TABLE 22
SUMMARY TABLE OF SPECIAL TOXICOLOGY STUDIES OF DOXIL

Report Number	Study Type	Species/ Strain/ Group size	Dose[a] (mg/kg)	DOXIL Lot No.	CONCLUSIONS
LTI-30-93-03	Local Tolerance (iv)	Rabbit/ Hra:(NZW) SPF/ 12M	DOXIL: 0.1, 1 mL/kg Dox HCl: 0.1, 1 ml/kg	[redacted]	• No test material-related gross or microscopic changes at injection sites in any dose group.
LTI-30-93-02	Local Tolerance (sc)	Rabbit/ Hra:(NZW) SPF/ 12M	DOXIL: 0.1, 1 mL/kg Dox HCl: 0.1, 1 ml/kg		• DOXIL induced reversible minimal to moderate edema, fibrosis and inflammation at injection sites. • Dox HCl induced moderate to moderately severe inflammation, and necrosis, with no evidence of resolution by 4 weeks post-treatment. • Placebo liposomes were without effect.
LTI-30-92-15	HP/BC[b]	In vitro/ (human blood. plasma, and serum)	DOXIL: 1 mg/mL		• No evidence of hemolysis of human erythrocytes by DOXIL or placebo liposomes. • No coagulation or precipitation of serum or plasma by DOXIL or placebo liposomes.
LTI-30-94-08	HP[c]	In vitro/ (rat blood)	DOXIL: 1 mg/mL		• The presence of up to 0.88 mg/mL lysophosphatidylcholine (LPC), a possible membrane-lytic degradation product of a lipid component of the liposome, had no effect on hemolysis.

[a] Dose route was intravenous bolus unless otherwise indicated.
[b] Hemolytic potential/blood compatibility.
[c] Hemolytic potential.

TABLE 22 (cont.)
SUMMARY TABLE OF SPECIAL TOXICOLOGY STUDIES OF DOXIL

Report Number	Study Type	Species	Dose[a] (mg/kg)	DOXIL Lot No.	CONCLUSIONS
			Other		
LTI-30-93-29	Acute	Mouse	MPEG-DSPE: 14, 284 mg/kg	NA	• No evidence of MPEG-DSPE-associated toxicty.
			DOXIL 1		
LTI-30-91-01	HP[b]	In vitro	DOXIL 1: 8.4, 81.2, 603 µg/mL Dox HCl: 363 µg/kg	[redacted]	• No evidence of hemolysis of human erythrocytes by DOXIL 1, placebo liposomes or Dox HCl.

[a] Dose route was intravenous bolus unless otherwise indicated.
[b] Hemolytic potential.

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TABLE 23
SUMMARY TABLE OF REPRODUCTIVE TOXICOLOGY STUDIES OF DOXIL

Report Number	Study Type	Species/ Strain/ Group size	Dose[a] (mg/kg)	DOXIL Lot No.	CONCLUSIONS
LTI-30-94-13	Segment II (Develop. Toxicity)	Rat/ Sprague Dawley/ 25F	DOXIL:[b] 0.1, 0.5, 1 Dox HCl:[c] 0.2, 0.4	[redacted]	• No effect of placebo liposomes or 0.1 mg/kg DOXIL on maternal or fetal endpoints. • Maternal toxicity observed at 0.5 and 1.0 mg/kg DOXIL and 0.2 and 0.4 mg/kg Dox HCl. • 1.0 mg/kg DOXIL induced decreased fetal weights, increase in resorptions and ossification retardation in caudal vertebrae and xiphoid centers. • No fetal effects were observed at either dose level of Dox HCl.
LTI-30-94-06	Segment II (Develop. Toxicity)	Rabbit/ NZW/ 5F	DOXIL:[d] 0.5, 1.5, 2.5		• DOXIL was embryotoxic and an abortifacient in rabbits. • Maternally toxicity observed at all doses.

