**IN THE SUPREME COURT**

**STATE OF FLORIDA**

CASE NO. SC00-490

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JOHN CASTILLO, a Minor By and Through his mother, next friend and natural guardian, Donna Castillo, DONNA CASTILLO and JUAN CASTILLO, individually,

*Petitioners*,

v.

E.I. DuPONT DE NEMOURS & COMPANY, INC.
and
PINE ISLAND FARMS, INC.,

*Respondents*.

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# BRIEF OF *AMICI CURIAE* MASON BARR, M.D., JAIME L. FRIAS, M.D., RICHARD K. MILLER, Ph.D., and JANINE E. POLIFKA, Ph.D. ON THE MERITS IN SUPPORT OF RESPONDENTS

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ON DISCRETIONARY REVIEW FROM THE
THIRD CIRCUIT COURT OF APPEAL

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## INTEREST OF *AMICI*

*Amici* are teratologists, and thus members of the specialized medical community most germane to the scientific issues in this case. The credentials of *amici* are described in the Biographical Addendum to this brief. They seek to inform the Court of the elements of the generally accepted methodology for determining human teratogenicity. *Amici* address whether Dr. Charles Vyvyan Howard, plaintiffs' expert witness, employed generally accepted methodology in arriving at his opinion, and we respectfully submit that the methodology employed by Dr. Howard is an unscientific departure from what is generally accepted in the fields of teratology and medical genetics.

*Amici*'s interest in this litigation derives from a concern that courts in the United States adopt appropriate and scientifically based methodologies. *Amici* submit this brief in support of Respondent DuPont.

## BACKGROUND

This case arises from the tragic fact that a child was born with microphthalmia, a birth defect involving severely underdeveloped eyes. But this case also involves the application of principles and methods of sound science to the adjudication of legal claims and important issues of allocation of legal liability.

Plaintiffs brought claims against DuPont, the manufacturer of the agricultural fungicide Benlate and the owner of a farm at which the fungicide was allegedly sprayed while the child's mother, who was pregnant with John at the time, was in the vicinity, alleging that the fungicide had been sprayed on

a field at the farm as the mother walked by, and that the mother's exposure to the fungicide caused the child's birth defect.[1]

Plaintiffs' case was based on the theory that the mist sprayed in the field, to which Mrs. Castillo had allegedly been exposed, contained Benlate, and that benomyl (the active ingredient in Benlate) entered her bloodstream and caused John's microphthalmia.

In support of their theory of liability, and as their sole causation evidence, plaintiffs proffered the expert testimony of Dr. Charles Vyvyan Howard. Dr. Howard testified, in pretrial deposition, that he believed that fetal exposure to benomyl at a concentration of twenty parts per billion in the maternal bloodstream would cause microphthalmia in humans. Dr. Howard based his conclusion on: 1) rat gavage studies and 2) lab experiments on human and rodent cells *in vitro*.

Defendants moved *in limine* to exclude Dr. Howard's testimony on the ground that his opinion is not based on scientific principles and discoveries that are generally accepted in the field" of teratology, and thus inadmissible.

After an evidentiary hearing, the trial court denied that motion and permitted Dr. Howard to testify to his opinion that benomyl is a human dermal teratogen that at fetal tissue levels of 20 parts per billion caused the birth defect microphthalmia in John Castillo.

At trial, plaintiffs claimed that a single incident, in which Mrs. Castillo was allegedly "drenched" with Benlate spray, caused John Castillo's birth defect. At the close of the evidence, DuPont moved for a directed verdict arguing that plaintiffs had failed to prove that Benlate is defective and that any such defect proximately caused

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[1] *Amici* limit themselves to the scientific issues regarding the generally accepted methodology for determining human teratogenicity, and assume for the purposes of their analysis that Mrs. Castillo was exposed to Benlate as she claims.

John's microphthalmia. The jury found for plaintiffs. DuPont and Pine Island moved to set aside the verdict and/or for a new trial, which motion the trial court denied. The Third District Court of Appeals reversed and remanded the case for entry of judgement on behalf of DuPont. This Court granted Petitioners' Petition for Discretionary Review.

## SUMMARY OF ARGUMENT

There is a generally accepted methodology in the field of teratology for determining whether a substance is a human teratogen. That methodology requires:

1. a specific pattern of birth defects across individuals that is associated with exposure;
2. epidemiological studies showing an association between exposure and birth defects;
3. positive cross-species test results at equivalent doses and by the same route of exposure as human exposure to establish a dose-response relationship;
4. *in vitro* tests[2] used to identify a mechanism of action; and
5. biological plausibility that the mechanism of action could cause the pattern of birth defects observed.

Dr. Howard did not follow this methodology. He ignored, rejected or misapplied all aspects of it, and instead applied a methodology of his own. His methodology involved determining that a substance, benomyl, is a human teratogen (and its threshold level of teratogenesis) based solely on (1) single-species

[2] *In vitro* tests are those conducted in the artificial environment of a test tube, petri dish, or similar laboratory vessel, rather than in live animals. Live animal testing is known as *in vivo* testing.

animal tests at high doses and a route of administration, gavage,[3] not found in human exposures (and certainly not claimed to have occurred in this case), and (2) *in vitro* cell culture tests with endpoints of neurite inhibition and micronuclei formation.

Dr. Howard's methodology is not scientifically valid and is not generally accepted in the fields of teratology and medical genetics. His erroneous methodology led him to conclude that benomyl is a human teratogen via dermal exposure, the first such teratogen whose effect is allegedly through dermal absorption. Dr. Howard's studies were done specifically for this litigation, and his methodology and conclusions have never been presented for peer review by the scientific community, and in particular the teratology community.

## ARGUMENT

*Amici* have reviewed Dr. Howard's testimony, and believe that Dr. Howard's analysis and methodology are not generally accepted among teratologists and epidemiologists, and that they are not scientifically sound. *Amici* agree with the District Court of Appeal that plaintiffs' scientific evidence should never have been admitted into evidence because it did not satisfy the test for admissibility set forth in *Frye v. United States*, 293 F. 1013 (D.C. Cir. 1923).

[3] Gavage studies involve the force-feeding of the test substance, usually by tube, directly into the stomach of the animal.

