

In the Supreme Court of Florida

CASE NO. SC00-490

JOHN CASTILLO, a minor by and
through his mother, next friend and
natural guardian, DONNA CASTILLO, and
DONNA CASTILLO and JUAN CASTILLO, individually,

Petitioners,

v.

E.I. DU PONT DE NEMOURS and COMPANY, INC.,
and PINE ISLAND FARMS, INC.,

Respondents.

ON DISCRETIONARY REVIEW FROM THE
THIRD DISTRICT COURT OF APPEAL

PETITIONERS' BRIEF ON THE MERITS

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CERTIFICATE OF TYPE SIZE AND STYLE

Petitioners are utilizing a fourteen (14) point Roman Regular font in this brief.

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STATEMENT OF THE CASE

A. Nature of the case and course of proceedings

This suit was brought by the Plaintiffs/Petitioners Donna and Juan Castillo ("Plaintiffs") claiming the damages sustained by their family as a result of their son John being born with the birth defect of microphthalmia due to his mother's exposure during pregnancy to a DuPont chemical fungicide called Benlate. (R. Vol. I, pp. 2-14).¹ Microphthalmia, and the closely related defect of anophthalmia, are conditions where a fetus fails to develop the eye organ properly and the baby is thus born without eyes. (R. Vol. I, pp. 2-14).

Plaintiffs' suit alleged that Defendant/Respondent DuPont negligently manufactured and distributed Benlate, an unreasonably dangerous and defective product due to its harmful capacity for causing birth defects. (R. Vol. I, pp. 2-13; 34-47). Plaintiffs also sued Defendant/Respondent Pine Island Farms for negligently spraying Benlate on its fields during periods of strong wind currents, thus allowing the chemical to blow into nearby

¹References to the record appear as (R. Vol. __, p. __), and references to the trial transcript appear as (T. Vol. __, p. __). All emphasis in this brief is supplied unless otherwise stated.

residential and shopping areas where people could be exposed to its harmful properties. (R. Vol. I, pp. 34-47).

After an extended period of discovery, the case was eventually scheduled for a jury trial in May of 1996. (R. Vol. XLIII-LXXXVIII). Upon motion of the Defendants, the trial court held an extended evidentiary *Frye*² hearing to resolve a motion in limine filed by the Defendants seeking to exclude the testimony of Plaintiff's expert. (T. Vol. XLV, XLVI, XLVII; S.R. 1-69). Concluding that the methodology employed by Plaintiff's expert for reaching his conclusions was that commonly and generally accepted in the relevant scientific fields, the trial court denied the defense motion in limine and the case proceeded to trial. (T. Vol. XLV, XLVI, XLVII; S.R. 1-69).

The trial lasted over a month and resulted in a jury verdict for the Plaintiffs against both Defendants. (T. Vol. LXXXIX, pp. 5573-5576). The jury awarded Plaintiffs damages in the combined amount of \$4,000,000 (T. Vol. LXXXIX, pp. 5573-5576).

B. Disposition in the lower tribunals and the petition for discretionary review by this Court

The Third District reversed and remanded for entry of judgment in favor of Defendants DuPont and Pine Island, ruling - erroneously, we contend - that (1) "the [P]laintiffs' scientific evidence, and the conclusions it embraces, should have been excluded"; and (2) while the Plaintiffs had sufficiently proven that Plaintiff Donna Castillo and her unborn child had been exposed to Benlate as to Defendant Pine Island because Pine

²*Frye v. United States*, 293 F. 1013 (D.C. Cir. 1923).

Island admitted that it was using Benlate on the field and time in question, Plaintiffs' proof of exposure was not sufficient as to Defendant DuPont. Plaintiffs thereupon sought discretionary review from this Court as Plaintiffs believe that the Third District misapplied the *Frye* test, as refined by this Court in *Ramirez v. State*, 651 So. 2d 1164 (Fla. 1995). Plaintiffs submit that the Third District's opinion incorrectly focused on the *conclusions* drawn by the Plaintiffs' experts rather than on the underlying scientific principles and methodologies they employed, which in fact were identical to those employed by the Defendants' own trial experts and, for that matter, by DuPont itself in obtaining approval to market Benlate. The opinion thus conflicts with *Brim v. State*, 695 So. 2d 268 (Fla. 1997) and *Berry v. CSX Transportation, Inc.* 709 So. 2d 552 (Fla. 1st DCA) *rev. denied*, 718 So. 2d 167 (1998), which acknowledge that "*Frye* allows opposite opinion testimony from experts relying upon the same generally accepted scientific principles and methodologies." *Berry*, 709 So. 2d at 567. *See also Brim*, 695 So. 2d at 269. Plaintiffs also contend that the Third District erred as a matter of law when it concluded that the Plaintiffs' evidence was sufficient to prove that the chemical spray to which Donna Castillo was exposed was Benlate in the case against Pine Island but not sufficient as to DuPont.

This Court issued an order accepting jurisdiction and directing the parties to brief the merits of the case, and these proceedings ensued.

STATEMENT OF THE FACTS

A. General facts on the issue of Benlate as a teratogen that caused John Castillo's microphthalmia

1. The evidence about the exposure and eventual discovery of the potential link between Benlate and John Castillo's birth defect

In 1989, Plaintiffs Juan and Donna Castillo and their 6-month old daughter Adriana were living in an apartment complex in Kendall, Florida. (T. Vol. LVI, p. 883). The complex was near a shopping plaza, across from which lay a strawberry and tomato U-Pic field operated by Pine Island Farms. (T. Vol. LVI, p. 904).

Sometime late in September of 1989, Mrs. Castillo became pregnant with her second child. (T. Vol. LVI, p. 932, T. Vol. LXVI, p. 2115). During her pregnancy, Mrs. Castillo took daily walks with her first child, Adriana, for exercise and as an outing for the child, and they often walked past the Pine Island U-Pic field on 137th Avenue. (T. Vol. LVI, p. 901).

One day while walking past the field, Mrs. Castillo was showered by a mist from the spray operations carried by wind drift. (T. Vol. LVI, p. 909). It was a warmish day in early November of 1989, and Mrs. Castillo, wearing a sleeveless blouse and shorts, felt the mist from the spray operation envelop her and wet her skin with what first seemed to her "like a sun shower." (T. Vol. LVI, pp. 905-911). The mist was cloudy white in color and did not have any odor. (T. Vol. LVI, pp. 908-911). The incident occurred on November 1st or 2nd of 1989. (T. Vol. LVI, pp. 905-906).

At the time, Mrs. Castillo was between the sixth and seventh weeks of pregnancy with her son-to-be John. (T. Vol. LVI, p. 932; Vol. LXVI, p. 2215). That sixth-to-seventh week time period is the critical stage during the growth of the human fetus for the development of eyes. (T. Vol. LXX, p. 2989; T. Vol. LXXI, p. 3004). When John was born in June of 1990, he had no eyes, a birth defect that her physician told her was referred to as microphthalmia. (T. Vol. LVI, p. 889). Physicians were able to pinpoint October 23 through November 5, 1989 as the time frame during which the arrest in development of John's eyes occurred, which was precisely the time Mrs. Castillo was misted by the wind-carried spray from the spray operations at the Pine Island U-Pic field. (T. Vol. LXXI, p. 3004).

The Castillos went to doctors and geneticists to see if some reason could be determined for John's birth defect, and to ascertain whether some genetic defect in either of their families should affect their decisions as to having other children in the future. (T. Vol. LVI, pp. 895-899, 1013; Vol. LXXIX, pp. 4083, 4093-4094). Every physician and doctor who testified in this case - including *all* of the expert witnesses for all parties - were in agreement that the Castillo family was subjected to the full battery of all available genetic tests and assessments, and that the test results showed that there was no known genetic cause for John's microphthalmia. (T. Vol. LXXII, pp. 3063-3064; R. Vol. XL, pp. 7970-7971).

With all known genetic causes ruled out, John's microphthalmia could only have been caused by an environmental agent, i.e., something to which his mother was exposed during pregnancy, or by a genetic defect of some type as yet unknown and undiscovered to science. (T. Vol. LXXXIV, pp. 4958-4962; R. Vol. XL, pp. 8131-8145). As to the environmental teratogens, it was determined - and the defense experts conceded - that all such environmental teratogens that are commonly encountered - such as Rubella, Vitamin A, PCB's, smoking, etc. - were ruled out in Donna Castillo's case. (T. Vol. LXXXIV, pp. 4958-4962; R. Vol. XL, p. 8142).

Elsewhere, in England, *The London Observer* newspaper happened to have undertaken an investigation in the early 1990's of a phenomenon which had been noticed in Great Britain consisting of an unusual number of cases of children being born without eyes. (T. Vol. LXI, pp. 1582-1583). Benlate was being investigated as a possible cause as the families of the afflicted children lived in the vicinity of farms where Benlate was being sprayed. (T. Vol. LXI, pp. 1586, 1624). The researchers for *The London Observer* initially investigated the cases in Great Britain, and then expanded their research beyond England to the United States and elsewhere. (T. Vol. LXI, p. 1584). They contacted medical authorities, educational authorities, and organizations concerned with the welfare of visually-impaired children seeking to get in touch with parents of children with microphthalmia and anophthalmia. (T. Vol. LXI, p. 1584).