[a] Dose route was intravenous bolus unless otherwise indicated.
[b] Treatment on gestation days (gd) 6, 9, 12 and 15.
[c] Daily treatment on gd 6-15.
[d] Treatment on gd 6, 9, 12, 15 and 18.

TABLE 24
SUMMARY TABLE OF MUTAGENICITY STUDIES OF DOXIL

Report Number	Study Type	Species/ Strain/ Group size	Dose[a] (mg/kg)	DOXIL Lot No.	CONCLUSIONS
Placebo Liposomes					
LTI-30-93-19	In vitro/ Ames test	Salmonella typhimurium TA98, TA100, TA1535, TA1537, TA1538 In vitro/ NA[b]	Placebo Liposomes: 13.7, 27.4, 41, 137, 274, 410 µg/plate	Placebo Lot: [redacted]	• DOXIL placebo liposomes negative with and without exogenous rat liver S9 metabolic activation system.
LTI-30-93-20	In vitro/ Mammalian forward mutation	Mouse Lymphoma/ L5178Y In vitro/ NA	Placebo Liposomes: 1.28, 2.56, 5.13, 10.3, 20.5, 41 µg/mL	Placebo Lot: [redacted]	• DOXIL placebo liposomes negative with and without exogenous rat liver S9 metabolic activation system.
LTI-30-93-21	In vitro/ Chrom. Aberration	CHO cells/ In vitro/ NA	Placebo Liposomes: 4.1, 10.3, 20.5, 30.8, 41 µg/mL	Placebo Lot: [redacted]	• DOXIL placebo liposomes negative with and without exogenous rat liver S9 metabolic activation system.
LTI-30-93-18	Micronucleus Assay	Mouse/ CD-1 (ICR)/ 15	Placebo Liposomes: 2.1, 4.1, 8.2 mg/kg	Placebo Lot: [redacted]	• No increase in micronucleated PCEs at any dose tested.

[a] Dose route was intravenous bolus unless otherwise indicated.
[b] NA = not applicable

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Nonclinical Toxicology Reports Referenced

Acute Toxicity Studies:

Report Number: LTI-30-92-05
Report Title: Pilot Acute Toxicity Study in Mice with DOXIL-155 and DOXIL-250
Amended Report Date: [redacted], 19[redacted]
Study Director: [redacted]
Study Site: Liposome Technology, Inc., Menlo Park, CA
DOXIL Lot No.: [redacted] (research lots)

Report Number: LTI-30-92-09
Report Title: Pilot Acute Toxicity Studies in Rats with DOXIL-155 and DOXIL-250
Report Date: [redacted], 19[redacted]
Study Director: [redacted]
Study Site: Liposome Technology, Inc., Menlo Park, CA
DOXIL Lot No.: [redacted]

Report Number: LTI-30-92-11[redacted]
Report Title: Single Dose Pharmacokinetic and Toxicity Study of DOXIL-155 and DOXIL-250 in Rats.
Report Date: [redacted] 19[redacted]
Study Director: [redacted]
Study Site:
DOXIL Lot No.:

Report Number: LTI-30-92-13 [redacted]
Report Title: Single Dose Intravenous Toxicity and Pharmacokinetic Study of DOXIL (Stealth Liposomal Doxorubicin Hydrochloride Injection) 155 and 250 in Dogs.
Report Date: [redacted], 19[redacted]
Study Director: [redacted]
Study Site:
DOXIL Lot No.:

Nonclinical Toxicology Reports Referenced (continued)

DOXIL 1 Acute Toxicity Studies:

Report Number: LTI-30-TM-92-01
Report Title: Single Dose Toxicity Screening Study in Mice (Mark I, Mark II and Mark IIe Process Products)
Report Date: [redacted], 19[redacted]
Study Director: [redacted]
Study Site: Liposome Technology, Inc., Menlo Park, CA
DOXIL Lot No.: [redacted]

