

Isotretinoin (Accutane) as a Teratogen ^[1]

By: Tantibanchachai, Chanapa Keywords: [Birth defects](#) ^[2] [Accutane](#) ^[3] [Hoffman-La Roche](#) ^[4]

Isotretinoin is a molecule and a byproduct (metabolite) of vitamin A, and in greater than normal amounts in pregnant women, it can cause fetal abnormalities including cleft lips, ear and eye defects, and mental [retardation](#) ^[5]. Isotretinoin is commonly called by its trade name Accutane, and it's a chemical compound derived from vitamin A, also called retinoic acid. Doctors prescribe isotretinoin to treat severe acne. For pregnant women, too much vitamin A or isotretinoin can also cause greater than normal rates of stillbirths and fetal disintegrations after the ninth week of [gestation](#) ^[6]. Women who use isotretinoin during the first [trimester](#) ^[7] of their pregnancies, even in small amounts, risk defects to their fetuses such as external ear malformations, cleft palates, undersized jaws (micrognathia), a variety of heart defects, buildups of fluids inside the skulls that leads to brain swelling ([hydrocephalus](#) ^[8]), small heads and brains ([microcephaly](#) ^[9]), and mental [retardation](#) ^[5].

Derivatives of vitamin A, called retinoids, function in proper embryonic development. With insufficient vitamin A, embryos fail to segment and grow, blood vessels fail to form, and the embryo is ultimately lost. Retinoids are involved in the expression of [Hox genes](#) ^[10], which function in signaling pathways that regulate the patterning of embryonic structures during the fourth week of development. However, embryos exposed to excess vitamin A have higher than normal amounts of retinoids, and their [Hox genes](#) ^[10] malfunction, disrupting genetic control of body shape (axial patterning) during the embryo's development. Such disruptions can lead to developmental defects, particularly in the embryonic spinal cord, [central nervous system](#) ^[11], and spinal cord, where retinoic acid synthesizes and where catabolic enzymes are located.

Researchers have studied the ability of large doses of vitamin A to cause [birth defects](#) ^[12], or teratogenicity, since the 1950s. In 1953 Sidney Q. Cohan, a researcher at the Beth Israel Hospital in New York City, New York, published research reporting the effects of excessive maternal vitamin A intake on newborn rats. Werner Bollag initially studied isotretinoin for the treatment of skin cancer at the Department of Experimental Medicine, Hoffman-La Roche laboratories in Basel, Switzerland, in the 1960s. In 1971, Bollag discovered the compound's ability to treat acne, but with isotretinoin's lack of effect in cancer treatments, Bollag abandoned it as a pharmaceutical.

In 1975 the Gary Peck and Frank Yoder in the US rediscovered isotretinoin's therapeutic effects for the treatment of cystic acne, a severe form of acne that causes inflammation deep below the skin's surface. Hoffman-La Roche registered isotretinoin as Accutane with the US [Food and Drug Administration](#) ^[13] (FDA) in Maryland in 1979, and they began marketing it as a prescription drug in 1982. The FDA recognized isotretinoin as teratogen before it was first marketed in 1982, and classified isotretinoin as a Category X drug. Category X, considered the most severe on the FDA's list of assigned [pregnancy](#) ^[14] categories, includes drugs for which studies in animals or [humans](#) ^[15] have displayed fetal abnormalities and that the use of the drug by pregnant women clearly outweighs any potential benefits.

In June 1983 doctors in New Jersey reported to the FDA the first incidence of human teratogenicity, or agent-caused developmental [birth defects](#) ^[12], linked to Accutane. The drug had been on the market for acne treatment for nine months. That same month, two additional cases were reported to the FDA. In August of 1983, Franz Rosa, working for the US FDA in Maryland, published an article describing twelve Accutane-related cases of embryotoxicity. In response, Hoffman-La Roche distributed red warning stickers to pharmacies for Accutane containers and revised Accutane's drug label to include more information about the possibility of [birth defects](#) ^[12]. The label was revised a second time in September 1983 when Public Citizen, an advocacy [organization](#) ^[16] in Washington, D.C., petitioned the FDA to require inserts in Accutane bottles explaining the possible side effects. The FDA denied Public Citizen's request.

Doctors prescribed Accutane to 400,000 patients within its first eighteen months of marketing, and by early 1984, Hoffman-La Roche received reports of twenty Accutane-affected infants. The reports prompted the FDA's Dermatologic Drugs Advisory Committee to address the issue. On 11 February 1988, based on an estimate that anywhere from 900 to 1,300 infants had been affected by Accutane in the US, several members of the committee urged that Accutane be removed from the market. The FDA, however, acknowledged only sixty-two reports of affected babies. One month later, the US Centers for Disease Control (CDC), headquartered in Atlanta, Georgia, released a report highlighting four New Jersey cases of babies exposed to Accutane prior to birth. All four babies were born with severe [birth defects](#) ^[12]. This report pushed the FDA to schedule a meeting with the Dermatologic Drugs Advisory Committee that spring.