In April or May of 1993, Donna Castillo was contacted by *London Observer* reporters John Ashton and John McGee, in the course of their investigation of the connection between Benlate and children with anophthalmia and microphthalmia. (T. Vol. LVI, pp. 917-918; T. Vol. LXI, pp. 1583-1586). In response to a series of questions asked her by the reporters in the course of her conversations with them, Mrs. Castillo told them about the U-Pic field in her neighborhood and her daily walks past it during her pregnancy. (T. Vol. LVI, pp. 917-918; T. Vol. LXI, pp. 1584-1586). On the basis of the information Mrs. Castillo provided, the reporters made a series of telephone calls and tracked down one Lynn Chaffin, the vice-president of Pine Island Farms, the farming company which operated this particular field as a U-Pic field in addition to larger commercial field operations it had throughout Kendall and Homestead. (T. Vol. LXI, pp. 1586-1592; T. Vol. LXVIII, pp. 2595-2598). Reporter Ashton called Chaffin by telephone from London, and, during the conversation, Chaffin told Ashton that Pine Island had used Benlate products up until 1991, and specifically told Ashton that Pine Island had used Benlate on the U-Pic field in question in November of 1989. (T. Vol. LXI, pp. 1592-1602, 1627).

Benlate, as it turns out, is a known teratogen - a fact which appears without dispute in this record and which has been specifically conceded by DuPont. (R. Vol. XV, p. 3136; R. Vol. XL, p. 7978; T. Vol. LXVII, pp. 2396-2402). Indeed, DuPont had little choice but to make the concession because DuPont's own rat studies of Benlate proved that it is a

teratogen, and, more significantly for purposes of this case, the DuPont studies specifically proved that a main birth defect caused by Benlate is the rare defect of microphthalmia. (T. Vol. LXVII, pp. 2384-2385, 2396-2418). DuPont's response in this litigation has simply been to take the position that there is no "proof" that Benlate is a *human* teratogen. In any event, other scientists have also performed animal studies which repeatedly confirmed Benlate's teratogenic effects including its causation of microphthalmia and anophthalmia.³

³See, e.g., E. Hoogenboom, et al: Effects on the fetal rat eye of maternal benomyl exposure and protein malnutrition, *Current Eye Research*, June 14, 1991; Hoogenboom E., et al: Effects of benomyl exposure and protein deficiency on the fetal rat eye. *Teratology* 37:465, 1988; F. Zeman, et al: Effects on the fetus of maternal benomyl exposure in the protein-deprived rat, *J. Toxicol Environ Health* 17:405-17, 1986; Developmental Toxicity Study of H-15647 Administered via Gavage to New Zealand White Rabbits, Angus Research Laboratories, Inc., July 3, 1985; S. Carter: Effect of benomyl on the reproductive development of male rats. Kavlock, R., Chernoff, N., U.S. Environmental Protection Agency, et al: Teratogenic effects of benomyl in the wistar rat and CD-1 Mouse, with emphasis on the route of administration, *Toxicology and Applied Pharmacology*, 1981; *J Toxicol Environ Health* 13:53-68, 1984; R. Culik, Senior Research Teratologist, Haskell Laboratory for Toxicology, Determination of Benomyl/Methyl-2-Benzimidazole Carbamate (MBC) Concentrations in Maternal Blood and in the Concepti of Rats Exposed to Benomyl and Benlate® by Diet, January 29, 1981; R.E. Staples, Study Director Staff Teratologist: Benomyl: Teratogenicity in the rat after administration by gavage, September 18, 1980.

In any event, to recap the evidence that led Plaintiffs to seek further information from scientific studies and from experts as to whether Benlate could have been the cause of their son's microphthalmia was: (1) John Castillo was born with microphthalmia; (2) there was no known genetic cause for his microphthalmia, leaving an overwhelming probability that the cause was an environmental exposure of his mother to a teratogen during the sixth to seventh week of her pregnancy when eyes begin to develop in the fetus; (3) all of the most common environmental teratogens had been ruled out in Mrs. Castillo's case; (4) Mrs. Castillo had in fact experienced an exposure incident during the sixth to seventh week of her pregnancy; (5) according to the information provided by Pine Island Farms, the chemical to which she was exposed was the fungicide Benlate; (6) Benlate is a known and proven teratogen as shown by DuPont's own rat studies; and (7) a specific teratogenic effect of Benlate is the generally very rare birth defect of microphthalmia. (T. Vol. LVI, p. 889; T. Vol. LXX, pp. 2980-2961; T. Vol. XLVII, p. 77; R. Vol. XL, pp. 7978, 8085).

2. The scientific evidence about Benlate's ability to reach a human fetus and to interfere with the normal development of its organs

As with any suspected link between a chemical and a birth defect, it must be determined whether the chemical could *reach* the fetus in an amount sufficient to cause the adverse effect. (T. Vol. LXX, pp. 2960-2962; T. Vol. LXXXIV, p. 4977). Here too DuPont's own studies were instrumental in providing the answers, as were studies by other scientists. (T. Vol. LXX, pp. 2962-2963; T. Vol. LXX, pp. 2972-2976).

Studies by DuPont's European affiliate ICI have shown - and it was undisputed among all the experts for all parties in the case - that where there has been a dermal exposure to Benlate, i.e., where the skin has been wetted or sprayed with Benlate, *the Benlate can travel through the skin and into the bloodstream*. (T. Vol. LXXXIV, p. 5018; T. Vol. LXX, pp. 2962-2963; T. Vol. LXX, pp. 2972-2976; R. Vol. XL, p. 7983). Once in the bloodstream, the active ingredient in Benlate - benomyl - is pumped through the circulatory system and, in the case of a pregnant mother, will travel through the mother's circulatory system into the placenta whereupon it reaches the fetal circulatory system. (T. Vol. LXX, pp. 2960, 2972-2976). Once there, the benomyl remains in the fetus' small circulatory system, and it is there, as the DuPont rat studies showed, that it works its teratogenic effects. (T. Vol. LXX, pp. 2972-2976; T. Vol. LXXXIV, p. 4977). The reason the fetus is affected while the mother is not is that an adult liver is able to break down and detoxify the benomyl, but the fetus' liver at this early stage is underdeveloped and unable to detoxify the chemical. (T. Vol. LXX, pp. 2973-2974).

Benlate is a fungicide, a product whose intended purpose is to interfere with or destroy the tubulins - or microtubules - which form fungus. (R. Vol. XL, p. 8149). This fact is significant because fetal growth from fertilized egg into human form with limbs and organs is dependent on functions that must be performed by developed and fully functional tubulins, which are referred to as neurites in the context of the fetal development process (T. Vol. LXX, pp. 2977-2979), as set forth next. The background information provided on

this subject of fetal development is common scientific knowledge, and nothing about this portion of the case was in dispute during the case or trial. (*R. passim*).

The development of a fetus into human form occurs by a process of cell division where cells divide rapidly, resulting in a great over-profusion of cells from which the body's limbs, organs, and systems will be formed. (T. Vol. LXX, pp. 2977-2979). From the plenitude of cells, certain cells are selected as the formative cells by a communication process that takes place among the cells via the hairlike tubulins, or neurites, which reach out and signal certain of the cells to assemble to become the eye, or liver, or other organ. (T. Vol. LXX, pp. 2977-2979). During the process, a specific time comes when the formative cells select, through use of the neurite connectors, the requisite number of additional cells for formation of a particular organ - like the eye - and the remaining, unselected cells from the over-profusion then undergo apoptosis, or self-programmed cell death. (T. Vol. LXX, pp. 2977-2978). Since the unselected cells are no longer necessary for organ formation, they initiate their own demise, fall away, and make themselves otherwise useful for the developing fetus by becoming nutrients. (T. Vol. LXX, pp. 2977-2978).

The effect of Benlate on this process - keeping in mind that its intended purpose is to break down fungus tubulins - is that when it has reached the fetal circulatory system such that it can come in contact with the fetus' organ formation process, it works the same effect on the fetal cell microtubules, or neurites, as on fungus tubulins. (T. Vol. LXX, pp. 2981-

2993). As the growth of the cells' neurites is interfered with or halted by the Benlate, the neurites are unable to connect with a sufficient number of formative cells at the appropriate time in the organ development process. (T. Vol. LXX, pp. 2981-2992). Having received no communication via neurite at the appropriate time, *no* cells have been "told" that they were selected as formative cells for the organ, so they *all* initiate apoptosis, i.e., self-programmed cell death, leaving the organ unformed and unable to form. (T. Vol. LXX, pp. 2981-2992).

In sum, if neurites or tubulins are interfered with or destroyed at a critical point in the development of the fetal eyes, for example, the cells have no ability to communicate and no eye organ is ever formed. (T. Vol. LXX, pp. 2981-2992). So, while Benlate's ability to destroy or interfere with the formation of tubulins is useful in preventing the development of fungus on plants, it is this same mechanism by which Benlate is able to interfere with the development of eyes.⁴ (T. Vol. LXX, pp. 2981-2982).

The final determination that was necessary was whether the amount of Benlate to which Mrs. Castillo had been exposed was sufficient to reach the fetus she was carrying and interfere with the cell division and selection process then ongoing within the fetus to

⁴Benlate can have the same effect on other organs and the animal studies show that it can cause multiple malformations - sometimes singly and sometimes in combination.

develop the baby's eyes. The evidence - again principally from DuPont's own studies - showed that it was.

