregnant women, and more vigilant when monitoring their possible health effects.

New Study: CCA Risk Remains Higher for DES-Era Women

Clear cell adenocarcinoma was the first condition that researchers discovered was linked to prenatal DES exposure, and it remains the signature adverse effect that many people associate with DES. It is such a clear connection that women diagnosed with CCA are considered DES-exposed, regardless of their medical records.

The many other adverse effects connected to DES since the discovery of the CCA link may have other causes besides DES, but the link between CCA and DES remains the strongest.

When the link between DES and CCA was first found in the 1970s, it was limited primarily to adolescents and younger women, but research since then has suggested the link persists throughout DES Daughters' lifetimes.

A recent study, published this past June, investigated the risk of CCA as DES Daughters continue to age. However, this study took a different approach to studying CCA than previous DES-related studies. (DOI: 10.1007/s10552-022-01598-3.)

Instead of comparing a group of known DES Daughters to known unexposed women, these researchers, led by Mary C. White at the CDC, focused on the eras when women were born.

That is, the researchers compared CCA rates among women born between 1947-1971 — the "DES era" — to women born before 1947. The authors did not look at documentation of DES exposure at all.

The drawback of this approach is that it's not possible to be certain of how many women in the 1947-1971 cohort were exposed to DES. But, in a way, that is also the study's strength.

Since so many women never learned of their DES exposure, a study like this can capture the impact of the drug's effects even among women who never knew—and still perhaps don't know—they were DES Daughters.

CCA is very rare overall, so when a study group of known DES Daughters, such as the NCI's long-term cohort study, is not large enough, it's difficult to detect patterns in diagnoses.

By looking at all CCA cases among all women during the DES era and before, it's more likely that the researchers can detect trends showing increased risks.

Although it differs from most other DES studies, this study is not the first one that compares women born in two different timespans. The authors of this study used the same approach in a study published in 2011, which found a higher incidence of CCA in women born from 1947-1971 than women born before or after this era. (DOI:10.1007/s10552-011-9855-z)

How the Study Was Done

Since this study focused on women at older ages, it only used women born before 1947 as a comparison group. The researchers used two federal databases for their statistics on CCA: the CDC's National Program of Cancer Registries and the National Cancer Institute's Surveillance, Epidemiology and End Results (SEER) Program. Combined, these databases cover nearly the entire U.S. population.

As is expected with the natural course of CCA, rates of the disease did increase with age in women born before 1947—those who would not have been exposed to DES in utero.

However, women born in the DES era, from 1947-1971, had higher rates of CCA at nearly every age group, compared to those born before the DES era. The only age group that did not show a higher CCA risk for those born during the DES era was ages 55-59.

The risk for women in this age group was similar whether they were born when DES was used or before the DES era. Still, "CCA risk appeared to increase among the DES-era birth cohort at ages 60–64 years and 65–69 years," the researchers concluded.

"These additional years of data also increased the size of the observed population at risk," the authors added. They also found elevated risk for those aged 40-44, 45-49, and 50-54, at a similar magnitude as seen in their previous research.

CCA Likely Underestimated

The authors noted several limitations to their study based on information they didn't have access to, but these limitations, if any, simply underestimated how much the risk of CCA likely was.

For example, "we had no information on hysterectomy status, and failure to adjust for hysterectomy status can lead to underestimates of cervical cancer incidence rates," the authors wrote.

Although there could always be other factors that play a role in differences between generational risk of CCA, the authors note that "previous studies of DES-exposed women found no relationship between CCA and oral contraception, pregnancy, or human papillomavirus," so it's unclear what those other factors might be.

The researchers also acknowledge that using only birth year is limiting on its own. An estimated 2-4 million women were exposed to DES, but this is still a small proportion of all the women born between 1947-1971.

"Treating all women born during this period as potentially exposed creates substantial misclassification of expoure and could dilute or mask the true measure of risk among those

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New Study: CCA Risk Remains Higher for DES-Era Women

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women with actual in utero exposure to DES," the authors wrote.

In other words, because they included a large population where most of the women were not exposed to DES, despite being born during that era, the risk of CCA among actual DES Daughters could be substantially higher if the researchers had been able to compare all DES Daughters to all unexposed women. Unfortunately, that's not possible.

Screening Guidelines Still Lacking

The authors reiterated that current cervical cancer screening guidelines and recommendations developed for average-risk women do not apply to those with prenatal DES exposure. Yet recommendations specifically for DES Daughters continue to be lacking since not enough evidence exists to be able to develop evidence-based guidance.

"The National Cancer Institute has noted the absence of published guidelines on medical examinations and screening from major organizations to address the specific needs of older DES daughters," the authors wrote.

While these findings aren't much of a surprise to DES Daughters and others familiar with the history of DES, they remain important since they show the continuation of essential research into DES effects and the importance of continued screening, separate from the US Preventive Services Task Force recommendations for average, unexposed women.

