



## ● *Reproductive Toxicology Review*

### **BENDECTIN: REVIEW OF THE MEDICAL LITERATURE OF A COMPREHENSIVELY STUDIED HUMAN NONTERATOGEN AND THE MOST PREVALENT TORTOGEN-LITIGEN**

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**Abstract — Objective:** to review the extensive literature pertaining to the reproductive and teratogenic effects of Bendectin and the opinions of the scientific experts for the defense and plaintiff. These data were evaluated with regard to the reproductive risks of Bendectin providing a scientific framework for evaluating the views of the experts in the Bendectin litigation. **Design:** the Bendectin literature was primarily obtained from articles cited in Research Alert of the Institute for Science Information. Other articles were obtained from Medline, review articles, and colleagues. An attempt was made to be all-inclusive, citing and reviewing all articles related to each subject being discussed. The literature includes epidemiologic studies, animal studies, in vitro studies, and basic science articles related to the principles of teratology and reproductive toxicology. Review articles, meta analyses, editorials, commentaries, articles in the press, and case reports were also included. **Methodology:** the methodology utilized for the evaluation of Bendectin teratogenicity was presented. It consists of a five-part analysis of epidemiologic studies, secular trend analysis, animal studies, dose-response relationships, and biologic plausibility. **Conclusion:** the five-part analysis of Bendectin reproductive effects indicates that therapeutic use of Bendectin has no measurable teratogenic effects. Presentations by many of the plaintiff's experts failed to meet the scientific standards that should be expected of knowledgeable scientists and contributed to the persistence of Bendectin litigation.

**Key Words:** Bendectin; epidemiology; expert witnesses; litigation; tortogen; litigen.

### **INTRODUCTION**

Bendectin was a frequently prescribed antiemetic preparation for the treatment of nausea and vomiting of pregnancy before 1983. I became familiar with Bendectin from several vantage points: as an investigator and teacher in the fields of teratology, genetics, and epidemiology; as a participant in a peer review of Bendectin with regard to its efficacy and risks; as a member of the Maternal Health Drug Committee of the FDA when Bendectin was a topic discussed at its committee meetings; as a member of an expert panel appointed by the Canadian government to review the data pertaining to the reproductive risks of Bendectin; as an author of commentaries indicating that my opinion was that Bendectin

did not produce a measurable increase in congenital malformations in women exposed to the drug during pregnancy (1,2); and as an expert witness for the defense in four Bendectin lawsuits and as a reviewer of materials in several other Bendectin lawsuits.

The purpose of this review is to demonstrate the methodology that can be utilized to determine whether a drug or other environmental agent presents reproductive risks to the exposed population. This review will focus on the scientific data and the methodology that can be used to evaluate the question of whether a drug or chemical presents a measurable teratogenic risk.

Bendectin was first formulated to contain 10 mg of doxylamine succinate (an antihistamine), 10 mg of dicyclomine (an antispasmodic), and 10 mg of pyridoxine. Later preparations did not contain the dicyclomine. Some lawyers, physicians, scientists, news media personnel, and lay individuals

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have inferred that there must be some truth to the allegation that Bendectin causes birth defects, otherwise these lawsuits would not have been initiated; but birth defect lawsuits may be initiated because they may be won, whether or not they have scientific merit (3–11).

### METHOD OF EVALUATING THE REPRODUCTIVE RISKS OF ENVIRONMENTAL AGENTS (TABLE 1)

Allegations of teratogenicity in the human can be evaluated in a logical and orderly fashion. The methodology utilized in this article has been utilized numerous times and is based on the principles established in the general field of epidemiology with appropriate modifications (1,2,12–15). The methodology has been discussed in teratology review articles (16–21) and in specific evaluations pertaining to individual environmental agents, such as Bendectin, sex steroids, ultrasound, caffeine, and electromagnetic fields (12,22–28).

This evaluation includes a) analysis and interpretation of human epidemiologic studies, b) the examination of the relationship between the secular trend of birth defects and the population exposure to drugs, c) the ability to develop an animal model, d) analysis of dose–response relationships and pharmacokinetics in an animal model and in humans, and e) the biological plausibility of the allegation of teratogenicity. The reproductive risks of Bendectin were evaluated using each of these parameters.

1. *In epidemiologic studies, does Bendectin consistently increase the incidence of particular*

Table 1. Characteristics of an environmental agent that is teratogenic in humans

1. Epidemiology studies *consistently* demonstrate an increase in the frequency of congenital malformations, and especially a recognizable syndrome in the exposed population.
2. Secular trend analysis reveals that the frequency of congenital malformations is associated with changes in population exposure, i.e., the introduction or withdrawal of environmental agents for which there has been a high population exposure.
3. An animal model has been developed that is similar to the reports in the human and can be produced with pharmacokinetically equivalent exposures.
4. In the appropriate animal model, the frequency and severity of the teratogenesis and/or embryopathology increases with a dose or exposure that is within the range of human exposures.
5. The teratogenic effect is consistent with the basic principles of embryology and teratology and does not contradict biologic principles or biologic common sense.