## I. THE LEGAL STANDARD

*Amici* are informed that courts in Florida apply the "Frye standard" (*Frye v. United States*, 293 F. 1013 (D.C. Cir. 1923)) for determining whether expert testimony is admissible. In *Frye*, the court espoused the requirement that scientific evidence be "generally accepted" within the relevant scientific community. 293 F. at 1014.

In *Murray v. State*, 692 So.2d 157, 161 (Fla. 1997) (quoting *Ramirez v. State*, 651 So.2d 1164, 1168 (Fla. 1995)), this Court held:

> [T]he burden is on the proponent of the evidence to prove the general acceptance of both the underlying scientific principle and the testing procedures used to apply that principle to the facts of the case at hand. ... The general acceptance under the Frye test must be established by a preponderance of the evidence.

*See also Hadden v. State*, 690 So.2d 573, 578 (Fla. 1997):

> [I]t is the function of the court to not permit cases to be resolved on the basis of evidence for which a predicate of reliability has not been established. Reliability is fundamental to issues involved in the admissibility of evidence....Novel scientific evidence must also be shown to be reliable on some basis other than simply that it is the opinion of the witness who seeks to offer the opinion.")

In *Ramirez v. State*, 651 So.2d 1164, 1168 (Fla. 1995), this Court outlined a four-step process for determining the admissibility of expert opinion testimony concerning a new or novel scientific principle:

> First, the trial judge must determine whether such expert testimony will assist the jury in understanding the evidence or in determining a fact in issue....Second, 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." Frye v. United States, 293 F. 1013, 1014 (D.C. Cir.1923)....The third step in the process is for the trial judge to determine whether a particular witness is qualified as an expert to present opinion testimony on the subject in issue.... Fourth, the judge may then allow the expert to render an opinion on the subject of his or her expertise, 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; *see also Murray*, 692 So.2d at 161.

## II. THE SCIENTIFIC ISSUES

### A. Introduction

The term “teratogen” is often misused to imply that a substance (an "agent") by itself either ***is*** or ***is not*** teratogenic. Viewed in this way, non-specialists tend to think that mere exposure to a “teratogen” will cause birth defects in the developing embryo. In reality, teratogenicity is a property of an “exposure” taken as a whole, which involves not only the physical and chemical nature of the agent but also the dose, route, and gestational timing involved. The occurrence of other, concurrent exposures as well as the biological susceptibility of the mother and embryo are also factors that may determine whether or not a particular exposure is likely to produce damage in a particular instance. Exposures, then, are teratogenic only under certain circumstances. To use an example, the risk of a woman having a malformed child following exposure to thalidomide (a drug which caused severe limb defects in exposed children) during pregnancy ranges between 25-50%. If mere exposure to thalidomide during pregnancy caused birth defects (as many people believe) then the risk would approach 100%. But we know from the literature that there were women exposed to thalidomide during

the critical period of development (from the third to the eighth week after conception) who gave birth to normal babies. So, the fact that an agent may be teratogenic under certain circumstances does not guarantee that it will be teratogenic in other circumstances. *See* J.M. Friedman, J.E. Polifka, Teratogenic Effects of Drugs: A Resource for Clinicians (TERIS) (2d ed. 2000); J.E. Polifka, J.M. Friedman, Clinical teratology: identifying teratogenic risks in humans, Clin. Genetics 56:409-420 (1999); J.M. Friedman, Practical teratology, in E. Jauniaux, E.R. Barnea, R.G. Edwards, eds. Embryonic Medicine and Therapy 481-505 (1997).[4]

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[4] The TERIS database and teratogen information services (TIS) are two examples of how clinical teratologists assess teratogenic risk in humans. TERIS is a computerized database that provides up-to-date, authoritative teratology information for health care professionals. TERIS is distributed internationally and has more than 1000 subscribers. It is the only peer-reviewed teratology database commercially available. TERIS was developed to help physicians counsel pregnant patients regarding their teratogenic risks. Documents summarizing the teratology literature (both animal and human) are sent to each member of the TERIS Advisory Board for independent review. Based on the summarized literature, each member rates the magnitude of teratogenic risk. The ratings range from Undetermined, Unlikely, None, Minimal, Small, Moderate, to High. Each member also rates the quality and quantity of data on which the first risk estimate is based. These ratings range from None, Limited, Fair, Good, or Excellent. This rating provides information regarding the degree of certainty with which risk assessment can be made. The assessment of data quality takes into account the reproducibility, consistency, and biologic plausibility of available clinical, epidemiologic, and experimental data. Reproducibility is determined by whether similar findings were obtained in independent studies. Concordance is considered to be particularly important if the studies were of a different design and if the types of anomalies observed in various studies were similar. Effects seen in mammalian studies are weighed more heavily if the exposure is similar in dosage and route to that encountered clinically, if the malformations produced are analogous to those reported in humans, and if the species tested are closely related to humans phylogenetically. Statistical associations between malformations in an infant and maternal exposure during pregnancy are considered causal only if the data do not contradict accepted biologic principles regarding absorption of the agent, gestational timing of the exposure, and dosage.

When assessing teratogenic potential in humans, TERIS gives more weight to controlled epidemiological studies than to case reports, clinical series, or animal studies. There is little confidence in the accuracy of a teratogenic risk assessment when the only data that are available are data from rodent studies, particularly if the doses used were much higher than those typically encountered by humans. For this reason, the TERIS Advisory Board assigns a teratogenic risk assessment of UNDETERMINED for agents for which only rodent studies are available. There is simply no way to predict whether or not that agent will be teratogenic in humans on the basis of those studies alone. *In vitro* and chick embryo studies are never included in TERIS agent summaries and are never used as a basis for any of the TERIS risk estimates for the reasons explained elsewhere in this brief.

There are approximately 40 teratology information services (TIS) throughout North America and a similar number in Europe. Medical doctors who have expertise in teratology generally administer these services. Other staff members, such as program coordinators and teratogen information specialists, all have expertise or have been trained in teratology. These services provide teratology information for health care professionals. The Organization of Teratology Information Services (OTIS), a national organization which oversees U.S. teratology information services, worked in conjunction with the Council of Regional Networks for Genetic Services (CORN), a federally-funded coalition of the 10 regional genetic networks, sickle cell agencies, and consumer groups, to develop a "*Framework for Provision of Teratology Information Services*". One of the purposes of this document was to develop a minimum data set in order to provide risk assessment regarding the exposure in question. Included in this minimum data set is information regarding dose of agent, route and timing of exposure, reason for exposure, the conditions surrounding her exposure, maternal symptoms from exposure, maternal illness or fever during pregnancy, exposure to other drugs, chemicals, and/or environmental agents, use of tobacco or alcohol, complications during pregnancy, maternal age, family and medical history, and maternal ethnicity. According to the framework, "responses provided by TIS staff should integrate current medical literature and other relevant information to provide a concise, understandable, timely, customized reproductive risk assessment." This framework is a formal effort to standardize aspects of the services provided by TIS for quality assurance purposes. It has been published in *Reproductive Toxicology* 8: 439-442 (1994).