In the DuPont *human dermal testing*, in which Benlate was being tested for its ability to pass through human skin and into the bloodstream, Benlate was applied to skin taken freshly from female post-mortem specimens (T. Vol. LXX, p. 2964) at a rate of 20 microliters per square centimeter of skin. (T. Vol. LXXI, pp. 3013-3017). The dermal studies established - as Defendants' experts have conceded - that 10% to 15% of the active ingredient in Benlate, i.e., benomyl, travels through the skin and into the bloodstream. (T. Vol. XLVII, pp. 93-94; R. Vol. XL, p. 7983).

In 1980, Dr. Staples, DuPont's Study Director and Staff Teratologist - who was later branded a 'Lone Ranger' at DuPont for being honest in reporting his initial testing results - performed rat studies using benomyl. (T. Vol. LXVII, pp. 2412-2420). To DuPont's dismay, Dr. Staples' tests showed that rat babies were being born with microphthalmia and anophthalmia at the extremely low Benlate dose to their mothers of 10 milligrams per kilogram of body weight per day. (T. Vol. LXVII, pp. 2358-2538). With these results, the EPA decided that warnings should be issued to pregnant women advising of the potential teratogenic properties of Benlate. (T. Vol. LXVII, pp. 2424-2425; T. LXXVI, pp. 3712-3720). DuPont thus had Dr. Staples redo the study - letting Dr. Staples know its "opinion that the 10 [milligrams per kilogram per day] shouldn't be called." (T. Vol. LXVII, p. 2430).

Dr. Staples thus re-did the study and report and republished it in 1982, this time reporting that the first level at which Benlate had an effect was 62.5 milligrams per kilogram per day and the no effect level was reported at 30 milligrams per kilogram a day. (T. Vol. LXVII, pp. 2412-2432). With the new DuPont test 'results', the EPA withdrew its stated intention to require a warning. (T. Vol. LXVII, pp. 2412-2432). When the 1980 Staples study was later summarized along with other DuPont studies, it had been altered to reflect a no-effect level of 30 milligrams per kilogram per day and a low effect level of 62.5 milligrams per kilogram per day, when that was neither what Dr. Staples' study had shown nor what it had reported. (T. Vol. LXVII, pp. 2523-2526). Dr. Staples "could not explain" that. (T. Vol. LXX, p. 2525).

Dr. Van Velzen, an expert for Plaintiffs whose testimony was never challenged by DuPont in its *Frye* motion in limine (T. Vol. XLV. p. 113), performed *in vitro* testing with Benlate, as did DuPont itself. (T. Vol. LXXIII, p. 3248). Dr. Van Velzen is a diagnostic pediatric and fetal pathologist and Professor of Pediatric Pathology at Dalhousie University in Halifax, Nova Scotia, who has been practicing in teratology for the past 17 years, and he explained *in vitro* testing for the jury:

An *in vitro* test is any test that is done using biologically living things. For example, if bacteria that you have in your lungs needed to be studied to see which drug would kill them to help treat you, you put the bacteria in a petri dish, you add the drug and you watch the bacteria - die or not. That is an *in vitro* test. The word means glass.

So any test that is done in the little glass dish or plastic dish is called an *in vitro* test, and *in vitro* tests can use cells or parts of body or whole pieces of skin or a slice of lung or whatever. As long as it is done in a dish, that is called *in vitro* and it uses live cells.

(T. Vol. LXXIII, pp. 3242-3249; T. Vol. XLV, pp. 117-118). Dr. Van Velzen's *in vitro* testing was performed using human fetal cells to determine the lowest concentration of benomyl that would induce apoptosis, or cell death as described above. (T. Vol. LXXIII, pp. 3248-3257). As Dr. Van Velzen explained, his tests - like all *in vitro* testing - were concerned with studying effects at the cell level; that is, by whatever route a chemical like Benlate reaches the cells, the level of concentration at which it will cause cell death:

A. ***I'm only interested in this study once it gets there, how much do you need in the tissue fluid to cause too many cells to die.*** And that is what I studied [with Benlate] and my findings were 20 ppb [parts per billion].

(T. Vol. LXXIII, pp. 3253-3254).

Plaintiffs' expert Dr. Howard, a fetal toxico-pathologist, also did *in vitro* testing on Benlate, but his testing was designed to study the level at which Benlate would - not cause cell *death* - but interfere with the ability of neurites (the cell's tubulins) to grow and perform their intended function as communicators. (T. Vol. LXX, pp. 2980-2983). Dr. Howard described his and other similar studies of Benlate's effect on neurites, which showed that at concentrations as low as 3 parts per billion Benlate could inhibit neurite growth. (T. Vol. LXX, pp. 2979-2983). Dr. Van Velzen's tests looked at the final step of at what point actual cell death or apoptosis would be induced, while the studies done and described by

Dr. Howard looked at neurite retraction or disturbance of neurite growth and ability to function. (T. Vol. LXX, pp. 2979-2983; Vol. LXXIII, pp. 3253-3254). Dr. Van Velzen explained the difference between his cell death study and Dr. Howard's neurite retraction studies:

Well, the neurite retraction study essentially is looking for effect while the cells are still alive. It looks for a disturbance of function. I'm one level of pathology over that. I'm looking for cell death.

(T. Vol. LXXIII, pp. 3254-3255).

Given the results from the rat studies of DuPont's Dr. Staples, from other animal studies of Benlate performed by other scientists (animal studies are also referred to as *in vivo* studies), and from the *in vitro* testing conducted by DuPont, by Dr. Van Velzen, by Dr. Howard, and by DuPont's European subsidiary ICI, Dr. Howard was able to calculate the amounts of Benlate that Mrs. Castillo absorbed through her skin and through inhalation from the spray drift incident which were then transported in her bloodstream to the fetus. (T. Vol. LXX, pp. 2944-2992; T. Vol. LXXI, pp. 3048; T. Vol. LXXII, pp. 3134-3135). With the amount of Mrs. Castillo's skin that was misted with Benlate, and with 10 to 15 percent of the benomyl crossing through the skin into the bloodstream (as the DuPont dermal studies had shown), the circulation of the benomyl-carrying blood through her circulatory system (90% of the first pass goes through the fetus before it even reaches the mother's liver), and the number of hours before the mother's liver can completely detoxify the benomyl during which period benomyl continues to reach the fetus, Dr. Howard was

able to calculate that benomyl would have reached the fetal blood supply in an initial concentration of 100 parts per billion. (T. Vol. LXXI, pp. 3027-3035). Dr. Howard's *in vitro* studies showed that at 3 parts per billion benomyl inhibits cells' neurite growth, and Dr. Van Velzen's studies showed that at 20 parts per billion benomyl causes cell death. (T. Vol. LXXI, pp. 3040-3041).

Dr. Howard thus testified that based on a reasonable degree of medical and scientific probability the 100 parts per billion concentration of benomyl that reached the fetal blood supply from the incident in which Mrs. Castillo was wetted with Benlate would cause cell death and certainly cause cell neurite growth inhibition. (R. Vol. LXXI, pp. 3042-3043). (T. Vol. LXX, pp. 2944-2992; T. Vol. LXXI, pp. 3048; T. Vol. LXXII, pp. 3134-3135). Dr. Howard also specifically addressed the subject which generated the unwarranted concerns of the Third District about Dr. Howard allegedly 'extrapolating' directly from the effects of doses to cells *in vitro* to the effects of doses on cells in a living embryo:

The whole idea of these tests is to try and find out at what tissue level effects would start occurring in the embryo.

Now, one has to say that the cells in the dish are not in exactly the same situation as the cells in the embryo because the embryo does have a circulation and it does have the ability to move things back across the placenta to the mother.

So, it is in a dynamic situation, whereas in the dish you put in the dose and it can't actually get out of the dish, ***but there are studies which show a high correlation between the effects that we see in vitro and effects that you will see in humans and all the major pharmaceutical companies use these tests on the standard test when they're looking at new molecules*** and indeed if

a test like the micronucleus test which you will hear about proves to be positive, in general that molecule is thrown away. They don't use it any further.

They use it as a screening test and they clearly believe that that test is of great significance in predicting various effects and *it is, of course, the closest that we can get to experimenting on human beings.*

(T. Vol. LXXI, pp. 3041-3042). DuPont expert Holmes agreed that animal studies are "very helpful" as a predictor of teratogenicity in humans. (R. Vol. XLI, p. 50; R. Vol. XLVII, p. 78). DuPont scientist Staples testified that "the government indicates that studies in rats and mice are acceptable" for the purpose of making scientific determinations that are designed to protect human beings that use products made by DuPont. (R. Vol. XIII, pp. 88-89).

B. Facts pertinent to the issue of exposure to Benlate

The Third District's opinion erroneously concludes that "as to DuPont" there was insufficient evidence presented at trial to show by the requisite greater weight of the evidence that Mrs. Castillo was exposed to Benlate. The detailed facts from the trial record are set forth next showing that the trial evidence confirms exactly the opposite of the Third District's conclusion. The Plaintiffs presented direct evidence that Donna Castillo was exposed to an odorless, colorless liquid spray that was windblown across 137th Street in Kendall, Florida from a Pine Island U-Pic farm in early November of 1989. Quite apart from Pine Island's vice president's admission that he was using Benlate on the U-Pic field

in early November of 1989, circumstantial evidence at trial conclusively established that the spray was - and could only have been - Benlate.