Report Number: LTI-30-TM-92-02
Report Title: Single Dose Toxicity Study of Mark I, II, IIe DOXIL Process Products in Mice.
Report Date: [redacted] 19[redacted]
Study Director: [redacted]
Study Site: Liposome Technology, Inc., Menlo Park, CA
DOXIL Lot No.: [redacted]

Report Number: LTI-30-92-02
Report Title: Single Dose Toxicity Screening Study in Mice
Report Date: [redacted], 19[redacted]
Study Director: [redacted]
Study Site: Liposome Technology, Inc., Menlo Park, CA
DOXIL Lot No.: [redacted]

Report Number: LTI-30-92-10
Report Title: Acute and Delayed Toxicity of DOXIL (Stealth liposomal doxorubicin HCl) Injection in Male Mice.
Report Date: [redacted] 19[redacted]
Study Director: [redacted]
Study Site: Liposome Technology, Inc., Menlo Park, CA
DOXIL Lot No.: [redacted]

Nonclinical Toxicology Reports Referenced (continued)

Report Number: LTI-30-92-12[redacted]
Report Title: Single Dose Toxicity of Study of DOXIL in Mice.
Report Date: [redacted] 19[redacted]
Study Director: [redacted]
Study Site:
DOXIL Lot No.:
Placebo Liposome Lot No.: [redacted]

Report Number: LTI-30-91-05
Report Title: Preclinical Toxicology Study of Doxorubicin Hydrochloride, Stealth Liposomal Doxorubicin Hydrochloride Injection and Placebo Liposomes Administered Intravenously to Beagle Dogs by a X1 Schedule.
Report Date: [redacted], 19[redacted]
Study Director: [redacted]
Study Site:
DOXIL Lot No.:
Placebo Liposome Lot No.: [redacted]

Report Number: LTI-30-92-04[redacted]
Report Title: Single Dose Intravenous Toxicity Study of DOXIL in the Beagle Dog.
Report Date: [redacted], 19[redacted]
Study Director: [redacted]
Study Site:
DOXIL Lot No.:

Repeat Dose Toxicity Studies:

Report Number: LTI-30-93-08[redacted]
Report Title: Intravenous Multiple Dose Toxicity and Pharmacokinetic Study of DOXIL (Stealth liposomal doxorubicin HCl) Injection in Rats.
Report Date: [redacted], 19[redacted]
Study Director: [redacted]
Study Site:
DOXIL Lot No.:
Placebo Liposome Lot No.: [redacted]

Nonclinical Toxicology Reports Referenced (continued)

Report Number: LTI-30-93-04[redacted]
Report Title: Four-Week Intravenous Tolerance Study of DOXIL-155 and DOXIL-250 in Male Beagle Dogs.
Report Date: [redacted], 19[redacted]
Study Director: [redacted]
Study Site:
DOXIL Lot No.:
Placebo Liposome Lot No.: [redacted]

Report Number: LTI-30-94-07[redacted]
Report Title: Multiple Dose Intravenous Toxicity Study of DOXIL (Stealth liposomal doxorubicin HCl) Injection in Beagle Dogs.
Report Date: [redacted], 19[redacted]
Study Director: [redacted]
Study Site:
DOXIL Lot No.:
Placebo Liposome Lot No.: [redacted]

DOXIL 1 Repeat Dose Toxicity Studies:

Report Number: LTI-30-92-08
Report Title: Pilot Repeat Dose-Ranging Study of DOXIL in Rats
Report Date: [redacted], 19[redacted]
Study Director: [redacted]
Study Site:
DOXIL Lot No.:
Placebo Liposome Lot No.: NA

Report Number: LTI-30-92-17 (HWI 6297-105)
Report Title: Multiple Dose Intravenous Toxicity Study of DOXIL (Stealth Liposomal Doxorubicin Hydrochloride Injection) in Rats.
Report Date: [redacted], 19[redacted]
Study Director: [redacted]
Study Site:
DOXIL Lot No.:
Placebo Liposome Lot No.: [redacted]

Nonclinical Toxicology Reports Referenced (Continued)