These services illustrate how clinical teratologists assess human teratogenicity. The standard methodology used by clinical teratologists is to review all of the relevant teratology studies and to use this information in conjunction with a detailed family and

## B. There Is A Generally Accepted Methodology Or Set Of Principles For Determining Whether A Substance Is A Human Teratogen

In numerous product liability cases courts have held that there is a specialized medical community that has developed the generally accepted methodology for determining whether a substance is a human teratogen. That community is composed of teratologists and medical geneticists. *See, e.g.*, *Wade-Greaux v. Whitehall Lab., Inc.*, 874 F. Supp.1441, 1478 (D.V.I. 1994), *aff'd*, 46 F.3d 1120 (3d Cir. 1994); *National Bank of Commerce v. Dow Chem. Co.*, 965 F. Supp. 1490, 1518-19 (E.D. Ark. 1996).

There is a generally accepted methodology for determining whether a substance is a human teratogen and it includes the following: (1) identifying a pattern of birth defects across individuals that is associated with exposure to a substance; (2) performing epidemiological studies to determine whether there is an association between exposure to the substance and the pattern of birth defects; (3) conducting animal (*in vivo*) tests in more than one species to establish a dose response relationship; (4) performing *in vitro* tests to identify a mechanism of action; and (5) determining whether there is "biological plausibility" that the mechanism of action, the dosage, and the route of exposure could cause the observed pattern of birth defects.

### 1. Pattern of Defect

Identifying a pattern of birth defects associated with exposure is an essential element of determining human teratogenicity. Human teratogens show a specific

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medical history to determine if an individual patient's exposure has increased her risk of giving birth to an infant with a major malformation above the 3-5% background risk that is present for all pregnant women. Clinical teratologists do not advise patients that they have a risk for a birth defect simply because abnormal development was detected in an *in vitro* or animal study. That would be grossly misleading.

pattern of defects, often with limited and predictable variability based on timing of exposure relative to stage of fetal development. Moreover, the pattern shown by human teratogens rarely, if ever, involves a single, unitary defect. Teratogens typically affect a number of systems developing in the fetus at the same time, producing a variety of defects. The existence of a single defect in an individual is a strong indication that the defect is *not* the result of teratogenic exposure.

There is no pattern of birth defect associated with Benlate exposure, either in the medical literature or in the testimony in this litigation. While Dr. Howard attributes John Castillo's microphthalmia to his mother's claimed exposure to Benlate, one alleged instance of birth defect and exposure does not establish the requisite pattern of defects associated with such exposure. There is no syndrome of birth defects that has been associated in the medical literature with Benlate exposure during the 30 years of Benlate use. Microphthalmia is a birth defect identified in the medical literature centuries before Benlate was invented. Microphthalmia has several known and many suspected genetic causes. One instance of defect and alleged exposure obviously does not constitute a pattern of defects.

**2. Epidemiology**

Epidemiology (studies to observe the effect of exposure of a single factor upon the incidence of disease in human populations)[5] is an essential element of the methodology of teratology.[6] Because there are differences between animal species,

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[5] An epidemiological study is one designed to "observe the effect of exposure to a single factor upon the incidence of disease in two otherwise identical populations." Black & Lilienfield, Epidemiologic Proof in Toxic Tort Litigation, 52 Fordham L. Rev. 732, 755 (1984).

[6] We recognize that the Third District Court of Appeal did not go so far. That court correctly concluded that other elements of plaintiffs' scientific proof (such as their experts' use of *in vivo* and *in vitro* studies) failed the "generally accepted" test, and the

examination of and reliance on human data is critical. While individual case reports can lead to identification of potential medical issues, and point to the need for further study, and on occasion lead to diagnoses and treatment in the individual case, studies of the incidence of disease in a population provide the only human data that gives the medical community information about association of exposure and birth defects. No published epidemiological study has shown an association between Benlate exposure and microphthalmia or any other birth defect. To the contrary, the three epidemiological studies on benomyl and birth defects conducted to date found no such association.[7]

When extensive epidemiological studies have shown that there was no association between a chemical and a birth defect or disease, contrary epidemiological studies are necessary to prove causation. *See Allen v. Pennsylvania Eng'g Corp.*, 102 F.3d 194 (5th Cir. 1996); *Brock v. Merrell Dow Pharm., Inc.*, 874 F.2d 307, 315 (5th Cir. 1989), *modified on reh'g*, 884 F.2d 166 (5th Cir. 1989), *cert denied*, 494 U.S. 1046 (1990) ("Assuredly, one day in the future, medical science may have a clearer understanding of the mechanics of tissue development in the fetus. However, that is

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court correctly decided on that basis to reverse the trial court's evidentiary ruling and the trial court's judgment. However, as scientists in this field, we urge this Court to adopt and articulate the proper scientific criteria, and to state that epidemiological proof is necessary before one can conclude that a substance is a human teratogen. *Amici* believe that as a matter of sound science, plaintiffs' science witnesses were seriously in error for failing to consider the complete absence of any epidemiologic studies link Benlate with teratogenic defects and their failure to consider the three epidemiologic studies which conclude that there is no association between Benlate and such defects.