*malformations or produce a recognizable syndrome of malformations?* A causal association cannot be determined from the results of one epidemiologic study, nor does a single negative epidemiologic study demonstrate the safety of a drug (13). Epidemiology studies determine whether a drug exposure is statistically associated with the occurrence of individual malformations. Because congenital malformation studies permit the investigator to evaluate the association of a multitude of malformations with a particular drug exposure, studies may find some positive associations even when there is no true effect. At the  $P < 0.05$  level of significance, 1 in 20 comparisons can be expected to be positive purely by chance. When examining the association between 40 malformations and a drug exposure in one study, it is likely that two malformations will be statistically associated with the drug exposure. Conversely, certain malformations may appear to occur in such a low frequency that one could conclude that the drug “prevented” malformations. Investigators ignore these negative association because they are usually not plausible. Inferring causality from inconsistent and nonreproducible associations also does not make scientific sense (13).

Shiono and Klebanoff (29) discussed this principle when they analyzed their own Bendectin epidemiologic study.

The relationship between Bendectin exposure during the first trimester of pregnancy and the occurrence of congenital malformations was prospectively studied in 31,564 newborns registered in the Northern California Kaiser Permanente Birth Defects Study. The odds ratio for any major malformation and Bendectin use was 1.0 (95% confidence interval 0.8–1.4). There were 58 categories of congenital malformations; three of them were statistically associated with Bendectin exposure (microcephaly—odds ratio = 5.3, 95% confidence interval = 1.8–15.6; congenital cataract—odds ratio = 5.3, 95% confidence interval = 1.2–24.3; lung malformations (ICD-8 codes 484.4–484.8)—odds ratio = 4.6, 95% confidence interval = 1.9–10.9). This is exactly the number of associations that would be expected by chance.

*Answer:* No drug has had its teratogenic potential studied in greater detail than Bendectin. Although it is true that epidemiologic studies can always be criticized or improved, the massive amount of data does not support a consistent statistical association between Bendectin usage in pregnancy and a particular syndrome or group of malformations. There are numerous cohort studies totaling over 120,000 controls and 13,000 Bendectin-exposed pregnant women (29–46) (Table 2). There are many case–control studies evaluating particular malformations—cleft pal-

Table 2. Bendectin and congenital malformation cohort studies

Reference	Study group	Exposed total	Exposed malformed	Nonexposed total	Nonexposed malformed	Relative risk	95% confidence interval
Heinonen et al., 1977 (37)	50,282	1,169	79	49,113	3,169	1.05	0.84–1.30
Fleming et al., 1981 (41)	22,977	620	31	22,357	1,208	0.93	0.65–1.31
Michaelis et al., 1983 (46)	1,748	874	18	874	19	0.95	0.50–1.79
Milkovich and van den Berg, 1976 (34)	10,205	628	14	9,577	343	0.62	0.37–1.06
Morelock et al., 1982 (45)	1,690	375	31	1,315	93	1.17	0.79–1.73
Aselton and Jick, 1983 (44)	5,254	1,364	2	3,890	4	1.43	0.26–7.78
Gibson et al., 1981 (42)	7,456	1,685	78	5,771	245	1.09	0.85–1.40
Jick et al., 1981 (43)	6,837	2,255	24	4,582	56	0.87	0.54–1.40
General Practitioner Research Group, 1963 (31)	661	72	2	589	18	0.91	0.22–3.84
Newman and Correy, 1977 (35)	7,933	1,192	6	6,741	70	0.48	0.21–1.11
Smithells and Sheppard, 1978 (38)	3,426	1,173	28	1,713	31	0.89	0.54–1.51
Bunde and Bowles, 1963 (30)	4,436	2,218	11	2,218	21	0.52	0.25–1.08
Shiono and Klebanoff, 1989 (29)	31,564	2,720	51	28,793	520	1.00	0.8 –1.4
Summary						0.95	0.62–1.45

Adapted from Einarson et al., 1988 (64). A second meta-analysis was performed by McKeigue et al., 1994 (65) with similar results.

ate and lip, pyloric stenosis, congenital heart disease, diaphragmatic hernia, etc. Whenever a positive association was found, further case-control studies were invariably negative and the association could not be confirmed (47–63) (Table 3).