Plaintiff put on direct evidence - Mrs. Castillo's testimony - that Pine Island Farms was spraying *something* on the U-Pic field on November 1 or November 2, 1989. (T. Vol. LVI,1 p. 905). Lynn Chaffin testified that tomatoes had been planted in the field between October 25 and October 27, 1989, seven or eight days before the November 1 or 2, 1989 spraying. (T. Vol. LIX, p. 1380). Pine Island's spray manager Eddie Sanders testified that Pine Island sprays its tomatoes with fungicides within a week to ten days of planting. (T. Vol. LXXIV, pp. 3364, 3395, 3396), and plant pathologist Dr. McMillan from the University of Florida confirmed that the use of fungicides on tomatoes during the first week after planting is the general practice in Homestead, and, indeed, throughout the United States. (T. Vol. LXXV, p. 3541). Pine Island's president and owner Jack Wishart also confirmed that fungicides are used prophylactically stating: "Of course it has always been the farm's practice to spray tomatoes to prevent disease." (T. LXVII, pp. 2606-2607). In fact, he said, "it has been that way as long as they have grown tomatoes." (T. LXVII, p. 2607).

Pine Island's chemical purchase records showed that the farm had Benlate available at the time (T. Vol. LVIII, p. 1187; T. Vol. LXXV, p. 3607; T. Vol. LIX, p. 1388), and Defendant Pine Island's answers to requests for admissions propounded by the Plaintiffs

— which were read to the jury at trial — established that no other fungicide was being used at the field in question on November 1 or 2, 1989. (T. Vol. LXI, pp. 1573-1579).

C. Facts relating to the *Frye* hearing

As indicated briefly above, prior to trial DuPont filed a motion in limine, adopted by reference by Pine Island, seeking to exclude the testimony of Dr. Howard, whom Plaintiffs planned to present at trial as their expert on the issue of the causal link between Mrs. Castillo's exposure to Benlate and John's microphthalmia. (R. Vol. XII, pp. 2494-2531; Vol. XIII, pp. 2744-2745). DuPont argued in the motion that Dr. Howard's qualifications and opinion testimony could not meet the *Frye* test utilized in this State for determining admissibility of scientific evidence. (R. Vol. XII, pp. 2494-2531).

At the *Frye* hearing Plaintiffs presented the testimony of various expert witnesses, as well as exhibits illustrating and supporting their testimony. (T. Vol. XLV, XLVI, XLVII; S.R. 1-69). Plaintiffs also filed the affidavit of Dr. Howard and numerous supporting scientific articles. (R. Vol. XV, pp. 3127-3154, 3160-3280; R. Vol. XVI, pp. 3281-3540; R. Vol. XVII, pp. 3541-3543). The Defendants presented nothing at the hearing and merely filed brief, conclusory affidavits after the hearing had concluded. (R. Vol. XV, pp. 3092-3099, 3106-3110).

The opinion of Dr. Howard which the Third District has erroneously held should have been excluded is that within reasonable medical probability it was more likely than not that John Castillo's microphthalmia was caused by his mother's exposure to Benlate

during the critical window of time when eyes begin to develop in a human fetus. (R. Vol. XV, pp. 3127-3154; R. Vol. XXXI, p. 6208).

Dr. Howard's methodology for reaching the opinion was set out at the *Frye* hearing and has been discussed in some detail above. In brief summary, Dr. Howard's entirely common and accepted approach was to consider information from all available sources, to wit: (1) the animal studies, including DuPont's own rat studies, which showed that Benlate is teratogenic and that it specifically causes microphthalmia and anophthalmia; (2) the *in vitro* tests performed by DuPont, by Dr. Van Velzen, and by Dr. Howard, which showed the low levels at which Benlate can impair neurite growth and functioning and induce cell death - either of which could impair or prevent development of the eyes; (3) the fact that clinical epidemiological studies are not available because Benlate is a toxic chemical and thus not suitable for human experiment (R. Vol. XL, pp. 8060-8061); (4) the fact that - as all experts agreed - geneticists had conducted every conceivable genetic test and could find no known genetic cause for John's microphthalmia; and (5) the fact that - as Defendants' experts also agreed - there was no evidence of any other environmental cause. (R. Vol. XV, pp. 3127-3138; R. Vol. XXXI, pp. 6203-6206).

After considering all of the available information, including a search for epidemiological studies,⁵ an assessment of biological plausibility of various causes, and

⁵There was one ecological epidemiological study done in Italy - the Spagnol study - but it concededly did nothing to

given the fact that all of the more likely causes of birth defects such as a known genetic defect and common environmental causes had been affirmatively eliminated as possibilities, Dr. Howard summed up his conclusion as to the cause of John's microphthalmia:

In a case where you have a known exposure to a known teratogen, during a window of vulnerability of a fetus for a particular organ and subsequently that organ is damaged, you are out of the realm of possibility and into the realm of probability.

(R. Vol. XXXI, p. 6209).

Dr. Howard's methodology for reaching this conclusion was confirmed as the generally accepted method by the testimony of Defendants' expert Dr. Brent, himself, except for Dr. Brent's (impossible in the case of toxic chemicals, even the Third District's decision acknowledges) requirement for 'positive epidemiologies'. (R. Vol. XV, p. 3095). As Dr. Brent stated after going over his criteria for determining human teratogenicity as a first step, in determining causation "one should eliminate the more likely causes of a birth defect before determining that another cause is probable. ***This is the generally accepted method.***" (R. Vol. XV, p. 3075).

It was established at the *Frye* hearing that deliberate epidemiological studies on humans are not possible when toxic chemicals are involved. (S.R. Tr. 4/30/96 Hearing, pp.

determinewhether anyof thepregnant women included in the studywere ever exposed to Benlate. (S.R. Tr. 4/30/96 Hearing, pp. 54-67).

34-36). It was also established that animal studies have been generally accepted since the early part of the century as an appropriate methodology for assessing toxicity and teratogenicity. (R. Vol. XV, p. 3136). The *in vitro* studies conducted by Plaintiffs' experts Dr. Van Velzen and Dr. Howard were undertaken to provide additional information as to Benlate's potential for causing teratogenic effects:

Although well conducted animal studies alone - such as the DuPont rat studies performed on Benlate - are a sufficient basis for reaching a conclusion of human teratogenicity, science is a continuing quest for greater accuracy. *In vitro* testing was thus developed as an additional means for assessing toxicity and teratogenicity, with particular developments in the field within the last fifteen years. ***It is generally accepted that in vitro testing is useful in providing confirming evidence of toxicity or teratogenicity. In fact, when I was advised that DuPont had, in this litigation, called into question the general acceptance of in vitro testing for toxicity using human cells and tissue, I contacted a colleague at the EPA. He, in turn, advised me that in vitro testing is widely used at the EPA.***

(R. Vol. XV, pp. 3136-3137). *See also* letter from Senior Research Scientist James P. O'Callaghan, Ph.D, of the United States Environmental Protection Agency, dated April 22, 1996. (R. Vol. XV, p. 3152) ("I can assure you that it is the policy of the U.S. Environmental Protection Agency to conduct research using tissues derived from experimental animals and humans. Indeed, it is the mission of the Agency to derive toxicological data that relate to the protection of human health against toxic agents in the environment. To that end, use of human tissue, when available, is often the first choice among toxicologists in our research facility.")

As Dr. Van Velzen pointed out during the *Frye* hearing, *in vitro* testing really gets to the most basic level at which a substance must be shown to have an adverse effect on fetal development if it is to be determined a teratogen. (T. Vol. XLV, p. 122). That is, whether the substance is administered orally or by spray or put in food, it must get to the fetal cells at some point if it is to have a teratogenic effect. (T. Vol. XLV, p. 122). Defense expert Dr. Holmes fully agreed that the real bottom line is not whether the route of intake is dermal or inhalation or ingestion but that the chemical gets into the bloodstream. (T. LXXXIV, p. 4977). And, as set out above and also confirmed by DuPont's own Dr. Brent, Benlate does enter the bloodstream and cross the placental barrier into the fetus' bloodstream both in rats and humans. (R. Vol. XL, pp. 8083-8086).

D. Facts relating to inaccuracies in the Third District's opinion

1. The record establishes that the trial judge understood and properly applied the *Frye* test

The Third District's opinion repeated DuPont's wholly unsupported appellate assertion that the trial court did not understand or apply the correct standard in ruling on the admissibility of Dr. Howard's testimony. Yet the record shows - and DuPont itself said - exactly the opposite on numerous occasions during the actual *Frye* hearing.

The Third District based its conclusion that the trial court did not properly apply the *Ramirez/Frye* test upon "three statements made by the trial judge at the time she ruled..." 748 So. 2d at 1114. We initially note that none of the statements was made *at the time* the

judge ruled, but rather throughout the course of the two day *Frye* hearing. (R. Vol. 45 and 46).

The first statement of the trial court was, in pertinent part:

In other words, if I believe that the science is reliable and the jury - it would assist the trier of fact [under] *Frye*, I'm going to let it in.

Although the Third District's opinion makes no mention of it, the trial court immediately followed up that statement with the following:

Now, here, in the test done by DuPont, the *in vivo* test on mouse bone marrow, they say in certain doses this is definitely - it produces micronucleus, which we now know are death of cells, right?

[DUPONT'S COUNSEL]: Yes.

THE COURT: So we know that *in vivo* that it does cause cell death in mice at certain levels.

[DUPONT'S COUNSEL]: Yes.

THE COURT: That's what DuPont scientists say.