Report Number: LTI-30-92-07[redacted]
Report Title: 5-Week Pilot Intravenous Toxicity Study of DOXIL (Stealth Liposomal Doxorubicin Hydrochloride Injection) in Dogs.
Report Date: [redacted], 19[redacted]
Study Director:
Study Site:
DOXIL Lot No.: [redacted]

Report Number: LTI-30-92-16[redacted]
Report Title: Pilot Study: Intravenous Toxicity Study of DOXIL (Stealth Liposomal Doxorubicin Hydrochloride Injection) and Doxorubicin Hydrochloride in Dogs.
Report Date: [redacted] 19[redacted]
Study Director:
Study Site:
DOXIL Lot No.: [redacted]

Special Toxicity Studies:

Report Number: LTI-30-93-03[redacted]
Report Title: Acute Intravenous Tolerance Study of DOXIL (Stealth Liposomal Doxorubicin Hydrochloride Injection) in Rabbits.
Report Date: [redacted], 19[redacted]
Study Director:
Study Site:
DOXIL Lot No.: [redacted]
Placebo Liposome Lot No.: [redacted]

Report Number: LTI-30-93-02[redacted]
Report Title: Acute Subcutaneous Tolerance Study of DOXIL (Stealth Liposomal Doxorubicin Hydrochloride Injection) in Rabbits.
Report Date: [redacted] 19[redacted]
Study Director:
Study Site:
DOXIL Lot No.: [redacted]
Placebo Liposome Lot No.: [redacted]

Nonclinical Toxicology Reports Referenced (continued)

Report Number: LTI-30-92-15 [redacted]
Report Title: Hemolytic Potential and Blood Compatibility Study of DOXIL (Stealth Liposomal Doxorubicin Hydrochloride Injection).
Report Date: [redacted], 19[redacted]
Study Director: [redacted]
Study Site: [redacted]
DOXIL Lot No.: [redacted]
Placebo Liposome Lot No.: [redacted]

Report Number: LTI-30-94-08
Report Title: Hemolytic Potential of DOXIL (Stealth liposomal doxorubicin HCl) Injection Containing Increased Concentrations of Lysophosphatidylcholine.
Report Date: [redacted], 19[redacted]
Study Director: [redacted]
Study Site: Liposome Technology, Inc., Menlo Park, CA
DOXIL Lot No.: [redacted]

Report Number: LTI-30-93-29
Report Title: Acute Toxicity of Methoxy-Polyethylene Glycol Distearoylphosphatidyl Ethanolamine (MPEG-DSPE) Micelles in Mice
Report Date: [redacted], 19[redacted]
Study Director: [redacted]
Study Site: Liposome Technology, Inc., Menlo Park, CA
DOXIL Lot No.: NA

<u>DOXIL 1 Special Toxicity Study:</u>

Report Number: LTI-30-91-01
Report Title: Hemolytic Activity of Stealth Liposomal Doxorubicin Hydrochloride Injection.
Report Date: [redacted], 19[redacted]
Study Director: [redacted]
Study Site: Liposome Technology, Inc., Menlo Park, CA
DOXIL Lot No.: [redacted]
Placebo Liposome Lot No.: [redacted]

Nonclinical Toxicology Reports Referenced (continued)

Reproductive Toxicity Studies:

Report Number: LTI-30-94-13
Report Title: Developmental Toxicity Study of DOXIL (Stealth liposomal doxorubicin HCl) Injection Administered Intravenously to Rats.
Report Date: [redacted], 19[redacted]
Study Director: [redacted]
Study Site:
DOXIL Lot No.:
Placebo Liposome Lot No.: [redacted]

Report Number: LTI-30-94-06
Report Title: Dosage Range Developmental Toxicity Study of DOXIL (Stealth liposomal doxorubicin HCl) Injection Administered Intravenously to New Zealand White Rabbits.
Report Date: [redacted], 19[redacted]
Study Director: [redacted]
Study Site:
DOXIL Lot No.:

Mutagenicity Studies:

Report Number: LTI-30-93-19[redacted]
Report Title: Mutagenicity Test of Stealth Liposome Placebo in the Salmonella Mammalian-Microsome Reverse Mutation Assay (AmesTest)
Report Date: [redacted], 19[redacted]
Study Director: [redacted]
Study Site:
Placebo Liposome Lot No.: [redacted]

Report Number: LTI-30-93-20[redacted]
Report Title: Mutagenicity Test of Stealth Liposome Placebo in the L5178Y TK+/- Mouse Lymphoma Forward Mutation Assay
Report Date: [redacted], 19[redacted]
Study Director: [redacted]
Study Site:
Placebo Liposome Lot No.: [redacted]

Nonclinical Toxicology Reports Referenced (continued)

Report Number: LTI-30-93-21 [redacted]
Report Title: Induction of Chromosomal Aberrations in Chinese Hamster Ovary (CHO) Cells by Stealth Liposome Placebo
Report Date: [redacted], 19[redacted]
Study Director: [redacted]
Study Site:
Placebo Liposome Lot No.: [redacted]

Report Number: LTI-30-93-18 [redacted]
Report Title: In Vivo Mammalian Micronucleus Assay with Stealth Liposome Placebo
Report Date: [redacted], 19[redacted]
Study Director: [redacted]
Study Site:
Placebo Liposome Lot No.: [redacted]

8. Final Summary

The efficacy of DOXIL has been established in a variety of different tumor models, including several human xenograft models. In every model examined DOXIL was more effective than the same doses of Adriamycin at inhibiting or halting tumor growth, at effecting cures and/or at prolonging survival times of tumor-bearing animals. Most often, all three endpoints were improved by DOXIL, and in no case was DOXIL less effective than Adriamycin. DOXIL was more active in both solid and dispersed tumors, and was more effective than Adriamycin in preventing spontaneous metastases from intramammary implants of two different mammary tumors in mice.

The plasma pharmacokinetics and tissue distribution of DOXIL have been extensively studied in mice, rats, rabbits, and dogs. Comparatively, the plasma pharmacokinetics of DOXIL and Adriamycin are substantially different. The plasma concentration of doxorubicin is up to 2000-fold higher in DOXIL-treated animals after intravenous injection of equivalent doses of DOXIL and Adriamycin. DOXIL has a significantly higher AUC and longer MRT, and a lower rate of clearance and volume of distribution compared to Adriamycin. The first phase of the biexponential plasma concentration-time curve is relatively short (half-life 1 to 3 hours), and the second phase, which represents the majority of the AUC, is prolonged, with a half-life ranging from 20 to 30 hours. Depending on the method employed, more than 93% and perhaps more than 99.9% of the doxorubicin measured in plasma during the two phases is liposome-encapsulated. After repeat dosing of DOXIL in rats, which resulted in residual amounts of doxorubicin in the plasma, plasma pharmacokinetics remained independent of dose, indicating that saturation had not occurred.

After a single intravenous dose of DOXIL, peak tissue concentrations of doxorubicin were lower and occurred later than after a single Adriamycin treatment. Doxorubicin persisted in the tissues in DOXIL-treated animals due to the slower clearance of liposome-associated drug. Levels of doxorubicin were higher in tumors from DOXIL-treated animals compared to animals treated with an equivalent dose of Adriamycin. There was no evidence suggesting that saturation of tissues had occurred. Doxorubicin did not accumulate in the heart following repeated administration of DOXIL. Doxorubicin concentrations were higher in skin lesions than in normal skin in both rats and dogs, and decreased rapidly as the lesions healed.

The toxicity observed following administration of DOXIL to mice, rats, rabbits and dogs was qualitatively similar with respect to the nature of the response. The acute toxicity of DOXIL following single administration is similar for mice, rats, and dogs. However, dogs

were the most sensitive species. High doses of DOXIL are associated with a treatment-related mortality. Treatment-related toxicity included dermal toxicity, hematologic changes, myelotoxicity, marginal clinical symptoms, gastrointestinal toxicity, reversible cutaneous lesions and persistent alopecia.