Because numerous statistical comparisons are performed in birth defect epidemiologic stud-

ies, it is likely that at least one positive association will be found although the association may have occurred by chance (13). That is why it is so important to demonstrate the consistency of any association. In the numerous cohort studies the results have been remarkably negative. Einarson et al. (64) and McKeigue et al. (65) performed meta-analyses on the numerous Bendec-

Table 3. Bendectin case control studies

Reference	Malformations	Odds ratio	Confidence limits	Significance
Greenberg et al., 1977 (62) <sup>a</sup>		0.84	0.62– 1.17	–
Rothman et al., 1979 (55) <sup>a</sup>	Congenital heart disease	1.8	1.2 – 2.7	+
Zierler and Rothman, 1985 (58) <sup>a</sup>	Congenital heart disease	1.09	0.76– 1.55	–
Golding et al., 1983 (47) <sup>a</sup>	Cleft lip and palate	2.88	1.19– 6.96	+
Eskenazi and Bracken, 1982 (60) <sup>a</sup>	Pyloric stenosis	4.33	1.75–10.75	+
Mitchell et al., 1981 (48)	Oral clefts	0.9	0.5 – 1.5	–
	cleft palate			
	cleft lip and palate	0.6	0.4 – 0.8	–
		0.64	0.12– 3.34	Oxford results
Elbourne et al., 1985 (51)	Oral clefts	0.37	0.09– 1.44	Aberdeen results
				–
Mitchell et al., 1983 (49)	Pyloric stenosis	0.9	0.6 – 1.2	–
McCredie et al., 1984 (57)	Limb reduction defects	1.1	0.8 – 1.5	First trimester
		1.0	0.7 – 1.4	–
Cordero et al., 1981 (59)	Limb reduction defects	1.18	0.65– 2.13	–
David, 1982 (63)	Poland anomaly			–
Bracken and Berg, 1983 (52)	Diaphragmatic hernia	1.6	0.3 – 8.7	–
Mitchell and Shapiro, 1983 (49)	Diaphragmatic hernia			–
Cordero et al., 1981 (59)	Diaphragmatic hernia	1.74	0.81– 3.76	–

<sup>a</sup>The first five case control studies were the only studies utilized in the meta analysis performed by Einarson et al. in 1988 (64). The notation (positive + or negative –) in the last column indicates whether the authors concluded that their results were statistically significant.

tin cohort and case-control studies that have been published. Einarsen et al. described their methodology for performing a meta-analysis in great detail and used the extensive literature dealing with Bendectin to perform the analysis. The authors presented the methodology that researchers would utilize to perform each of 22 steps in six major areas. "The illustrative meta analysis confirmed previous traditional narrative literature reviews that Bendectin is not related to teratogenic outcomes in humans." (64) Einarsen et al. reported an OR (odds ratio) for the Bendectin cohort studies that was 1.01 (95% confidence interval 0.66–1.55). The OR for the case-control studies was 1.27 (95% CI, 0.83–1.94). The corresponding chi-square values were not statistically significant. McKeigue et al. (65) conducted a meta analysis of 16 cohort studies and 11 case control studies that report birth defects from Bendectin-exposed pregnancies. "The pooled estimate of the relative risk of any malformation at birth in association with Bendectin in the first trimester was 0.95 (95% CI 0.88–1.04). Separate analyses were undertaken for cardiac defects, limb reduction defects, oral clefts, and genital tract malformations. In these categories, the pooled estimates of relative risks ranged from 0.81 for oral clefts to 1.11 for limb reductions, with all 95% confidence intervals enclosing unity. These studies, as a group, showed no difference in the risk of birth defects between those infants whose mothers had taken Bendectin during the first trimester of pregnancy and those infants whose mothers had not." (65) The analyses of the cohort studies (Table 2) and the case control studies (Table 3) do not indicate that Bendectin exposure during pregnancy presents a measurable risk to the human embryo.

2. Do secular trend data support an association of Bendectin with the incidence of birth defects or a particular birth defect? (Figure 1)

*Answer:* No. There has been a dramatic change in the exposure of pregnant women to Bendectin. Bendectin was prescribed in the 1970s in the USA in 10 to 30% of pregnancies for nausea and vomiting. In 1983, Bendectin production was discontinued and sales ceased abruptly (9,66,67). During the time frame when Bendectin exposures were reduced and eliminated, there has been no concomitant reduction in those malformations alleged to be associated with Bendectin exposure (13,67,68). One must remember that in the 30 million estimated pregnancy exposures to Bendectin, one would expect, by chance alone,