[7] There have been three epidemiological studies of Benlate and birth defects undertaken in the wake of media reports in England of "clusters" of eye defects.

not the case today, and speculation unconfirmed by epidemiologic proof cannot form the basis for causation in a court of law."); *Richardson by Richardson v. Richardson-Merrell, Inc.*, 857 F.2d 823, 832 (D.C. Cir. 1988) ("Bendectin...has been extensively studied and a wealth of published epidemiological data has been amassed, none of which has concluded that the drug is teratogenic. Uniquely to this case, the law now has the benefit of twenty years of scientific study, and the published results must be given their just due."); *Lynch v. Merrell-National Labs., Div. of Richardson-Merrell, Inc.*, 830 F.2d 1190 (1st Cir. 1987); *Wade-Greaux v. Whitehall Labs., Inc.*, 874 F. Supp. 1441, 1451 (D.V.I. 1994) ("Regardless of the particular articulation of the teratology community's methodology, positive human epidemiologic studies are always required to reach a conclusion as to whether a specific agent is teratogenic in humans."); *Cadarian v. Merrell Dow Pharms., Inc.*, 745 F. Supp. 409, 412 (E.D. Mich. 1989) ("in vivo and in vitro animal studies...are insufficient to prove causation in human beings in the absence of confirmatory epidemiological evidence."). Other factors that courts have considered in weighing scientific evidence in the absence of positive epidemiology are the failure of experts to publish or submit their studies for peer review, *see Brock*, 874 F.2d at 313 ("While we do not hold that [failure to publish a study or conclusions for the purposes of peer review], in and of itself, renders his conclusions inadmissible, courts must nonetheless be especially skeptical of medical and other scientific evidence that has not been subjected to thorough peer review."); *see also Daubert v. Merrell Dow Pharmaceuticals, Inc.*, 509 U.S. 579, 113 S.Ct. 2786 at 2797 (1993). The "overriding significance" of epidemiological studies in determining human teratogenicity has been accepted judicially and scientifically. *Oxendine v. Merrell Dow Pharm., Inc.*, 1996 WL 680992 at *7, Civ. No. 82-1245 (D.C. Super. Ct., Oct. 24, 1996); *see also DePyper v. Navarro*, 1996 WL 788828 (Mich. Cir. Ct. Nov. 27, 1996).

### 3. Cross-Species Animal Tests

The methodologies developed by teratologists for the use of animal test data are based on the recognition that there are differences between species in reacting to various substances. Because of differences between species, it is almost impossible to extrapolate animal findings to humans with any certainty. *See Viterbo v. Dow Chem. Co.*, 826 F.2d 420, 424 (5th Cir. 1987) ("the effects of chemicals differ between humans and rats"); *DePyper v. Navarro*, 1995 WL 788828, at *30 (Mich. Cir. Ct. Nov. 27, 1995) ("substances which are teratogens in animals are not necessarily, or even likely to be, teratogens in humans"); *Turpin v. Merrell Dow Pharm., Inc.*, 959 F.2d 1349, 1359 (6th Cir. 1992), *cert. denied*, 506 U.S. 826 (1992) ("different species of animals react differently to the same stimuli"); *National Bank of Commerce v. Dow Chem. Co.*, 965 F. Supp. 1490, 1527 (E.D. Ark. 1996) ("There are millions of different species of animals. Each has its own physiological, biochemical and metabolic systems. One cannot correctly conclude from a determination that a chemical agent has a teratogenic effect in one species that it will have such effect in another species."), *citing Wade-Greaux v. Whitehall Lab., Inc.*, 874 F. Supp. 1441, 1453-54 (D.V.I. 1994), *aff'd*, 46 F.3d 1120 (3d Cir. 1994).

One of the uncertainties is associated with extrapolation both from animals to humans and from high to low doses. *See* REFERENCE MANUAL ON SCIENTIFIC EVIDENCE 202 (Federal Judicial Center 1994); *see also Brock*, 874 F.2d 307, 313 (5th Cir. 1989) ("This circuit has previously realized the very limited usefulness of animal studies when confronted with questions of toxicity....The court noted several methodological flaws which rendered the rat study inconclusive; specifically, the court focused on the small number of rats used in the study, the high (sometimes near-lethal) doses given, and the difficulty of extrapolating those results to humans."); *Merrell*

*Dow Pharms., Inc. v. Havner*, 953 S.W.2d 706, 729 (Tex. 1997), *cert. denied*, 523 U.S. 1119 (1998). The generally accepted methodology for determining teratogenicity requires positive results in tests on more than one species and supporting epidemiological evidence.

There is no support in the scientific literature for the proposition that single-species animal tests can be extrapolated to a conclusion of human teratogenicity. The experience with benomyl in tests on different animal species demonstrates the reality of species differences and underscores the validity of the principle requiring positive test results in more than one species: repeated developmental toxicology tests of benomyl carried out on rabbits and mice by gavage show no microphthalmia, unlike the similar tests on rats.[8] There are, moreover, numerous decisions recognizing the inherent limitations of extrapolating human teratogenicity from *in vivo* studies.[9]

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[8] *See*, R. Kavlock, et al., Teratogenic Effects of Benomyl in the Wistar Rat and CD-1 Mouse, with Emphasis on the Route of Administration, Toxicol. Appl. Pharmacol. 62:44-54.

[9] *See, e.g.*, *Cavallo v. Star Enter.*, 892 F. Supp. 756, 770-71 (E.D.Va. 1995); *Wade-Greaux*, 874 F.Supp. 1441, 1458; *Cavallo v. Star Enter.*, 892 F. Supp. 756 (E.D. Va. 1995) (excluding expert testimony on human teratogenesis where expert "is unable to provide any scientifically valid basis to support the leap from those [animal] studies to his opinion in this case."), *aff'd in pertinent part*, 100 F.3d 1150 (4th Cir. 1996); *Merrell-Dow Pharm., Inc. v. Havner*, 953 S.W.2d 706, 729 (Tex. 1997) ("[S]cientific methodology would not rely on animal studies, standing alone, as conclusive evidence that a substance is a teratogen in humans."); *Raynor v. Merrell Pharm., Inc.*, 104 F.3d 1371, 1375 (D.C. Cir. 1997) (the only way to test whether data from non-human studies can be extrapolated to humans would be to conduct human experiments or to use epidemiological data); *Elkins v. Richardson-Merrell, Inc.*, 8 F.3d 1068, 1071 (6th Cir. 1993) (expert opinion indicating a basis of support in animal studies is inadequate to permit a jury to conclude that Bendectin more probably than not causes limb defects); *Lynch v. Merrell-National Lab.*, 830 F.2d 1190, 1194 (1st Cir. 1987) (*in vivo* animal studies do not have the capability of proving causation in human beings

Cross-species animal tests are required before we can infer human teratogenicity[10] of a substance and the generally accepted methodology requires that the animal tests demonstrate a dose response relationship. If human exposure is dermal, the animal tests should employ dermal exposure. If the

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in the absence of any confirming epidemiological data); *Brock v. Merrell Dow Pharm., Inc.*, 874 F.2d 307, 313 (5th Cir. 1989), *modified on reh'g*, 884 F.2d 166 (5th Cir. 1989), *cert. denied*, 494 U.S. 1046 (1990) (animal studies are of limited usefulness in determining human toxicity).