At the FDA's Dermatologic Drugs Advisory Committee meeting in 1988, some argued that Accutane should remain available as an acne treatment due to its exceptional efficacy and short treatment duration of fifteen to twenty weeks. The committee voted four-to-three to allow Accutane to remain on the market with restricted access. A month later, the FDA announced that it would not follow the committee's recommendation to restrict the drug and instead issued new label warnings.

In October 1988 the FDA's required that Hoffman-La Roche implement a Pregnancy Prevention Program (PPP) for Accutane. The PPP informed patients about the risks and benefits associated with isotretinoin, assisted physicians in complying with the package insert requirements, and evaluated a patient's ability to adhere to the requirement of not being or becoming pregnant one month before, during the course of, or one month after therapy. The PPP protocol required that women use two forms of effective contraceptive during therapy, follow-up with officials through phone calls and questionnaires, and that they be offered reimbursement for contraceptive counseling and [pregnancy](#)^[14] testing.

Throughout the 1990s, Hoffman-La Roche struggled with the consequences of Accutane's teratogenicity, and the company became involved in several court cases in Ohio and New Jersey about Accutane's teratogenicity. Of these cases, a number involved documents that allegedly indicated Hoffman-La Roche's negligence. In one case, Hoffman-La Roche sued Frank Yoder, the co-discoverer of Accutane's therapeutic effects, for his attempt to threaten the company into purchasing his private collection of documents, which according to Yoder, dealt with "the development, use, and misuse of isotretinoin (Accutane)."

In another case, Thelma and Marvin Louis Hammocks sued Hoffman-La Roche in 1995 for their son Marvin Louis Jr.'s Accutane-induced [birth defects](#)^[12]. After the case was settled, Hoffman-La Roche requested that the documents obtained by the Hammocks during discovery be sealed. Public Citizen challenged the court's decision to seal the documents. Eventually, the New Jersey Supreme Court concluded that based on the policy of public access to information about health, safety, and welfare, the documents should be released. On 9 May 1996, the documents were officially unsealed.

The documents, however, did not provide the conclusive evidence that Public Citizen had expected; records showed that within a year of releasing the drug to the market, the company became anxious about Accutane and its related [birth defects](#)^[12], and that the first documented Accutane baby was born on 29 April 1983. Although Yoder and Public Citizen failed to provide evidence that Hoffman-La Roche indeed withheld information from the FDA and researchers in the US, the three aforementioned cases prompted some to question Hoffman-La Roche's behavior, including the company's initial proposal to give Accutane a [pregnancy](#)^[14] risk rating of category C, meaning that the drug adversely affects fetuses, but that the benefits of the drug outweigh the risks for [humans](#)^[15].

The FDA instituted a program on 1 March 2006 called iPLEDGE as a way to allow patients to use isotretinoin, an otherwise safe and effective drug. US patients using Accutane must enroll in this risk management program designed to prevent fetal exposure to isotretinoin. Physicians and pharmacies must enroll in the program before they may prescribe or dispense isotretinoin. For a woman to receive isotretinoin, iPLEDGE requires that she must use two forms of [contraception](#)^[17], submit a negative [pregnancy](#)^[14] test to her physician each month over the course of her therapy, answer questions about iPLEDGE each month before receiving her prescription via the online iPLEDGE system, and pick up her prescription within a seven-day window. During the first year of the program, 122 women on isotretinoin became pregnant, about the same number of pregnancies as the year prior. However, much fewer patients were treated with isotretinoin.

Since its release, Accutane has been prescribed to approximately five million people nationwide and twelve million worldwide, with eighty-five percent of all treated patients achieving complete elimination of acne after a course of therapy. Although the risks associated with isotretinoin remain, and fetal exposure to the drug has not been completely eliminated.

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[Teratogenic agents](#) ^[29] [Vitamin A](#) ^[30] [Isotretinoin](#) ^[31] [Abnormalities, Human](#) ^[32] [Isotretinoin](#) ^[33] [Teratogens](#) ^[34]

Topic

[Reproduction](#) ^[35] [Disorders](#) ^[36]

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- [1] <https://embryo.asu.edu/pages/isotretinoin-accutane-teratogen>
- [2] <https://embryo.asu.edu/keywords/birth-defects>
- [3] <https://embryo.asu.edu/keywords/accutane>
- [4] <https://embryo.asu.edu/keywords/hoffman-la-roche>
- [5] <https://embryo.asu.edu/search?text=retardation>
- [6] <https://embryo.asu.edu/search?text=gestation>
- [7] <https://embryo.asu.edu/search?text=trimester>
- [8] <https://embryo.asu.edu/search?text=hydrocephalus>
- [9] <https://embryo.asu.edu/search?text=microcephaly>
- [10] <https://embryo.asu.edu/search?text=genes>
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- [12] <https://embryo.asu.edu/search?text=birth%20defects>
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- [14] <https://embryo.asu.edu/search?text=pregnancy>
- [15] <https://embryo.asu.edu/search?text=humans>
- [16] <https://embryo.asu.edu/search?text=organization>
- [17] <https://embryo.asu.edu/search?text=contraception>
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- [33] <https://embryo.asu.edu/medical-subject-headings/isotretinoin>
- [34] <https://embryo.asu.edu/medical-subject-headings/teratogens>
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