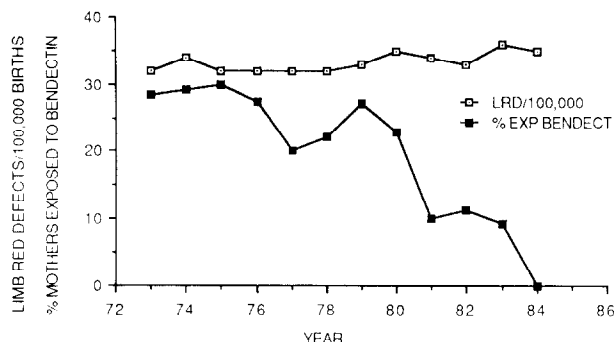


Fig. 1. Incidence of limb reduction defects in the United States and the percentage of pregnant women who were prescribed Bendectin during the years 1972 to 1984. The congenital malformation data, the frequency of exposure, and the declining use of Bendectin were reported by the Center for Disease Control (68) and the sales figures obtained from the pharmaceutical company that distributed Bendectin. The data for limb reduction defects and many other malformations demonstrate no correlation between Bendectin exposure and the incidence of defects in spite of the fact that at peak exposure periods a significant proportion of pregnant women were exposed to Bendectin. Thus, secular trend analysis does not demonstrate an association between Bendectin exposure and the occurrence of limb reduction defects.

an occurrence of approximately 10,000 limb reduction defects and 240,000 congenital heart malformations, the same rates that would be expected in 30 million unexposed pregnant women. The frequent use of Bendectin demonstrates that, although the analysis of secular trend malformation data for drugs with a low frequency of exposure would be purposeless, this analysis can be quite useful as one component in the evaluation of the alleged teratogenicity of drugs with frequent exposures.

3. Have investigators been able to demonstrate teratogenesis in laboratory animals using doses that are equivalent to the human pharmacokinetically equivalent dose? (Table 4)

*Answer:* None of the animal studies resulted in teratogenesis at exposures equivalent to or substantially above the human therapeutic dose of Bendectin. It should be pointed out that in the FDA-sponsored rat study (74) embryotoxicity did appear when Bendectin was given at doses of 800 mg/kg, which is greater than approximately 1000 times the human therapeutic dose. At this dose, there was also an increase in maternal mortality. The LD<sub>50</sub> for Bendectin is higher than for most commonly ingested electrolytes and minerals. One tablet of Bendectin administered

Table 4. Bendectin animal studies<sup>a</sup>

Reference	Species	Dose	Results	Comments
Gibson et al., 1968 (69)	Rabbit rat	3, 6, 30 mg/kg 10, 30, 100 mg/kg	No increase in malformations.	Study performed in house by the Bendectin manufacturer.
Hendrickx et al., 1985 (70,71)	Macaque baboon Cynomolgous	10 to 40 times the human dose 2 to 20 times the human therapeutic dose	Slowing of the closure of the interventricular septum. No other increase in malformations.	Study performed at the Davis Primate Center supported by the drug manufacturer. Hendrickx testified as a defense expert in Bendectin litigation.
Tyl et al., 1988 (74)	CD rat	200 to 800 mg/kg	No increase in malformations. Maternal death and fetal growth retardation at maternally toxic dose.	Very large rat study planned and administered by FDA scientists. Tyl testified as a defense expert in Bendectin litigation.
Roll (72)	Rat (unpublished)	50–300 mg/kg	Low incidence of the occurrence of spontaneous diaphragmatic hernia in this strain of rats.	Pharmaceutical company employee in Germany. Study was never published in a peer reviewed journal or duplicated.
McClure (73) McBride et al., 1984 (75)	Rhesus (unpublished) Rabbit	7 mg/kg/day 40 to 115 mg/kg	No malformations Very large doses were utilized. An increase in malformations were reported but the quality of the research has been criticized.	Study performed by one of the plaintiffs' expert witnesses.
McBride, 1985 (76)	Marmoset	170 to 445 times the human therapeutic dose	Four or five mothers aborted. Gave massive dose at the incorrect stage of embryonic development.	Study performed by plaintiff's expert witness.

<sup>a</sup>One tablet of Bendectin contained 10 mg of doxylamine, 10 mg of pyridoxine, and 10 mg of dicyclomine. Later formulations did not include dicyclomine. One tablet administered to a 50 kg patient is equivalent to 0.2 mg/kg for each of the constituents.

to a 50 kg women provides a dose of 0.2 mg/kg for each of the constituents of Bendectin.

5. *Does the allegation of Bendectin teratogenicity in the human make scientific or biologic sense?*

In evaluating the reproductive risks of an environmental agent there are important scientific principles that should guide the analysis of human epidemiology and animal teratology studies. An allegation of reproductive toxicity may be supported or refuted, depending on the magnitude of the compliance or noncompliance with these principles.

1. Exposure to teratogens exhibit a dose–response relationship. With proven teratogens there is a threshold below which no effect will be observed and, as the dose of the teratogen is increased, both the severity and frequency of reproductive effects will increase. (16–20,22–24)
2. The stage of gestation and duration of exposure is critical in determining what effects will be produced and whether any effects can be produced by a known teratogen.