[DUPONT'S COUNSEL]: Yes.

THE COURT: Is it a far stretch for a scientist to say, given that, and since we cannot do *in vivo* tests on human beings, that it is teratogenic in human beings, as well?

[DUPONT'S COUNSEL]: Yes. Most assuredly, yes. That's what I have to convince you of. * * *

THE COURT: So you are trying to tell me that a compound that is toxic, that they find it toxic in mice, no scientist would say 'give it to a human being, we will do an *in vivo* test, because just because it's toxic in mice, there's

absolutely no correlation between toxicity in human beings,' and you want me to believe that?

[DUPONT'S COUNSEL]: That's not what I'm saying.

(R. Vol. 47, pp. 52-53).

The Third District was also critical of a second statement by the trial court that "the *Frye* hearing is not to decide the very seminal issue of this case, whether or not it is a teratogen, it's to decide whether or not the scientists who want to talk about it have reliability, and that is the sole purpose of *Frye*." 748 So. 2d at 1115. However, when the trial court made that statement at the *Frye* hearing, *DuPont's counsel* responded: "***I agree with you wholeheartedly....***" (R. Vol. 47, p. 62).

The Third District then completely took out of context a third statement by the trial court concerning the "quantum leap" (with which DuPont's counsel agreed, in any event). 748 So. 2d at 1115. The statement occurred during a colloquy between the trial court and Mr. Glynn, DuPont's lead counsel:

THE COURT: O.K., and then you said, "He is the only scientist who would say it is a human teratogen."

MR. GLYNN: Yes, at 20 parts per billion.

THE COURT: O.K. Would you please stop there. He is the only scientist who will say it is a human teratogen; is that true? Don't try to qualify it. Just answer that question.

MR. GLYNN: ***I don't know if there is any other scientist who says it's a human teratogen. There probably is, because a lot of things, including***

salt, are human teratogens at a certain level. But we are talking about dose, so that's why I put it up there with the 20 parts per billion.

THE COURT: So now we know it's possibly a human teratogen because obviously we can't give it to people to find out.

MR. GLYNN: *I can't say that it is not. I don't know that it's not.*

* * *

THE COURT: We are narrowing this. We are really getting to it.

MR. GLYNN: *Yes, we are narrowing and focusing sharply on what the issue is.*

* * *

MR. CHUMBLEY [co-counsel for DuPont]: This question here, whether or not Benlate is a human teratogen, alright, that's part of what we are here about in this whole case, but that doesn't satisfy the Plaintiffs' burden, because that determination, assuming that you're Honor or the jury or whomever accepts the fact that it may be or is a human teratogen, which we say it is not -

THE COURT: Well, just two seconds ago he [Mr. Glynn] said it was [a human teratogen].

MR. CHUMBLEY: I know, and I think he was confused. But let's just say for the sake of argument that the jury finds -

THE COURT: I have to tell you I find it a human teratogen too, so you're really going to have a problem. I don't know what it is in levels, but I'm going to tell you that if it's a rat teratogen, most probably it's a human teratogen, and I'm going to make that *quantum leap*.⁶

⁶Taken in context, then, and coming as it did on the heels of DuPont's concession that Benlate is a human teratogen (although DuPont contested the dose level asserted by Dr. Howard), the trial court's reference to a "quantum leap" could only have been a sarcastic overstatement.

MR. CHUMBLEY: You have indicated that, but that doesn't get them anywhere, Judge.

THE COURT: *I already agreed it's the dose level that counts. We were at the same point, absolutely at the same point.*

MR. CHUMBLEY: *Fine. I understand. Thank you, your Honor.*

(R. Vol. 47, pp. 66-69).

2. The Third District's opinion also misconstrues the testimony of Plaintiffs' experts

With a virtually wholesale adoption of DuPont's inaccurate arguments, the Third District opinion assumes that Plaintiffs' experts were using some novel "direct extrapolation method" in which they directly extrapolated from "in vitro test results to determine a teratogenic exposure level in a living being." 748 So. 2d at 1140. The record shows, however, that this is not a true statement, and not what Plaintiffs' experts did at all.

Dr. Van Velzen, who performed the in vitro testing on human fetal cells, used his testing in precisely the same way that all scientists use in vitro testing, i.e., to determine at what level, or dosage, cells in a petri dish will react to a given substance, in this instance, a chemical. (R. Vol. XLV, pp. 137-138). His test showed that the lowest level of exposure of the cell to benomyl to cause effect was at a concentration of 20 parts per billion." (R. Vol. XLV, p. 138).

Dr. Van Velzen was clear in pointing out that such in vitro testing is just one of the tools used by scientists to assess potential toxicity or teratogenicity of drugs and chemicals;

it is a starting point for determining whether the substance has the ability at the most basic and controlled level - cells in a laboratory dish - to cause any adverse effect at all. (R. Vol. XLV, p. 121). As he explained, the fact that the substance has no effect no matter how high the dosage does not necessarily rule out toxicity because when ingested or otherwise absorbed into an actual living organism it may metabolize into something toxic. (R. Vol. XLV, p. 122). But if the in vitro testing of a substance does have an adverse affect on the cells, it provides indicia of its potential for toxicity and requires further testing to ascertain whether its interaction with a living organism to determine whether metabolic processes will increase, decrease, or have no effect on its toxicity. (R. Vol. XLV, pp.121-123). So, generally accepted methodology approaches assessment of potential toxicity both at the cell level and in the living organism: "[T]here is a two step program. You always have to do it completely." (R. Vol. XLV, p. 122).

Of course, in the case of potentially toxic chemicals, the living organism testing must be done with animals - not humans. (R. Vol. XLV, p. 283-285). Hence, in the case of benomyl, various rat, mouse, and rabbit studies were conducted by DuPont and other scientists. (R. Vol. XLV, p. 283-285).

But - in express contrast with the Third District's statement that Plaintiffs' experts relied on direct extrapolation from in vitro test results to determine a teratogenic exposure level in a living being - Dr. Van Velzen stated in the *Frye* hearing that he was *not* making

any such direct extrapolation, notwithstanding the suggestion DuPont had made during cross-examination that he was:

Q. What you do or what you did with the in vitro test, that confirms that you will get a teratogenic effect. But in and of itself if you have no way of determining a low effect level, meaning how much gets into the mother's bloodstream to cause an effect, you have no way to really calculate that just with an in vitro test or a micronucleus test, correct?

A. You cannot calculate a low effect level in the mother simply from the [in vitro] micronucleus test for exactly the reasons you give.

(R. Vol. XLV, p. 284). Dr. Van Velzen explained why in vitro test results showing the concentrations at which the cell will be affected cannot be directly translated into dosages at the in vivo level:

Q. Doctor, there was reference in one of the objections that I heard to in vivo versus in vitro, and based on your training and experience would you expect a different result if benomyl was exposed to a human fetal cell in vivo versus in vitro? In other words, meaning that the benomyl got to the cell in the in vivo setting and the benomyl got to the cell in the in vitro setting?

A. The answer to that is you would expect no difference. The important additional information is that everybody else will point that out as well, that you then immediately have to ask yourself the question how much gets there, is it metabolized, transported and what is the sensitivity in that surrounding, and you can argue that up, but you can also argue it down. Let me explain what I mean.

Another rapidly growing organ at this time is the heart, and if you stop the heart from growing or reduce its growth, you're going to reduce blood supply to this rapidly-growing brain. So you could get compounding of any effect and, therefore, it is bad enough that cells whether they sit in tissue fluid and are soaked in benomyl can be directly compared to cells when they sit in the culture dish and are soaked in benomyl, but in real life on the one hand the baby's liver or fetus' liver or mother's liver takes some benomyl away once

you give a large dose early, but in reality in the fetus, in the embryo effects of benomyl elsewhere can make life for the brain much more difficult.

So it is very difficult to say other than I would expect on a cellular level dose for dose, concentration for concentration the effects to be the same. It is still difficult to predict from that that there would be no effect in the fetus, there would be a lot of effect or other would be even worse effects, but on a cell to cell level, if it kills at 20 ppb, it is tissue fluid, I don't see why it wouldn't kill at 20 ppb in tissue fluid around the individual cells.

(R. Vol. XLV, pp. 178-179).

It was DuPont's counsel on cross-examination - trying to create a *Frye* issue where none really exists - who repeatedly tried to get Dr. Van Velzen to characterize his in vitro testing as methodology he was using in a novel, pioneering way to directly extrapolate from the cell concentration lowest observable effect level (or LOEL as scientists have come to refer to it) to the lowest observable effect level for Benlate in live humans:

Q. Right. So you have determined based on the test methodology that you used what you have said is the LOEL for Benlate in humans, correct?

A. No. I'm much more scientific than that.

Q. Correct me, please.

A. I have said the lowest observed effect on human fetal fibroblast cells in culture in this way is as a medium concentration of 20 ppb after 24 hours exposure, and the rest is, the rest is estimation, guesstimate, projection, as is the whole of clinical teratology.

Q. But when Mr. Ferraro asked you do you know of any reason that it wouldn't also be 20 ppb in the living fetus, you said no.

A. If you check the transcripts, I'm sure he didn't use the word 20 ppb. When he said that he specifically asked, Would you, therefore,

conclude that it would produce teratogenesis in man, and I said it is highly likely and my answer to anybody asking me it would be yes.