[10] We would also point out that animal studies do ***not*** enable us to ***predict*** whether or not an agent will be teratogenic in humans. Animal studies may provide supportive information, they may provide information regarding mechanisms of potential teratogenicity, but they are only one small piece of the puzzle. They tell us that at *this* particular dose, in *this* one species under *these specially-controlled circumstances*, the agent is teratogenic. The environment of humans is not controlled, humans are not laboratory bred, and humans are not rats or mice. Thus, the information from single species animal studies does not allow us to predict human teratogenicity.

human exposure involves low dose, such as the 20 parts per billion posited by Dr. Howard, the animal tests should involve similarly low doses. Scientists, and courts, reject the applicability of high-dose animal tests because any substance can be teratogenic when given at sufficiently high doses. As one leading teratologist notes: "Most teratologists accept [the] principle that any agent can be shown to be teratogenic in an animal provided enough is given at the right time. For instance, both sodium chloride [salt] and sucrose [sugar] have been shown to produce animal teratogenicity." Thomas J. Shepard, Human Teratogenicity, 33 Advances in Pediatrics 225, 227 (1986). Comparable doses are necessary in order to appropriately apply animal data to humans.

Teratologists also require that animal tests involve the same or equivalent routes of exposure as human exposure before they extrapolate animal test results to humans because the route of exposure can dramatically affect whether a substance is teratogenic. This has been demonstrated with respect to benomyl in rat tests. In the rat gavage tests relied on by Dr. Howard, the rats showed teratogenic effects above a certain threshold dose. When the rats were administered benomyl in the diet rather than by gavage, however, there were no teratogenic effects at dose levels five times higher than the gavage threshold dose.[11] Gavage studies are not applicable to predicting dermal teratogenesis. *See Chikovsky v. Ortho Pharm. Corp.*, 332 F. Supp. 341 (S.D. Fla. 1996).

**4. *In Vitro* Tests**

In vitro studies are generally useful in identifying the potential target organ toxicity and mechanisms of toxic action. *See* Bernard D. Goldstein and Mary Sue

[11] *See* H. Sherman, *et al.*, Reproduction, Teratogenic, and Mutagenic Studies With Benomyl, Toxicol. Appl. Pharmacol. 32:305-15 (1975).

Henifin, Reference Guide on Toxicology, in REFERENCE MANUAL ON SCIENTIFIC EVIDENCE 181, 203 (Federal Judicial Center 1994).

*In vitro* teratogenic testing involves the transplantation of fetal cells into a medium where they are subjected to agents to study the effect on the transplanted tissues. It is not scientifically valid or generally accepted in the field of teratology to extrapolate human teratogenicity or a human threshold dose for teratogenesis from *in vitro* cell culture studies. *See* Gerald W. Boston, A Mass-Exposure Model of Toxic Causation: The Content of Scientific Proof and the Regulatory Experience, 18 Col. J. Env. L. 181, 218 (1998). There is nothing in the scientific literature that would permit such a use of *in vitro* studies.

*In vitro* tests are not used as indicators of human teratogenicity for several reasons: they do not replicate the *in vivo* situation; they do not reflect the influences of the placental barrier and other mother-fetus interactions; the human processes of metabolism, distribution, and excretion are not duplicated in the test tube; cells in a test tube or petri dish culture lack some of the biochemical processes found in cells in a living organism. The cases have recognized this scientific principle. *See Wade-Greaux*, 874 F. Supp. 1441, 1453; *Richardson v. Richardson-Merrell, Inc.*, 857 F.2d 823,830 (D.C. Cir. 1988), *cert. denied*, 496 U.S. 882 (1989); *DePyper v. Navarro*, 1996 WL 788828. Although *in vitro* tests are used to identify mechanisms of action in teratology investigations, they have never been accepted as tests for human teratogenicity or human teratogenic dose level. None of the *in vitro* tests relied on by Dr. Howard address the mechanism of action of benomyl and he does not use them for that purpose.

### 5. Biological Plausibility

Once a mechanism of action is identified through *in vitro* testing, that mechanism must be evaluated for its plausibility in light of known biological data and principles. If the mechanism of action identified in the *in vitro* testing is, for example, inhibition of neurite growth (as in Dr. Howard's tests) it is not biologically plausible to ascribe that mode of action as a causal element of microphthalmia unless there are neurites present in the developing eye to be inhibited. Because there are generally no neurites present at the early stages of development of the fetal eye, a teratologist will not find it biologically plausible that an agent causing neurite inhibition is teratogenic and capable of causing microphthalmia.

## C. Dr. Howard's Methodology Is Not Generally Accepted in the Relevant Scientific Community

*Amici* submit that the methodological and scientific inadequacies of Dr. Howard's opinion testimony, which require its exclusion under *Frye* (and under *Daubert v. Merrell Dow Pharmaceuticals, Inc.*, 509 U.S. 579 (1993)), include the following:

- His reliance on single-species animal studies to infer the human teratogenicity of benomyl, the active ingredient in Benlate.

- His use of *in vitro* cell culture studies to establish a dose or tissue level at which benomyl causes teratogenesis in humans.

- His use of a methodology for determining human teratogenicity which is not accepted by teratologists and is contrary to accepted medical practice.

- His opinions and methodologies have never been applied in medical practice by him or anyone else, and were developed solely for litigation purposes.

### 1. Dr. Howard's Methodology

Petitioners' brief describes Dr. Howard's methodology for determining whether a substance is a human teratogen as "entirely common and accepted." Pet. Initial Br. 20. That is wrong. None of the five elements of Dr. Howard's

methodology set forth in Petitioners' brief are accepted methodology for determining human teratogenesis.

According to Petitioners, the five elements of Dr. Howard's methodology are:

1. refusal to use epidemiology (allegedly because such studies are not available and cannot be done with benomyl in any event);

2. extrapolation from gavage administered high dosage tests on a single species of animal to human beings to conclude that benomyl causes microphthalmia in human beings through low dose dermal exposure;

3. use of *in vitro* cell culture tests to establish the threshold level at which benomyl is teratogenic in human beings;

4. exclusion of genetic causes of microphthalmia; and

5. exclusion of other environmental causes of microphthalmia.