3. Even the most potent teratogenic agent cannot produce every type of malformation. Most teratogens have a confined group of congenital malformations (the syndrome) that result after exposure during the stages of embryonic development that are sensitive to that teratogen. This syndrome will include malformations that

Table 5. Medical and scientific experts who have testified for the defense in Bendectin litigation<sup>a</sup>

Michael Bracken	Lewis Holmes	William Scott
Robert L. Brent	Marshal Johnson	Raymond Seltzer
Peter Dignan	Mark Klebanoff	Richard Skalko
John P. Gibson	Steven Lamm	David W. Smith
James Goddard	Paul Leitman	Samuel S. Shapiro
Jan Friedman	Widukind Lenz	Trent Stephens
Judith Hall	R. Brian Lowry	Paul Stolley
James Hanson	Richard Monson	James Wilson
Raymond Harbison	Brian MacMahon	Nicholas Wright
David Harris	James Newberne	Sally Zierler
Ollie Heinonen	Kenneth Rosenbaum	

<sup>a</sup>Provided by the law firm of Dismore and Shohl, one of the law firms for the defendant. The list may not be complete.

Table 6. Medical and scientific experts who have testified for the plaintiff in Bendectin litigation<sup>a</sup>

Frederick Crescitelli	William McBride	Donald Patterson
Alan Done	Michael Melnick	Wayne Snodgrass III
Alan Garfinkel	Stewart Newman	Shanna Swan
Jay Glasser	John Palmer	Mark Thoman
Stanley Glauser	Roger Palmer	Johannes Thiersch
Adrian Gross		

<sup>a</sup>Provided by the law firm of Dismore and Shohl, one of the law firms for the defendant. The list may not be complete.

invariably occur and several other malformations or effects that will occur in lower frequencies in the affected offspring. (16–20)

4. Although a group of malformations may suggest the possibility that a particular teratogen was responsible, there may be other causes than the suspected teratogen. On the other hand, the presence of certain malformations may eliminate a causal association for a particular teratogenic agent.

Applying these principles to the present analysis reveals three findings that make it scientifically implausible that therapeutic doses of Bendectin are teratogenic.

#### *The nature of teratogenic syndromes*

Most teratogens produce a recognizable syndrome or group of malformations (77–83). Neither researchers nor expert witnesses for the defense (Table 5) or the plaintiff (Table 6) have identified a Bendectin syndrome. Some expert witnesses have sought to implicate Bendectin as the cause of many unrelated malformations (Table 7) and every type of

limb reduction defect (genetically determined, due to vascular disruption, congenital amputations, and malformations resulting from failures during very early organogenesis). We know that even thalidomide, as well as other proven teratogens, have the potential to produce only certain types of limb defects (23,81,84). Hemimelia or transverse amputations, as well as severe unilateral limb defects, are not part of the thalidomide syndrome (81,84). Therefore, after scores of Bendectin studies, and numerous animal studies, one can state that Bendectin has not been identified with a recognizable syndrome. No proven teratogen produces isolated malformations of various organs without any interrelationship between the occurrence of the individual malformations.

#### *Threshold concept*

Teratogenesis is predominantly a *threshold phenomenon* (83,85–87). Therefore drugs that produce embryotoxicity at several orders of magnitude above the therapeutic dose in animals and have no measurable deleterious effects at the human therapeutic dose would not be expected to be embryotoxic to the human embryo. If teratogenicity were not a threshold phenomenon, we would not use supplemental vitamin A and D therapy, aspirin, many antihistamines, many antibiotics, etc., in pregnant women. Many agents are used for the benefit of the patient at doses below the dose that produces embryotoxicity, just as we use other therapeutic pharmacologic agents that may be toxic or lethal at higher doses.

#### *In vitro studies (Table 8)*

On occasion, some individuals have attempted to utilize in vitro studies to support their opinion that Bendectin may produce malformations in humans just because some cellular effects have been demonstrated in an in vitro system. In vitro studies can never establish human teratogenicity by themselves (88). It is not scientifically supportable to infer teratogenicity from an in vitro study if the animal and human in vivo studies do not indicate a teratogenic effect. In vitro studies are useful to screen for cellular toxicity and to study mechanisms of teratogenesis of known teratogens, but in vitro studies do not predict a drug's potential human teratogenicity better than in vivo animal studies and human epidemiologic studies (88,89). Most of the in vitro studies performed with Bendectin (mutagenicity, neural crest differentiation, mouse limb bud cell culture, attachment of ascites tumor cells, chondro-

Table 7. Plaintiff's malformations in Bendectin lawsuits<sup>a</sup>

Split hand, split foot
Potter's syndrome
Bladder extrophy
Mental retardation
Cleft lip and palate
Noonan's syndrome
Sarcoma of the vagina
Omphalocele
Imperforate anus
Caudal regression syndrome
Cranial synostosis
Marcus Gunn syndrome
Hydrocephalus
Deafness
Right optic nerve coloboma
Limb reduction defects due to vascular disruption
Hereditary malformations
Club feet

<sup>a</sup>Provided by the law firm of Dismore and Shohl, one of the law firms for the defendant. The list may not be complete.