The toxicity profile of DOXIL following repeated administration was similar in rats and dogs and an extension of the findings from the acute studies. Treatment-related effects included dermatologic toxicity, body weight and food consumption changes, alopecia, myelotoxicity (bone marrow cellularity changes), and hematologic effects (leukopenia and lower erythron mass). Dogs, the more sensitive species, also exhibited gastrointestinal toxicity and no pathologic signs of cardiac toxicity.

Toxicity observed following DOXIL administration is ascribable to the doxorubicin HCl rather than the Stealth liposome component. Adverse effects observed in animals administered empty placebo liposomes were limited to minimal clinical observations during the time of infusion. In dogs, reversible cardiovascular effects were limited to the infusion period and were presumed to be related to the relatively rapid infusion of a large amount of lipid intravenously. No liposome-related neurobehavioral changes were observed in rats. Placebo Stealth liposomes were neither genotoxic nor mutagenic.

In general, the toxicity observed in animals following DOXIL administration was similar to, but less severe than, the known toxicity of doxorubicin HCl. There were, however, several substantial differences in the toxicity profile of DOXIL and non-liposomal doxorubicin in laboratory animals. Cardiotoxicity was either absent or present at substantially decreased incidence and severity in rats and dogs administered DOXIL. In contrast, evidence of cardiotoxicity is frequently observed in animals and man administered doxorubicin HCl. Similarly, there was no evidence of nephrotoxicity in DOXIL-treated animals. Nephrotoxicity is another well-established adverse effect of doxorubicin HCl. Myelotoxicity was observed in rats and dogs following DOXIL administration, however, the incidence and severity were slightly decreased when compared to animals that received equivalent cumulative doses of doxorubicin HCl. Doxorubicin-associated nephrotoxicity, cardiotoxicity and myelotoxicity are well correlated with high peak plasma levels. The decreased relative toxicity of DOXIL is believed to be due to the decreased peak concentration of free, non-liposomal doxorubicin in the plasma and tissues of treated animals.

Another difference in the observed toxicity of DOXIL compared to the toxicity of doxorubicin HCl administered as a bolus injection is the treatment-related appearance of reversible, cutaneous lesions and persistent alopecia, primarily on the feet and legs of

animals administered multiple doses of DOXIL, but not doxorubicin HCl. A similar finding, known as palmar-plantar erythrodysesthesia or hand-and-foot syndrome, has been reported in several clinical studies in which patients received continuous intravenous infusions of doxorubicin HCl.[99-102] Degenerative changes in the skin have also been described in hamsters following multiple intraperitoneal injections of doxorubicin HCl.[103] Thus, the cutaneous lesions seen in DOXIL-treated animals appear to be consistent with a known dermatologic toxicity of doxorubicin HCl and does not represent a toxicity unique to DOXIL. The appearance and resolution of these lesions correlated with an increased or decreased concentration of doxorubicin HCl in the skin lesion, respectively.

Non-liposomal doxorubicin HCl is considered embryotoxic and teratogenic in rats and embryotoxic and an abortifacient in rabbits.[104] High doses of doxorubicin result in increased fetal resorptions and decreased fetal body weight.[98] Similarly, in developmental toxicity (Segment II) studies in rats and rabbits, DOXIL administration was associated with maternal and fetal toxicity, increased fetal resorptions, and retardation in ossification believed related to the decreased fetal body weight. In rabbits, DOXIL was also an abortifacient. Fertility studies in males and females have not been conducted with DOXIL, however, apparently irreversible or slowly resolving testicular atrophy was observed in rats and dogs after multiple DOXIL doses. Non-liposomal doxorubicin HCl is reported to cause damage to the spermatogenic cells in male animals and humans, and may induce long-term or permanent sterility.[105-108] Therefore, it is likely that DOXIL will be associated with an effect on fertility.