*See* Pet. Initial Br. 20-21.

This is not the generally accepted methodology for determining human teratogenesis. Exclusion of possible genetic and environmental causes is incorrect because the generally accepted methodology is an affirmative approach for ruling in particular causes.

### 2. Dr. Howard's Refusal To Consider Epidemiology Is Not Scientifically Valid And Not Generally Accepted In The Field Of Teratology.

Epidemiology is a generally accepted element of the methodology for determining human teratogenicity. "[A]n essential element of the generally accepted methodology is that exposure during pregnancy should be associated with an increased frequency of a distinctive pattern of birth defects, as shown through repeated, consistent human epidemiological studies." *Wade-Greaux*, 874 F. Supp. at 1478 (emphasis supplied). Dr. Howard's methodology, as described by Petitioners, does not include consideration of epidemiology. Petitioners assert that epidemiological studies of benomyl are not available and that they are not even possible. This is untrue. Epidemiological studies of benomyl are available. As noted above, three studies have been done in three different countries and none of them shows an association between benomyl use and birth defects.[12] Individually and collectively

[12] A case-control study of over 940,000 newborns in Italy for possible links between eye defects and Benlate usage found that parental occupation in agriculture, where the bulk of benomyl exposure occurs, was not associated with eye defects and there was no association of eye defects with areas of high benomyl use. A. Spagnolo, *et al.*, Anophthalmia and Benomyl in Italy: A Multicenter Study Based on 940,615 Newborns, Repro. Toxicology 8:397-408 (1994).

A cohort study that the incidence of microphthalmia and anophthalmia among

these studies support a conclusion that there is no association between benomyl exposure and microphthalmia. It is improbable that three large studies using three different approaches (cohort study, case-control study, and descriptive clusters study) would miss such an association, particularly if Benlate were effective in humans at the extremely low doses Dr. Howard suggests.

Dr. Howard's refusal to consider any such studies in his methodology is not accepted practice in the field of teratology.

The suggestion in Petitioners' brief that benomyl epidemiology is not possible because Benlate is "toxic" and thus "not suitable for human experiment" reflects a lack of understanding of the field of epidemiology and its use in teratology. "Experimental" epidemiology studies, involving administration of a test substance to a set of test subjects, are only one type of epidemiology study and are not likely to be used for agricultural chemicals. There are, however, other types of epidemiological studies that are commonly used in teratology investigations of substances not intended for direct human consumption. They include "observational" studies in which a group of individuals who have been exposed to the substance of interest is observed and compared with another group that has not been exposed. There are two main types of observational studies, cohort studies and case-control studies. In cohort studies the incidence of disease is measured in the exposed and unexposed groups. In case-

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children born to farm workers in Norway potentially exposed to benomyl was not different from the incidence within the general population. P. Kristensen, *et al.*, Birth Defects among Offspring of Norwegian Farmers, Epidemiology 8:537-44 (1997).

An epidemiological study of media-reported clusters of microphthalmia/anophthalmia in the United Kingdom did not find any such clusters or any association between Benlate and ocular defects. H. Dolk, *et al.*, Geographical Variation in Anophthalmia and Microphthalmia in England, 1988-94, British Medical Journal, 317:905-09 (1998).

control studies the frequency/extent of exposure is

measured in a group with disease and in a group without disease. In both types of study the goal is to determine whether there is an association between exposure to a substance and disease. *See*, M.D. Green, D.M Freedman, L. Gordis, Reference Guide On Epidemiology, in REFERENCE MANUAL ON SCIENTIFIC EVIDENCE, 333, 338-340 (Federal Judicial Center 2000).

Observational studies, such as the three studies of benomyl, are generally accepted and commonly used in the field of teratology to assess human teratogenicity. Either of these types of observational epidemiology studies can be used to study the effects of benomyl. Dr. Howard's refusal to consider these studies is completely contrary to accepted methodology in the field; his exclusion of critical epidemiological data contravenes the accepted principles of science and teratology. The existing epidemiological data on Benlate, if

properly considered, would contradict a conclusion that Benlate is a human teratogen.

### 3. Dr. Howard's Determination Of Benomyl Human Teratogenicity From Single-Species Gavage Tests Is Not Scientifically Valid And Not Generally Accepted In The Field Of Teratology

Dr. Howard's methodology for determining human teratogenicity relies on developmental toxicology tests performed by DuPont, by the U.S. Environmental Protection Agency, and by independent researchers which showed anophthalmia and microphthalmia in fetuses of pregnant rats when benomyl was administered by gavage at a dose of 62.5 mg/kg body weight. Gavage tests in other species of animals (rabbits and mice) showed no anophthalmia or microphthalmia at the same or higher doses of benomyl.

It is scientifically invalid to extrapolate observations of teratogenesis from single-species animal tests directly to humans. That is not an accepted methodology in the field of teratology, and Dr. Howard's extrapolation was methodologically incorrect. It was particularly inappropriate for him to select and use the results of tests in one species (rat) and ignore the contradicting results of tests in two other species (rabbits and mice). This is not just an issue of the weight of the evidence and medical judgment -- the fact that benomyl test results differ across species demonstrates why teratologists do not rely on single-species animal tests to determine human teratogenicity. Different species have different physiological, biochemical, and metabolic mechanism that process and break down chemicals so that from species to species and there are dramatic differences in bioavailability and detoxification of a drug or chemical. *See In re Paoli Railroad Yard PCB Litigation*, No. 86-2229, 1992 WL 323633 *5 (E.D.Pa. 1992).[13] The different results in cross-species tests of the effect of benomyl shows that different species react differently to the same substance. A single species test result does not inform teratologists what might occur if the substance is ingested by a human being.

Not only are animal test results impacted by species differences, but such tests frequently involve extremely high doses relative to human exposures.[14]

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[13] *See National Bank of Commerce*, 965 F. Supp. at 1527 ("One cannot scientifically conclude from a determination that a chemical agent has a teratogenic effect in one species that it will have such effect in another species."), citing *Wade-Greaux v. Whitehall Lab.*, 874 F. Supp. 1441, 1453-54 (D.V.I. 1994); *Sorenson v. Shaklee Corp.*, 31 F.3d 638, 646 n.12 (8th Cir. 1994) ("Because of the dose-response differential between animals and humans, however, extrapolating to humans from animal studies is problematic.").