Q. But so is it not your testimony, then, it is not your testimony that if 20 parts per billion is the low effect level in the dish with harvested cells, that it is likely that that is also the low effect level in the developing fetus; that is not your opinion?

A. I've actually explained in great detail how the cell sitting in its bath of tissue fluids in a medium that contains just like that, 20 ppb, might have less problems, bigger problems or the same, and I've tried to explain why.

Q. You see, I just need to try to get very straight, simple answers.

(R. Vol. XLV, pp. 254-255). When DuPont's counsel continued to press for an opinion as to whether Dr. Van Velzen thought that if 20 parts per billion is the LOEL in vitro it is also likely the LOEL in a developing fetus - which was *not*, as Dr. Van Velzen had made clear in his testimony, the question his in vitro testing was conducted to answer any more than the in vitro testing of any other scientist is conducted to answer that question - Dr. Van Velzen said that if asked to formulate such an opinion his answer would be that it was probable:

THE WITNESS: Just please redo the question.

Q. Let me do that, sir. The question is is it your opinion that if 20 parts per billion is the low effect level in the dish, is it also likely that that is the low effect level in the developing fetus?

A. My opinion is that that is yes, the most probable fact.

Q. Thank you. Now, do you know of any other scientists in your discipline or any others who have said that it is valid science to take the

low effect level determined in a dish and to conclude that that is the probable low effect level in the human being, in the developing fetus, anyone ever?

A. No, but then they don't get asked that question.

(R. Vol. XLV, p. 257). It was at that point that DuPont's counsel tried to have Dr. Van Velzen characterize himself as a "pioneer", only to have Dr. Van Velzen again make it clear that his in vitro test results could *not* be taken alone or taken as intending to represent the LOEL in a developing fetus:

Q. So you don't know of a single authoritative peer reviewed work in which a scientist has used this technique to reach the conclusion that you've reached regarding low effect level in benomyl, correct?

A. Yes.

Q. So you're the first, you're the pioneer?

A. Well, it is a position I'm not comfortable in.

Q. But is it true, you're the pioneer of this?

A. *But I haven't said that. What I've said, literally what I've done is complete data by others, it can't be taken on its own. I do not pretend with this test alone to make a statement to the strength of what you say. The strongest interpretation that I give is added to everything else it should get us worried about that exposure level tissue concentration.*

(R. Vol. XLV, pp. 257-258).

3. The Third District's statements about the EPA disregard the record evidence about DuPont's improprieties in presenting test results to governmental agencies

The Third District's opinion states:

[C]ontrary to the negative conclusions drawn by Howard and Van Velzen from these *in vivo* studies, the Environmental Protection Agency . . . determined that it did not present a danger to pregnant women either through inhalation or dermal exposure.

748 So. 2d at 1120. This statement by the Third District disregards the record evidence set forth above that DuPont manipulated its test results for the sake of obtaining unwarranted EPA approval for DuPont to distribute Benlate without warnings to pregnant women.

The record also showed that DuPont incorrectly reported its test results to try to persuade the State of California to keep benomyl off its list of reproductive toxins. Dr. Staples testified in his deposition that the version of his 1980 study that he presented to the California State Board under Proposition 65 some time in 1993 incorrectly recited his actual findings. (R. Vol. XIII, p. 2720).

SUMMARY OF ARGUMENT

The Third District's opinion represents a fundamental misunderstanding of the scientifically valid basis upon which the Plaintiffs' expert opinions were premised, and a misuse of *Frye*. The purpose of a *Frye* hearing is to determine "whether the expert's testimony is **based** on a scientific principle or discovery that is 'sufficiently established to have gained general acceptance in the particular field in which it belongs.'" *Ramirez v. State*, 651 So. 2d 1164, 1167 (Fla. 1995), *quoting Frye v. U.S.*, 293 F. 1013, 1014 (D.C. Cir. 1923). The inquiry should focus upon (1) the general acceptance of the underlying

scientific principle, and (2) *the testing procedures* used to apply that principle to the facts of the case at hand. *Id.* The trial judge understood and properly conducted that inquiry, and appropriately denied DuPont's motion to exclude the testimony of Plaintiffs' expert Dr. Howard. The Third District then incorrectly ruled that the trial court misunderstood *Frye* and that the Plaintiffs' expert testimony should have been excluded.

The Third District began with a correct acknowledgment that there are three types of evidence available to scientists in order to establish causation in a case such as this: (1) epidemiology (studies to observe the effect of exposure to particular substances upon the incidents of disease in *human* populations); (2) *in vivo* testing (animal testing); and (3) *in vitro* testing (analysis of the effects of particular substances on isolated cell systems). 748 So. 2d at 1116.

As the Third District readily acknowledged, epidemiological evidence is not generally available for chemicals such as Benlate because it would be unethical to use humans for toxicity or teratogenicity testing. *Id.* In the case of chemicals, researchers must rely primarily upon animal studies to determine potential toxicity or teratogenicity on humans. DuPont itself conducted such animal studies in testing Benlate. *Id.* The Third District, in fact, acknowledged that animal studies have some advantages over epidemiological studies because researchers can control the environment, reduce the likelihood of biases affecting the results, and administer large doses of an agent over a short period of time. *Id.*

As to in vitro studies, numerous peer-reviewed and published studies introduced through Dr. Van Velzen at the *Frye* hearing demonstrate that in vitro testing on animal and human tissues has been used worldwide for decades - by governments, by industry, and by educational institutions - as a tool in assessing substances' potential for toxicity, including developmental toxicity or teratogenicity, with the same methodology and towards precisely the same end as that of Plaintiffs' experts in conducting his in vitro testing of benomyl. (R. Vol. XLV, pp. 144-151; R. Vol. XV, pp. 3163-3280). As but one example, a 1993 Reproductive Toxicology article notes in its abstract:

Much progress has been made over the past decades in the development of in vitro techniques for the assessment of chemically induced effects in embryonic and fetal development. * * * Today these tests cannot replace the existing in vivo developmental toxicity tests. They can, however, be used to screen chemicals for further development or further testing. ***In addition, these in vitro tests provide valuable information on the mechanisms of developmental toxicity and help to understand the relevancy of findings for humans. In vitro systems, combined with selected in vivo testing and pharmacokinetic investigations in animals and humans, can thus provide essential information for human risk assessment.***

B. Schmid, et. al., *Embryonic and Fetal Development: Fundamental Research*, Reproductive Toxicology, Vol. 7, pp. 155-164, 1993. Evidence at the Frye hearing showed that DuPont itself has used in vitro testing in assessing the teratogenicity of benomyl. (R. Vol. XLV, pp. 150-151).

Notwithstanding the fact that Plaintiffs' experts had used precisely the same methodology as all scientists and as DuPont itself, the Third District determined that the

trial court had erred by admitting the testimony of Plaintiffs' experts, because the trial judge misunderstood *Frye* and because of "uncertainties associated with *extrapolation* both from animals to humans and from high to low doses." *Id.* at 1116-1117.

The record of the *Frye* hearing, however, affirmatively demonstrated - in contrast with the statements made in the Third District's opinion - that the trial judge was perfectly conversant with the appropriate determinations to be made at a *Frye* hearing, and that the Plaintiffs' experts' testimony was based only on generally accepted methodologies and uses of in vivo and in vitro studies in assessing human teratogenicity. As was pointed out during the *Frye* hearing, the *only* purpose for scientists throughout the world - including DuPont's scientists - to conduct in vitro and in vivo testing to assess potential teratogenicity is for the sake of assessing potential *human* teratogenicity. The testing is most assuredly not done to devote monumental amounts of time and funding to trying to prevent birth defects in rats. All scientists involved in the field are accordingly extrapolating to greater and lesser degrees from in vivo and in vitro studies to human teratogenicity, which in turn always depends upon dose. Thus, the Third District's opinion itself misunderstood the basic science in suggesting that extrapolation from in vitro and/or in vivo testing to human teratogenicity and dosage is unprecedented or novel or deserving of exclusion under *Frye*.

The Third District's decision represents a misapplication of *Frye* that signals that an expert's testimony may be excluded in the name of *Frye* if a court disagrees with the expert's *conclusions*, even if the record reflects that his or her methodology was based

upon generally accepted scientific principles. The decision also signals that in the case of toxic chemicals, humans and their unborn children must stand without recourse as the guinea pigs, or rats, for the DuPonts of the world in determining human teratogenicity and toxicity. DuPont and its ilk may use their animal and in vitro studies to get EPA approval for launching their products without warnings onto the unsuspecting public, but the victims of their toxic products may not use those same - obviously generally accepted - studies to prove their claims in court.

The Third District's conclusions about the exposure evidence and the *de minimus* 'clusters' references were also unwarranted by the record. The Third District's decision should be reversed and the case remanded for reinstatement of the judgment entered on the jury's verdict.

ARGUMENT

POINT I

THE THIRD DISTRICT'S DECISION MUST BE REVERSED BECAUSE IT MISUSES *FRYE* AND UNFAIRLY CLOSES THE COURTS TO CLAIMANTS INJURED BY TOXIC CHEMICAL EXPOSURE

Notwithstanding the Third District's misinterpretation of Dr. Howard and Dr. Van Velzen's testimony, and its mistaken suggestion that the Plaintiffs' experts had "conceded" that their "direct extrapolation" method was new, the record confirms that the Plaintiffs utilized no such method to begin with. To the contrary, as we have painstakingly

established, *supra*, Drs. Howard and Van Velzen utilized the exact same tests that were utilized by DuPont and other scientists, for the exact same purpose. The Third District simply misunderstood the testimony and misapplied the *Frye* test.