Table 8. Bendectin in vitro studies<sup>a</sup>

Reference	Test	Results
Simmons and Marx, 1979 (90) Budroe et al., 1984 (95) Greenberg, 1982 (92) Braun et al., 1982 (93)	Ames test (test for mutagenicity) Hepatocyte DNA repair assay Differentiating neural crest cells Inhibition of ascites tumor attachments	Negative Minimal effect <sup>b</sup> No effect at 250 $\mu\text{g/mL}$ or 50 $\mu\text{g/mL}$ Bendectin used in very high doses. No effect
Guntakatta et al., 1984 (91)	Limb bud culture proteoglycan synthesis	No effect of Bendectin at 15 $\mu\text{g/mL}$ (100 times the human peak blood level)
Hassell and Horigan, 1984 (94)	Teratogenic potential utilizing limb bud mesenchyme cells for 6 days and staining with Alcian Blue. This test is inappropriate for determining the etiology of limb reduction defects that do not have a problem with cartilage formation.	Bendectin, 50 $\mu\text{g/mL}$ (500 times the human peak blood level) inhibited proteoglycan synthesis
Steele et al., 1988 (96) The authors concluded that "in vitro systems are limited" in their ability to determine risk for the reasons they explain in their paper.	Utilized the human embryonic palatal mesenchymal cell growth inhibition assay (HEPM) and the mouse ovarian tumor cell attachment inhibition assay (MOT)	Forty-four compounds were tested with these assays. The authors considered the MOT assay to be negative for doxylamine succinate. The HEPM assay was positive at concentrations far above the levels reached following the administration of Bendectin to humans.
Muller et al., 1989 (97)	Transplacental exposure of mouse embryos to doxylamine succinate followed by analysis of mouse cells for sister chromatid exchange (SCE), bone marrow micronuclei, human lymphocytes for SCE, and chromosomal aberrations in mouse cells.	The authors concluded that "mutagenic potential" could not be concluded from these studies.

<sup>a</sup>Most of these in vitro tests were negative and the two that were positive were at drug concentrations far above the human therapeutic range. Furthermore, in vitro tests are useless in predicting human risks if the human epidemiology studies and in vivo animal studies do not indicate the presence of reproductive toxicity. There is not a single human teratogen that has been identified by the scientific community from in vitro studies when epidemiologic and animal studies are negative.

<sup>b</sup>The minimal effect of Bendectin on the rate of DNA repair reported by Budroe must be evaluated with the knowledge that the Ames Test is negative and that very large doses of Bendectin in vivo do not result in significant cell killing of proliferating cells.

genesis, and hepatocyte DNA repair assay (90–97) (Table 6) were negative even at higher concentrations than are attained in the human. The in vitro study by Hassell and Horigan (94) demonstrated that cartilage differentiation was inhibited at concentrations of 50  $\mu\text{g/mL}$ . Pharmacologic studies indicate that this concentration would not be attained in the human, since Kohlof et al. (98) administered a 25 mg dose of doxylamine and noted that the peak blood level was 150 ng/mL. The amount of doxylamine in a Bendectin dose is 10 mg, therefore, Hassell and Horigan demonstrated toxicity at approximately a 1000-fold greater concentration than typically attained in the human at therapeutic doses. In addition, abnormal cartilage differentiation is not the basic pathology of limb reduction defects produced by drugs or chemicals that act during the early stages of organogenesis (81,99). Doxylamine metabolism and pharmacokinetics have been extensively studied in several species

(98,100–111). These studies further indicate that the human, rat, and monkey pharmacokinetics are worthwhile avenues of investigation because they are helpful in understanding and evaluating the in vitro studies that used concentrations of Bendectin that are much greater than the levels attained following human exposure.

The analysis of cohort and case-control epidemiologic studies, secular trend analysis, animal teratology studies, and biologic plausibility clearly indicates that the therapeutic use of Bendectin has no measurable human teratogenic potential. There has never been a drug that has been studied so completely. The number of patients in the epidemiologic studies is immense. Some of the animal studies included large numbers of animals, multiple species, and were well designed (70,71,74). These data do not even suggest that Bendectin administration during pregnancy represents a reproductive or teratogenic risk.