[14] This is particularly so considering the brief dermal exposure claimed in this case. "[T]he phenomenon that different routes of administration affect the teratogenic impact

of an agent has been repeatedly tested and confirmed." *Wade-Greaux*, 874 F. Supp. at 1480. *See also* Roth-Nelson & Verdeal, Risk Evidence in Toxic Torts, 2 Envt'l Law 405, 420 (1996) (disputing the usefulness of "exotic" routes of exposure).

Courts have recognized this basic scientific consideration, and have consistently refused to allow experts to testify that a substance causes birth defects in humans based on animal tests conducted at higher dose levels than likely human exposure. *See, e.g., Viterbo v. Dow Chem. Co.*, 826 F.2d 420, 424(5th Cir. 1987); *Turpin v. Merrell Dow Pharm., Inc.*, 959 F.2d 1349 (6th Cir. 1992) (citing James Wilson, Current Status of Teratology, in HANDBOOK OF TERATOLOGY 60 (1977); *cf. Brock v. Merrell Dow Pharm., Inc.*, 874 F.2d 307, 313 (5th Cir. 1989), *modified on reh'g*, 884 F.2d 166 (5th Cir. 1989), *cert denied*, 494 U.S. 1046 (1990) (rejecting results of gavage doses 100 to 500 times the drug dose normally given to humans in the context of assessing human teratogenicity).

**4. Dr. Howard's Use Of *In Vitro* Cell Culture Tests To Establish The Tissue Level At Which Benomyl Causes Microphthalmia In Humans Is Not Scientifically Valid And Is Not Generally Accepted In The Field Of Teratology.**

Dr. Howard used the results of two *in vitro* cell culture studies of benomyl to

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Comparable doses are essential to appropriately apply animal data to humans. Results of animal studies typically cannot be extrapolated to humans because such studies often intentionally employ quantities of the test agent far greater than any conceivable human dose in order to get a positive result. *National Bank of Commerce*, 965 F. Supp. at 1527, *citing Wade-Greaux*, 874 F. Supp. 1441, 1453-54 (D.V.I. 1994), *aff'd*, 46 F.3d 1120 (3d Cir. 1994). As the court in *DePyper v. Navarro*, 1995 WL 788828, *30 (Mich. Cir. Ct. Nov. 27, 1995) noted: "[A]nimal experiments employ dosages that far exceed those normally given to human beings, and further . . . there is no basis for concluding that a particular substance is teratogenic in all species." This is true in the case of the rat gavage studies relied on by Dr. Howard, where rats were exposed to enormous quantities of benomyl.

extrapolate a threshold tissue level that he says will cause microphthalmia in humans -- 20 parts per billion. That extrapolation is not scientifically valid, nor is it generally accepted in the field of teratology.

The *in vitro* tests relied on by Dr. Howard were (1) tests on human fetal lung cells which showed micronuclei formation following a 24 hour soak in benomyl at 20 ppb, which the researcher, Dr. Dick van Velzen, interpreted or used as a surrogate for apoptosis, or programmed cell death; and (2) tests on cancerous human nerve cells which, according to Dr. Howard showed a reduction of neurite growth following a 24 hour soak in benomyl at similarly low levels.

There are numerous problems with the use made by Dr. Howard of these *in vitro* tests. We will identify some of the more serious, based on general principles governing scientific validity.

First, neither test design has ever been validated as a measure of teratogenicity or teratogenic threshold. Nowhere in the scientific literature has such a use been made of these or any other *in vitro* tests. To the contrary, at least one study has concluded that *in vitro* neurite growth inhibition, observed in Dr. Howard's neurite tests, is not predictive of teratogenicity. *See* C. Mummery, *et al.*, A Short-term Screening Test for Teratogens Using Differentiating Neuroblastoma Cells In Vitro, Teratology 29:271-279 (1984).

Second, the effect observed by Dr. van Velzen, micronuclei formation, is not a valid measure of cell apoptosis; and apoptosis is not a validated indicator of human teratogenicity. Both uses (i.e., of micronuclei formation and apoptosis) are novel as applied to a teratogenicity determination, are unsupported by the scientific literature, and not generally accepted in the field of teratology.

Third, the selection of cells for the *in vitro* tests is not consistent with the conclusions Dr. Howard is attempting to draw. The use of cancer cells is not appropriate for growth-related testing because cancer cells do not grow normally in any event. Likewise, neurite growth is not a relevant consideration

in assessing impact on developing eye cells because the bulk of developing eye cells do not even have neurites.

Fourth, allowing the cells to soak in an undiminished bath of benomyl for 24 hours creates a circumstance that is irrelevant to the experience of a living fetus. Normal metabolic processes and excretion of the benomyl metabolites would result in a relatively brief exposure time as well as a rapid reduction of the tissue exposure level in a living organism.

Fifth, teratologists do not accept the notion that one can extrapolate from *in vitro* tests to establish human teratogenicity or teratogenic threshold. Such tests are used in the field of teratology primarily to identify mechanisms of action. Neither of the *in vitro* assays or the endpoints examined by Dr. van Velzen and Dr. Howard have been validated as a test for teratogenicity.[15] That use of these tests is new and not generally accepted. Scientists do not generally accept the proposition that *in vitro* test results can be directly extrapolated to a living body. "*[I]n vitro* animal test data are not relied upon by experts in the field of teratology for extrapolating the results found directly to the human experience." *Wade-Greaux*, 874 F. Supp. at 1484 (emphasis added). Both Dr. van Velzen and Dr. Howard testified at trial that no scientific

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[15] Neither Dr. van Velzen nor Dr. Howard offered his study for independent or objective verification or publication in a peer-reviewed scientific journal. Tr. (4/30/96) at 236, 241-44; Tr. at 3297-98.

publication, governmental agency, or academic group had ever before relied on direct extrapolation from *in vitro* test results to determine a teratogenic exposure level in a living being. Tr. at 3304-06, 3186-88. "Positive results from *in vitro* studies may provide a clue signaling the need for further research, but alone do not provide a satisfactory basis for opining about causation or threshold level effect in the human context." *Richardson*, 857 F.2d at 830.