In *Ramirez v. State*, 651 So. 2d 1164 (Fla. 1995), this Court established a four step process for determining the admissibility of expert opinion testimony:

- (1) The trial judge must determine whether such expert testimony will assist the jury in understanding the evidence or in determining the fact at issue;
- (2) The trial judge must decide whether the expert's testimony is based on a scientific principle or discovery that is "sufficiently established to have gained general acceptance in the particular field in which it belongs" [the *Frye* test];
- (3) The trial judge must determine whether a particular witness is qualified as an expert to present opinion testimony on the subject at issue; and
- (4) If so, the judge may then allow the expert to render an opinion, and it is then up to the jury to determine the credibility of the expert's opinion, which it may either accept or reject.

Ramirez, 651 So. 2d at 1167.

Thus, the *Ramirez* test requires the trial court to make three determinations; the fourth step is simply to allow the expert to testify, which necessarily follows if the first three steps are satisfied. *Nelson v. State*, 748 So. 2d 237 (Fla. 1999), *cert. denied*, 120 S. Ct. 950, 45 L. Ed. 2d 825 (2000). The Third District noted that the trial court had appropriately accomplished the first two steps. 748 So. 2d at 1115 n.7. However, the Third District erroneously concluded that the trial court had failed to "make the finding required by *Frye* ..." *Id.*

The Third District misapplied *Frye* in several respects. First, despite its claims to the contrary, it incorrectly focused upon the conclusions of the Plaintiffs' experts, rather than whether those conclusions were based upon underlying scientific principles and testing methodologies which are generally accepted in the scientific community. Then, after improperly turning its focus upon the conclusions of the Plaintiffs' experts, the court relied almost exclusively upon federal and state case law which applies a Daubert standard, rather than the *Frye* test. In particular, the District Court relied upon a series of Daubert-based disallowances of expert testimony in cases involving the pharmaceutical drug Bendectin, all of which were decided in the context of overwhelming and uncontradicted epidemiological evidence that Bendectin is not a human teratogenic.

Under Florida's *Frye* standard, contrasting conclusions, based upon the same scientifically acceptable tests, present a classic difference of opinion which, according to *Mills v. State*, 476 So. 2d 172 (Fla. 1985), and *Berry v. CSX Transportation, Inc.*, 709 So. 2d 552 (Fla. 1st DCA 1998), *rev. denied*, 718 So. 2d 167 (Fla. 1998), ***must be resolved by the trier of fact***. As the *Berry* Court observed, "*Frye* allows opposite opinion testimony from experts relying upon the same generally accepted scientific principles and methodologies." *Berry*, 709 So. 2d at 567. *Accord Brim v. State*, 695 So. 2d 268, 269 (Fla. 1997). And, the *Berry* court concluded that:

Under *Frye* and its Florida progeny, when the expert's opinion is well founded and based upon generally accepted scientific

principles and methodology, it is not necessary that the expert's opinion be generally accepted as well.

709 So. 2d at 567. The *Berry* court went on to observe that:

Plaintiffs and the defendant's experts relied on essentially the same diagnostic methodologies but drew opposite conclusions from the available information.

Id., quoting *Christophersen v. Allied Signal Corp.*, 939 F.2d 1106, 1111 (5th Cir. 1991), *cert. denied*, 503 U.S. 912 (1992).

Here, both the Castillos' experts and DuPont's experts relied upon the very same scientifically accepted tests to arrive at opposite conclusions. Yet, in express and direct conflict with *Berry*, the Third District of Appeal here ruled that the *Frye* standard was not met.

In so doing, the Third District made the same legal mistake as did the *Berry* trial court, which mistake was corrected by the First District in the *Berry v. CSX Transportation* decision cited herein. Unlike the experts here, the experts in *Berry* did have available epidemiological studies. The *Berry* court's discussion of those epidemiological studies applies equally here:

From epidemiological studies demonstrating an association, an epidemiologist may or may not infer that a causal relationship exists. However, the epidemiological studies themselves are not designed to demonstrate whether a particular agent did cause the disease, and the trial court erred in concluding that the studies were unreliable because they failed to establish causal relationship.

Berry, supra, 709 So. 2d at 567-68.

We have already demonstrated that Florida's application of *Frye* opens the courthouse door to competing conclusions drawn from the same scientifically accepted studies. The Third District, following DuPont's siren's song has suggested that the Plaintiffs' claim that benomyl is a human teratogen is "junk science."

But that notion has been rejected by the State of California which has now officially recognized benomyl as a "chemical known . . . to cause reproductive toxicity," i.e., a human teratogen. 22 California Code of Regulations §12000(c)(1). In *Western Crop Protection Assn v. Davis*, 95 Cal. Rptr.2d 631 (Cal. Ct. App. May 9, 2000), the court described the two methods used for determining whether a substance should be listed as a chemical known to the state to cause reproductive toxicity:

The first involves the judgment of the state's qualified experts that a chemical "has been clearly shown through scientific valid testing according to generally accepted principles to cause . . . reproductive toxicity" The second involves the judgment of a body, considered to be authoritative by the state's experts, that has formally identified the chemical as causing reproductive toxicity.

95 Cal. Rptr.2d at 633. The court went on to note that "in view of the ethical prohibition in testing humans", the State of California accepts "studies in experimental animals which indicate . . . an association between adverse reproductive effects in humans and the toxic agent in question as biologically plausible." *Id.* at 636.

Although the Third District purports to base its decision on a *Frye* inquiry, in the final analysis, the Third District embraced *Daubert*-spawned federal and (non-Florida) state law precedent. *See, e.g., Merrell-Dow Pharmaceuticals, Inc. v. Havner*, 953 S.W.2d 706 (Tex. 1997). Moreover, despite acknowledging that it would be unethical to conduct epidemiological tests of the teratogenic effect of Benlate on humans, the Third District ultimately relied upon the body of case law which has arisen out of Bendectin litigation, where the overwhelming weight of epidemiological studies demonstrated that Bendectin was *not* a human teratogen. *See, e.g., Havner*, and cases cited therein. DuPont has no such body of science to tip the scales in its favor in this case.

Here, the Plaintiffs established, via recognized and authenticated scientific testing, that benomyl causes human cell death *in vitro*, and that it can make its way to a rat's fetus *in vivo*. DuPont's own expert conceded that if benomyl could find its way to the rat's fetus, it would likewise find its way to a human fetus. In the final analysis, after reviewing all available evidence, including *in vivo* and *in vitro* test results, Dr. Howard's opinion was that Benlate more likely than not caused John Castillo's birth defect; Drs. Holmes and Brent testified, based upon the same evidence, that more likely than not, there was some other (unknown) cause of John's birth defect. According to this Court's application of *Frye*, both of those competing conclusions were admissible.

Although the Third District gave nodding recognition to the proposition that "the test for allowing a plaintiff to recover in a tort suit of this type is not scientific certainly but legal

sufficiency," *Ferebee v. Chevron Chemical Company*, 736 F.2d 1529, 1535 (D.C. Cir. 1984), *cert. denied*, 469 U.S. 1062 (1984) the Court proceeded to announce a rule which requires scientific certainty.

The Third District acknowledged that epidemiological studies are not a "mandatory pre-requisite to establish a toxic substance's teratogenicity in human beings[.]" 748 So. 2d at 1120. Nevertheless, the Third District improperly went on to hold that a plaintiff who wishes to establish a substance's teratogenicity in human beings must not only establish that the *methodology* used in these studies is generally accepted, but must also establish that the method of "extrapolating" from the achieved results is generally accepted in the relevant scientific community. *Id.* What the Third District overlooked was that "extrapolation" is but a synonym for "conclusion."⁷

In short, the Third District has held that in order to meet the *Frye* admissibility standard, the plaintiff must establish that his or her experts' *conclusions* are widely accepted in the scientific community. As we noted above, this is expressly and directly at odds with *Frye*, *Ramirez*, *Brim*, and *Berry v. CSX Transp., Inc.*

In light of the fact that it is undisputed that epidemiological tests are not available, the Third District has in essence told the Plaintiffs that even though science considers

⁷The Concise Oxford Dictionary defines "extrapolate" as "infer more widely from a limited range of known facts," while it defines "conclude" as "infer (from given premises)."

Benlate to be too dangerous to humans to conduct studies of its effects on pregnant women, the resulting lack of positive proof of its harmful effect in the form of human epidemiological research - despite the fact that there is no countervailing proof that it is *not* a human teratogen - results in a liability windfall for DuPont and effectively bars the Castillos' access to the courts.

The Third District's opinion is also squarely at odds with the overwhelming majority of federal circuit courts of appeal (applying *Daubert*) which have held that "a medical opinion on causation based upon a reliable differential diagnosis is sufficiently valid [.]"
Westberry v. Gislaved Gummi AB, 178 F. 3d 257, 263 (4th Cir. 1999); *Heller v. Shaw Industries, Inc.*, 167 F.3d 146 (3d Cir. 1999); *Kennedy v. Collagen Corp.*, 161 F.3d 1226 (9th Cir. 1998), *cert. denied*, 526 U.S. 1099 (1999); *Baker v. Dalkon Shield Claimants Trust*, 156 F.3d 248 (1st Cir. 1998); *Zuchowicz v. United States*, 140 F. 3d 381 (2nd Cir. 1998); *Ambrosini, supra*.