## DISCUSSION

The major purpose of this review is to evaluate the scientific data as they pertain to the reproductive effects of Bendectin exposure during pregnancy. A secondary benefit of an in-depth review also permits the evaluation of the opinions of the experts involved in the Bendectin litigation in order to determine the level of scholarship provided to the courts. Recently the scientific community has expressed concern about the diminished reputation of scientists because of notoriety regarding scientific fraud and partisan testimony. Suggestions have been made to remedy these problems (112–120).

Although one may not expect a high level of scientific scholarship or rigorous adherence to the scientific method from lawyers, jurors, news commentators, or the public, one should expect scholarship from scientists who enter the courtroom to provide their expertise to the judge and jurors. Bendectin litigation could not have proceeded without the participation of scientists who failed in their role as objective experts during the Bendectin litigation. There is a formidable inertia and fearfulness among the leaders of organized biomedicine to solve this problem.

How is it that scientists and physicians can enter the halls of justice and present to the court their view that a particular child's birth defect was due to Bendectin "with a reasonable degree of certainty"? The motivation for testifying as an expert is varied and complex, and it is not the purpose of this analysis to determine the experts' motivation. Whatever the motivation, an expert's main responsibility is to bring scholarship to the courtroom. One might infer that there has been an "army" of experts testifying for the plaintiffs and defendant in the Bendectin litigation. In reality, there have been a small number. Tables 5 and 6 list experts who have testified for the plaintiff and defense in Bendectin lawsuits. Their testimony is public record and should be read, because it will focus on the magnitude of the problem pertaining to the proper role of an expert (112).

The most dramatic and visible difference between the plaintiff and defense experts is their publication and public statements pertaining to the teratogenicity or absence of teratogenicity of Bendectin. Many of the defense experts have performed investigations or published their opinions in the scientific literature (1,2,29,36,37,58,69,121–128). Only two of the plaintiff's experts (Table 8) have published their views on Bendectin (75,76,129,130). None of the plaintiffs' experts have published an analysis, review, or research paper

that indicated that Bendectin was a human teratogen. McBride's teratology research using scopolamine was the subject of an investigation at Foundation 41, in Australia, the site of his research activities and later by a Medical Tribunal of New South Wales, Australia. His research was judged to be fraudulent, the committee concluding that "... deliberate falsification did occur ..." (131). Other comments on McBride's activities and scientific studies have been published (117,132).

In Newman's letter to the editor in JAMA, he indicated that in vitro tests can support proof of teratogenicity, even when the human and in vivo animal studies are negative (130). Newman was critical of Skolnick's article (132) in JAMA. Skolnick (132) reported charges of fraudulence against McBride and concluded that "nearly every study provided reassuring evidence that Bendectin was safe." Newman disagreed with Skolnick that Bendectin was safe and suggested that the epidemiologic studies were "inconclusive" (130). Newman highlighted some in vitro studies that supported his opinion; namely, that "Bendectin at a concentration of 10 mg/L, drastically curtails the formation of embryonic cartilage, the tissue that forms the primordia of embryonic cartilage" (130). Abnormal cartilage development is not the primary basis for congenital limb reduction defects. The mesenchyme and pre-mesenchyme are the primordia of the limbs and abnormalities in these structures account for some limb reduction defects. Most importantly, Newman ignores the importance of dose in these in vitro studies. He compares the blood levels of phenytoin and doxylamine succinate as if their clinical doses are comparable. Phenytoin is given at a much higher dose than doxylamine succinate and, therefore, the blood levels attained with phenytoin therapy are not attained with a 10 mg dose of doxylamine succinate. The concentration of doxylamine succinate used in the in vitro study that Dr. Newman discusses is approximately 500 times the blood level achieved with Bendectin therapy. Newman's position is especially indefensible because analysis of the in vitro studies was not supportive of his position.

It is unfortunate that an individual would testify that a drug caused a congenital malformations based on in vitro studies that showed effects rarely and only with massive concentration of the drug; a result that cannot be converted to a useful or plausible risk estimate for human teratogenicity, especially when the epidemiologic studies and in vivo animal studies are negative.

There have been a number of individual scien-



tists, physicians, and writers who were uncertain about the reproductive and teratogenic risks of Bendectin (129–131,133–147). Unfortunately, many of these uncertainties were based on case reports and clusters that can be very misleading (12,22). Patterson (133) described an infant with limb defects who was exposed to Bendectin and in a report 8 years later he concluded “that Bendectin may not be safely used in pregnancy” (134). Some authors reported the possibility that Bendectin may be teratogenic in a letter to the editor (131,140,144). Others reported case control studies indicating an association of Bendectin exposure with a particular malformation. But those findings were not confirmed in other studies. Occasional positive associations are expected with a multitude of studies. Most importantly, these associations were not consistent, an important first step in confirming an association (47,59,60,61,145).