Dr. Howard's conclusion that benomyl is a human teratogen at 20 ppb -- the linchpin of his ultimate conclusion that Benlate caused John Castillo's microphthalmia -- was not based on "generally accepted" methodology.[16]

### 5. The Exclusion of Possible Genetic or Environmental Causes of John Castillo's Microphtalimia Was Incorrect

[16] If this Court were inclined to adopt a *Daubert* test for admissibility, rather than the *Frye* test currently mandated in this State, we respectfully submit that Dr. Howard's testimony should also be excluded. The analytical gap between the *in vitro* results relied upon by Dr. Howard and John Castillo's birth defects is too great, and Dr. Howard's unsupported leap from one to the other is erroneous and without basis. *See General Elec. Co. v. Joiner*, ___ U.S. ___, 118 S.Ct. 512, 519 (1997) ([N]othing in either *Daubert* or the Federal Rules of Evidence requires a district court to admit opinion evidence which is connected to existing data only by the *ipse dixit* of the expert. A court may conclude that there is simply too great an analytical gap between the data and the opinion proffered). Moreover, the fact that Dr. Howard's and Dr. van Velsen's studies were prepared for the purpose of litigation, and were not submitted for peer review or publication would militate against admissibility.

Exclusion of genetic and other environmental cause is part of the process of differential diagnosis which follows only after, and quite apart from, a determination of human teratogenicity of a substance. The process of differential diagnosis and the process for determining human teratogenicity are separate methodologies addressing different issues of medical causation (*i.e.*, is the substance capable of causing a birth defect (general causation), on the one hand, and did it in fact cause a birth defect in this instance (specific causation), on the other hand). While Dr. Howard employed a generally accepted methodology for addressing specific medical causation (differential diagnosis), he did not use a generally accepted methodology for determining whether a substance is a human teratogen.

Before a conclusion on medical causation can be reached reliably, an expert must make a reasonable attempt to determine cause by including and then systematically eliminating the most likely *possible* causes, until one cause remains. In medical terms, this process is known as differential diagnosis. The process of conducting a differential diagnosis is critically important to the question of causation in this case. "If other possible causes of injury cannot be ruled out, or at least the probability of their contribution minimized, then the 'more likely than not' threshold for proving causation may not be met." *Cavallo v. Star Enter.*, 892 F. Supp. 756, 770-71 (E.D. Va. 1995). "In determining the cause of birth defects, it is necessary not only to rule in a particular cause, but also to rule out other possible causes." *See National Bank of Commerce v. Dow Chem. Co.*, 965 F. Supp. 1490, 1520 (E.D. Ark. 1996) (emphasis added).

An expert witness who offers testimony as to the specific causation of a

plaintiff's injuries must undertake a thorough differential diagnosis, and a proper differential diagnosis to rule out other potential causes can only be performed by a *qualified* expert. David Levy, Scientific Evidence After *Daubert*, Litigation (Fall 1995), quoted in *National Bank of Commerce*, 965 F. Supp. at 1513; *see In re Joint Eastern & Southern District Asbestos Litigation*, 827 F. Supp. 1014, 1048-49 (S.D.N.Y. 1993) (dismissing plaintiff's claim that asbestos exposure caused his colon cancer because plaintiff's expert failed to perform an adequate differential diagnosis even though the plaintiff was young, had no family history of cancer, suffered from no special disease, and had no other high risk exposures); *Diaz v. Johnson Matthey, Inc.*, 893 F. Supp. 358 (D.N.J. 1995) (excluding expert testimony under *Daubert* for failure to conduct a proper differential diagnosis).

Dr. Howard has failed to do either in this case. He has not "ruled in" benomyl as a cause because, as demonstrated above, he has not used a generally accepted methodology that would permit the determination that benomyl is a human teratogen. In addition, and in spite of the assertion in Petitioners' brief that geneticists "could find no known genetic cause" for John Castillo's microphthalmia (Pet. Initial Br. 20), Dr. Howard has not, in fact, properly excluded genetics as a cause of the microphthalmia in this case. Without a proper differential diagnosis, Plaintiffs cannot prove causation.

The differential diagnosis analysis must start with the fact that the cause of approximately fifty percent of all birth defects is unknown. With respect to those for which there are known causes, including microphthalmia, the overwhelming majority are genetically caused. Its presence in mankind, long before benomyl was produced, points to its genetic origin, either through a recessive or dominant mode of inheritance or as a point mutation. Mutation of genes is very common.

The fact that geneticists involved in this case did not identify a specific gene defect in John Castillo is not significant. Medical science has not yet developed tests for most genetic defects. *DeLuca v. Merrell Dow Pharm., Inc.*, 791 F. Supp. 1042, 1044 (D.N.J. 1992). The fact that John Castillo's chromosome study might be normal does not rule out genetic defect. Chromosome tests detect less that twenty percent of known genetic defects. Nor does the absence of a family history of microphthalmia rule out a genetic cause; recessive inheritance or gene mutation are likely causes and microphthalmia would not show up in other family members in that event. In short, no medical test or analysis has ruled out genetic cause in the case of John Castillo's microphthalmia.

The likelihood that many if not most cases of microphthalmia are in fact of genetic origin requires teratologists to be extremely careful before reaching any conclusion regarding a non-genetic cause of a single instance of microphthalmia. Dr. Howard has ignored this caution and simply jumped to the erroneous conclusion that John Castillo's microphthalmia cannot be genetic because his karyotype is negative and his condition does not fit a known genetic syndrome.

## CONCLUSION

There is a generally accepted methodology in the field of teratology for identifying human teratogens. Dr. Howard has not employed that accepted methodology; in fact, he has rejected the generally accepted methodology and applied something of his own invention. His own invention is unscientific and its elements rejected in the field of teratology.

The Third District Court of Appeals was correct in excluding the causation

testimony of Dr. Howard because he used a methodology which is not generally accepted with the meaning of *Frye*.

Dated: November 6, 2000

Respectfully submitted,

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## CERTIFICATE

I hereby certify that this Brief of Amicus Curiae on the Merits was produced using WordPerfect 6.0 for DOS, and is printed in Dutch 801 Roman (Speedo), 14 point, proportionately spaced typeface.

Dated: November 6, 2000

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Martin S. Kaufman

## CERTIFICATE OF SERVICE

I hereby certify that a copy of the Motion for Leave to File Brief of Amicus Curiae on the Merits and a copy of the Brief of Amicus Curiae on the Merits was faxed and mailed, by first class mail, postage prepaid on November 6, 2000 to:

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