As indicated in *Westberry*, "differential diagnosis, or differential etiology, is a standard scientific technique of identifying the cause of a medical problem by eliminating the likely causes until the most probable one is isolated." 178 F. 3d at 262. Both the Plaintiffs' expert Dr. Howard and the defense expert Dr. Brent specifically concurred that this is the correct methodology. As stated most succinctly and correctly by Dr. Brent: "the generally accepted method" is that "one should eliminate the more likely causes of a birth

defect before determining that another cause is probable."⁸ (R. Vol. XV, p. 3075). That is precisely what the plaintiffs here did. Accordingly, the jury's verdict should be reinstated.

⁸In Florida, the causation standard is "more likely than not." *Gooding v. University Hosp. Bldg., Inc.*, 445 So. 2d 1015 (Fla. 1984). It is not 95% or 80%, but 51%. *Rivet v. Perez*, 655 So. 2d 1169 (Fla. 3d DCA 1995). And this Court has expressly held in a Frye context that expert evidence is admissible even if it does not reach a conclusive result. *Mills v. State*, 476 So. 2d 172, 176-177 (Fla. 1985). In *Mills*, this Court ruled that scientific evidence of a neutron activation analysis was properly admitted into evidence even though the test "does not conclusively establish whether the subject has really fired a gun." The neutron activation analysis was "relevant because it shows a probability that the subject did or did not fire a gun, and its probative value is for the jury to determine." 476 So. 2d at

POINT II

PETITIONERS PRESENTED MORE THAN SUFFICIENT DIRECT AND CIRCUMSTANTIAL EVIDENCE TO CREATE A JURY QUESTION ON THE ISSUE OF WHETHER THE COLORLESS AND ODORLESS LIQUID SUBSTANCE WHICH WAS BEING SPRAYED ON THE U-PIC FIELD AND WHICH MISTED DONNA CASTILLO WAS THE DU POINT FUNGICIDE BENLATE⁹

Both DuPont and Pine Island moved for a directed verdict at the conclusion of the Plaintiffs' case in chief, arguing that the Plaintiffs had failed to present a jury question on the issue of whether the spray which misted Donna Castillo was the DuPont fungicide, Benlate. Pine Island championed, and DuPont adopted, the argument that the Petitioners had stacked "inference upon inference" in order to reach that conclusion.

The Third District acknowledged that Pine Island had raised the argument and made reference to the authorities relied upon by Pine Island. However, the Third District properly rejected Pine Island's argument since the testimony of Pine Island's own Lynn Chaffin constituted "direct evidence that Benlate was sprayed on the field in November, 1989." 748 So. 2d at 1112.

Next, however, the Third District inaccurately stated that Chaffin's testimony was "the only direct evidence presented by Plaintiffs that Benlate was, in fact, used during the

⁹Having accepted jurisdiction, this Court may review the district court's decision for any error. *Leisure Resorts, Inc. v. Frank J. Rooney, Inc.*, 654 So. 2d 911 (Fla. 1995).

time in question." 748 So. 2d at 1113. The Third District then held, without citing any authority whatsoever, that although Mr. Chaffin's admission was admissible against Pine Island, it was inadmissible hearsay as to DuPont, and that "without his admission, there is insufficient evidence in this record to establish that Benlate was sprayed on the farm on the dates in question." 748 So. 2d at 1113.

Given DuPont's reliance upon the remainder of Chaffin's testimony, and the testimony of other Pine Island witnesses with respect to what Pine Island did or did not do, we believe that the Third District erred by ruling that Chaffin's admission was not binding on -- indeed, could not even be considered as to -- DuPont. Regardless, the Plaintiffs presented more than sufficient evidence as to both Defendants, even without Chaffin's admission.

In order to establish a jury question on the issue of Donna Castillo's exposure to Benlate, the Plaintiffs relied upon (1) direct evidence in the form of Donna Castillo's own testimony that she was misted by an odorless and colorless liquid that was being sprayed upon the U-Pic field by a tractor on the date in question; and (2) circumstantial evidence that the substance could only have been Benlate. Since the first fact necessary to establish that Mrs. Castillo was sprayed by the DuPont fungicide Benlate was established by direct evidence, the *Voelker* "inference upon inference" rule does not apply. Long before *Voelker*, this Court recognized the propriety of relying upon circumstantial evidence in civil cases. *King v. Weis-Patterson Lumber Company*, 168 So. 858 (Fla. 1936); *Fireman's Fund*

Indemnity Company v. Perry, 5 So. 2d 862 (Fla. 1942). The inference established by circumstantial evidence need only outweigh contrary reasonable inferences by a *simple preponderance* of the evidence. *Id.* at 859. This distinction was reiterated in *Voelker*, and also in *Nielsen v. City of Sarasota*, 117 So. 2d 731, 733 (Fla. 1960) ("in a civil case, a fact may be established by circumstantial evidence as effectively and as conclusively as it may be proved by direct positive evidence").

In *Voelker*, there were no eyewitnesses to an apparent accident; the testimony was composed "*entirely of circumstantial evidence.*" 73 So. 2d at 404. That fact pattern resulted in a rather unusual legal development, the prohibition against stacking "inference upon inference." Michael Foster, A Review and Reconsideration of Florida's Rule Against Basing A Inference on an Inference in Civil Cases, 23 Stetson L. Rev. 743, 788 (1994). Here, Donna Castillo presented direct evidence that she had been exposed to spray from a tractor on the U-Pic field in early November 1989. Thus, the Plaintiffs needed to establish only one fact, or inference, through the use of circumstantial evidence: that the spray in question was Benlate.

This case is most closely analogous to *Teate v. Winn-Dixie Stores, Inc.*, 524 So. 2d 1060 (Fla. 3d DCA 1988), *rev. denied*, 534 So. 2d 402 (Fla. 1988), which properly rejected the defendant's attempt to utilize the rule prohibiting the stacking of inference upon inference to a situation where only one inference needed to be drawn. Charlie Teate slipped and fell on some peas in the frozen food department of a Winn-Dixie Supermarket.

Id. It was Teate's contention that the water was there because the peas had been on the floor for a sufficient period of time to have thawed. Winn-Dixie's theory was that the water was as a result of "permafrost" or ice crystals on the bag of peas that instantly melted when it hit the floor. Since it was established that there was *some* water on the floor, it was completely within the jury's province to decide *why* the water was there: "The jury needed to draw only one inference [how the water got there] from direct evidence [there was water in the floor] to reach a decision as to the defendant's constructive notice of the condition."

Id. Similarly, the jury here needed only to draw one inference from the direct evidence, and the jury was justified in concluding, from all of the circumstances reflected in the record that the spray to which Donna Castillo was exposed in early November 1989 was, in fact, DuPont's fungicide Benlate. *See also C.R. Bard, Inc. v. Mason*, 247 So. 2d 471 (Fla. 2d DCA 1971), *cert. denied*, 251 So. 2d 878 (Fla. 1971) (rejecting application of inference upon inference rule where the initial inference is established to the exclusion of any other reasonable theory); *Fritts v. Collins*, 144 So. 2d 850 (Fla. 2d DCA 1962)(same).

POINT III

THE THIRD DISTRICT ERRED AS TO THE 'CLUSTERS' EVIDENCE

It will be recalled that Donna Castillo was contacted by a British reporter who was investigating a possible link between the use of Benlate and "clusters" of children born in Great Britain suffering from microphthalmia. During the month long trial in this case, there

were only the most minor references to the word. The subject "clusters." This was in no way made a feature of the trial, and the defense made more reference to clusters than did the Plaintiffs. Accordingly, the isolated references to what the Third District termed "vague and indefinite" evidence in the first place, did not and does not warrant reversal. *See, e.g., McCarthy v. Zdenek*, 508 So. 2d 408 (Fla. 2nd DCA 1987).

Furthermore, the Third District determined - without finding an abuse of discretion - that whatever relevance the evidence had was outweighed by its potential to prejudice the jury. Thus, the Third District's decision is contrary to *Sims v. Brown*, 574 So. 2d 131 (Fla. 1991) in which this Court noted that "the weighing of relevance versus prejudice or confusion is best performed by the trial judge who is present and best able to compare the two." 534 So. 2d at 133.

CONCLUSION

Based on the foregoing facts and authorities, Plaintiffs/Petitioners respectfully submit that the decision of the Third District should be reversed and the case remanded with directions to reinstate the judgment entered on the jury verdict in favor of the Plaintiffs/Petitioners.

Respectfully submitted,

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CERTIFICATE OF SERVICE

WE HEREBY CERTIFY that a true and correct copy of Petitioners' Brief on the Merits was mailed this 2nd day of October, 2000 to: Edward W. Warren, Esquire, Christopher Landau, Esquire, Jeffrey Bossert Clark, Esquire, Kirkland and Ellis, Counsel for Appellant DuPont, 655 Fifteenth Street, N.W., Suite 1200, Washington, D.C. 20006; Arthur J. England, Jr., Greenberg, Traurig, Hoffman, et al., Co-Counsel for Appellant DuPont, 1221 Brickell Avenue, Miami, Florida 33131; and David Kleinberg, Esquire, Gaebe, Murphy, Mullen & Antonelli, Counsel for Appellant Pine Island Farms, Inc., 420 South Dixie Highway, 3rd Floor, Miami, Florida 33146.