This study also shows that it is possible to continue studying DES effects even without the continuation, for now, of the National Cancer Institute's long-term DES Daughters study.

DES Action USA will continue to reach out to the NIH and our congressional representatives to educate them on the need for funding to continue the previous NCI study as well as other studies that investigate the risks of DES exposure as people age. -TH

New CCA Study in DES Daughters Has Faulty Conclusion

Only one case of DES-related cancer was found in a population of older DES Daughters at a single Boston hospital, according to a new study.

The finding of a single case in those over age 50, and no cases in women older than 65, led the authors to conclude that the additional screening recommendations for DES Daughters might be able to be reduced.

A closer look at the study, however, reveals flaws that contradict this conclusion. The research was published in the Journal of Lower Genital Tract Disease. (Doi: 10.1097/LGT.0000000000000713.)

The researchers examined 503 medical charts of women with confirmed DES exposure who had been seen at least twice between 2000-2019 at Beth Israel Deaconess Medical Center in Boston.

Of these women, 28 had gynecologic cancer, including 10 with cervical cancer and one with vaginal cancer. One patient over 50 years old developed a DES-related cancer while no patients over age 65 did.

The researchers concluded that "DES-related gynecological malignancy after age 50 years was rare" and that this rarity can "inform changes in screening guidelines for patients exposed to DES in utero."

The authors noted that current recommendations advise DES Daughters to have lifetime annual vaginal and cervical cytology, even past age 65, but they appear to question whether these recommendations are appropriate, using their data to "[suggest] that screening recommendations could be changed for these patients to align with current screening guidelines" [for all women].

There are two major problems with this conclusion. First, the authors note early in their study that the risk of CCA is approximately 1 in 750 to 1 in 1,000 for DES Daughters under age 50.

Yet this study only includes 503 women. A single case of DES-caused cancer in such a small population falls within that statistic, suggesting that the risk in DES Daughters over age 50 is at least the same as that in Daughters under 50.

The researchers then conclude that women over age 65 don't have an increased risk since they found no cancers in this group. But of the study's 503 women, only 49 were over age 65.

That's not nearly enough women over age 65 to conclude anything about the risk of DES-related cancer. A larger study of DES Daughters over 65 might find many more cases.

Another red flag in the study is a statement that "In DES-exposed patients, the incidence of cancer peaks at age 20 and then decreases after age 30 years."

The three cited studies for this statement were published in 1977, 1979, and 1987. DES was given to women over more than three decades, from 1940 until at least 1971, and many doctors continued to give it out after 1971.

By 1987, about a third of DES Daughters hadn't even turned 30 yet, so no research published through that date can claim that incidence of CCA drops after age 30.

Though it's good to see individual hospitals conducting research related to DES Daughters, this study only confirms the need for larger, better-quality studies to continue in large populations of DES Daughters. -TH

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Did DES Cause MRKH? No, It Can't.

Most people probably haven't heard of Mayer-Rokitansky-Küster-Hauser (MRKH) syndrome, a developmental disorder of the female reproductive system, but it shares some similar effects as DES exposure, such as a higher risk of infertility and an abnormal uterus.

Further, a 2020 study found that three of 12 DES Granddaughters with uterine defects had MRKH—about 20 times more than expected in the general population.

That raises the question of whether DES exposure could cause MRKH, but a research letter in the journal Therapies explains why that's not possible. (doi: 10.1016/j.therap.2022.02.003)

MRKH affects approximately 1 in 4,500 women, but it's the second most common cause of never getting a period, after other atypical development of the sex organs. The main sign of MRKH is an underdeveloped or missing uterus, upper vagina and sometimes Fallopian tubes.

MRKH effects occur early in embryonic development and are not affected by estrogen or other hormone levels. The defects caused by DES, on the other hand, such as a T-shaped uterus, involve a different set of genes that act at a later stage of fetal development, after the initial development of any uterus or vagina at all.

Since MRKH effects occur before the effects of DES can occur and involve a completely different set of non-hormone-related mechanisms, it's not possible for DES exposure to cause MRKH.

In DES Granddaughters, the genital birth defects in the study with three MRKH cases are similar to those that occur in the general population and, except MRKH, occurred about as often as in the general population.

It's unlikely that the epigenetic effects of DES exposure are responsible for those MRKH cases, the researchers write, because they would expect to find far more MRKH cases among Third Generation women in general.

The authors leave open the possibility, however, that genital defects in the Third Generation more broadly could be occurring, especially given the increased incidence of hypospadias in DES Grandsons, where the opening in the penis is located along the shaft instead of at the tip.

So far, then, the evidence does not show a link between DES exposure and MRKH in DES Daughters or Granddaughters. - TH