Most scientists and scientific commentators who have written about the therapeutic use of Bendectin have been adamant about Bendectin’s nonteratogenicity or were not convinced of its teratogenic potential in humans (1,2,4–6,10,11,38,64,65,77–79,89,118,122,125,148–178).

Furthermore, the conclusions based on scholarly reviews have been emphatic and convincing. Schardein (89) summarized as follows:

The hysteria manifested in litigation associating it (Bendectin) with birth defects before its removal from the market are a sad commentary, given the available knowledge we have concerning its teratogenic potential. All evidence to date indicates a notable absence of malformation induction.

The U.S. F.D.A. concluded that there was no adequate evidence linking Bendectin with an increased risk of birth defects (159). Across the ocean, the British parliament also heard a report on drug safety (157).

... to suggest that the Health Minister of this country should act in response to scare mongering or the verdict of a lay jury in the United States rather than of the advice of expert committees, is to align oneself with a movement which is at heart antiscience, antiprogress, antimedicine and anti- the welfare of the people of this country.

Hays (166) concluded, “Some attorneys continue to press these cases (Bendectin) when there is no scientific evidence to support them.” Sheffield and Batagol, (175) in their article on the creation of therapeutic orphans, concluded that any litigation against Debendox (Bendectin) as a cause of specific birth defects would not be worth pursuing.” Kerr (170) was very critical of the expert witnesses for the plaintiff.

It takes only one or two expert witnesses supporting the case for harmful consequences (from Bendectin) to throw both the courts and the public into confusion—McBride and anyone else with special knowledge have a perfect right to relate what they believe to be hazardous to pregnancies—the question is whether their opinions which encouraged withdrawal of a useful drug combination are ethically tenable when there is massive evidence interpreted by scientific principles and expressed in terms of the risk-benefit concept to support the contrary position.

Lasagna and Shulman (9) reviewed the scientific literature and the legal decisions pertaining to Bendectin. While they concluded that Bendectin was not teratogenic, they also reaffirmed a well-known principle that seems to have been ignored by many participants in the Bendectin saga, “Proving that Bendectin does not cause birth defects is logically impossible.”

Ayala and Black (118) concluded,

Claims that have not been subject to peer review should be treated skeptically, especially if they represent a significant departure from generally accepted scientific knowledge.

### *The expert witnesses*

The biomedical community of physicians and scientists is partly responsible for the plethora of Bendectin lawsuits. With regard to the matter of the expert witness, it appears that professional medical and scientific organizations and universities are immobilized by the presence of an irresponsible expert witness in their membership (112,113). Although organizations and universities are quick to act if an individual is accused of fraudulent research or plagiarism (114), irresponsible testimony in the courtroom does not evoke a similar response. There have been suggestions for raising the quality of expert witness testimony, but they are being adopted very slowly (112,113,115). Although there is much criticism of the irresponsible and partisan scientist who testifies in court (1,112,116–120), there is little that organized medicine and organized science is doing to correct the situation.

## CONCLUSIONS

This article is a review of the scientific literature and commentaries pertaining to the reproductive toxicity and teratogenesis of Bendectin. Multitudes of lawsuits have been initiated, alleging that Bendectin exposure during pregnancy was responsible for an infant’s birth defect. The epidemiologic and experimental data indicate that the clinical use of Bendectin does not increase the risk of birth defects in populations of exposed pregnant women. Cohort studies include over 120,000 nonexposed and over 13,000 exposed pregnant women. There is

no malformation or group of malformations that has consistently been reported to be increased in the exposed populations. Two meta-analyses of the epidemiologic studies both conclude that pregnant women exposed to Bendectin do not have an increased risk of delivering infants with birth defects. Secular trend data also indicate that the frequency of birth defects is not associated with the changes in population exposures to Bendectin. Animal studies and in vitro studies similarly indicate no measurable effect of Bendectin in the therapeutic range and, in most instances, even when the drug concentration is considerably above the therapeutic range. Pharmacokinetic studies and the FDA-sponsored animal teratology study performed at the National Center for Toxicological Research are recent studies that assist in evaluating the reproductive effects of Bendectin. An analysis of the alleged cases of malformed children whose mothers took Bendectin indicates the absence of a *Bendectin Syndrome*, a characteristic of proven human teratogens. Presentations by many of the plaintiff's experts failed to meet the scientific standards that should be expected of scientists knowledgeable in the fields of teratology, embryology, genetics, and epidemiology. Furthermore, while many of the defense experts expressed their opinions in the medical literature and at scientific meetings, as well as in court, the plaintiffs experts primarily confined their opinions to the courts. There is not a single scientific review of Bendectin in a medical journal by any of the plaintiff's experts. There are many factors that contribute to the pursuit of nonmeritorious litigation. The experts for the plaintiff have had a major role in this process by presenting to the courts partisan presentations rather than an objective scientific analysis.

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