Injection site reactions are commonly associated with administration of doxorubicin HCl. Paravasal leakage of doxorubicin HCl causes severe necrosis of skin and adjacent tissues at the site of extravasation, which shows no tendency to spontaneous healing.[95,109] The extent of the lesion necrosis depends upon the degree of extravasation,[110] and an appropriate antidote is not available.[70] DOXIL did not cause irritation after intravenous injection in rabbits, and was substantially less irritating than doxorubicin HCl when injected subcutaneously. However, in two dogs administered a single dose of DOXIL, severe injection site lesions that were possibly due to extravasation of DOXIL were observed. No similar lesions were observed in 4-week and 10-week repeat dose studies in dogs, and only minimal evidence of injection site irritation was seen in single and repeat dose rat studies. It is likely that the vesicant damage of doxorubicin HCl is minimized in animals that receive DOXIL subcutaneously because intact liposomes are drained from the injection site by blood and lymph and removed by phagocytic scavenger cells before any significant amount of drug is released. However, the potential for doxorubicin HCl-related skin injury exists, and care should be taken to avoid extravasation of DOXIL.

Given as a standard intravenous bolus, cumulative doses of doxorubicin pose a significant risk of cardiotoxicity in humans.[111,112] Doxorubicin HCl cardiotoxicity appears to be related to its peak plasma concentration.[97] Repeat administration of doxorubicin HCl bolus injections on a weekly schedule, and the resultant high plasma concentrations of doxorubicin, have been associated with increased risk of cardiotoxicity.[112] Less rapid development of cardiotoxicity was observed when doxorubicin HCl was administered as fractionated doses or as long-term infusions, without loss of antineoplastic activity.[14,97,113,114] Cumulative doses up to 1100 mg/m^2 have been delivered as 48- and 96-hour infusions without significant cardiotoxicity.[115] Long-term or continuous infusions avoid the high peak plasma concentrations believed responsible for the development of cardiotoxicity while maintaining concentrations in the plasma without loss of efficacy.[70,72] Myelosuppression and alopecia appear to be schedule independent, and stomatitis is variably associated with dosing schedule. The most common reported dose-limiting side effect of doxorubicin HCl administered as a long-term infusion has been stomatitis, sometimes accompanied by hand-and-foot syndrome.[101,102]

The toxicity profile of DOXIL in animals is similar to that reported for continuous or long-term infusion of doxorubicin HCl in humans. Doxorubicin HCl administered as a continuous or long-term infusion is characterized by reduced cardiotoxicity, increased stomatitis, the appearance of hand-and-foot syndrome and minimal effects on myelotoxicity. Comparatively, administration of doxorubicin HCl as long-circulating DOXIL liposomes in animals is characterized by reduced cardiotoxicity, increased dermal ulcerations, particularly of the feet and legs, and marginally reduced myelosuppression. In general, the efficacy of Adriamycin has been limited by its toxicity. DOXIL could be used at a higher dose, increasing its therapeutic advantage without increasing toxicity.

In summary, DOXIL, a long-circulating liposomal formulation of doxorubicin HCl, is less cardiotoxic, nephrotoxic and marginally less myelotoxic than an equivalent dose of doxorubicin HCl when administered as an intravenous bolus. Subcutaneous local tolerance studies suggest that DOXIL poses a significantly lower risk of injury to skin and adjacent tissues than doxorubicin HCl if extravasated. DOXIL is teratogenic and embryotoxic in rats and embryotoxic and abortifacient in rabbits. Doxorubicin is mutagenic and carcinogenic; therefore, DOXIL is presumed to be mutagenic and carcinogenic. Placebo liposomes are neither mutagenic nor genotoxic. In general, the toxicity profile of DOXIL in animals is similar to that reported for continuous or long-term infusions of doxorubicin HCl in humans, with lessened cardiotoxicity and increased dermatologic toxicity. Based on the results of these nonclinical safety studies, DOXIL appears to be a potentially safer formulation of doxorubicin HCl.