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In Vitro Determination of Uptake, Retention, Distribution, Biological Efficacy, and Toxicity of Boronated Compounds for Neutron Capture Therapy: A Comparison of Porphyrins with Sulfhydryl Boron Hydrides[1]

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ABSTRACT

A major problem remaining in the evaluation of boronated compounds for neutron capture therapy (NCT) is the need to know the intra- or extracellular microdistribution of boron. This is a consequence of the short range of the $^{10}B(n,\alpha)^7Li$ reaction products (~10 μm), such that biological efficacy is dependent upon intracellular distribution. In particular, if boron location is predominantly extracellular, a significant reduction in efficacy would be expected.

The *in vitro* procedure described here was developed mainly to provide information regarding the intra- and extracellular location and concentration of boron. However, use of the technique also allows the measurement of compound uptake and retention (binding) and the determination of biological efficacy by the evaluation of survival curves obtained following irradiation with thermal neutrons. Comparison is made to results obtained with boric acid ($H_3{}^{10}BO_3$) and to results calculated for various boron distributions. Concomitantly, an indication of compound toxicity can be obtained from the plating efficiency of unirradiated control cells.

Currently, most investigators utilize *in vivo* systems for testing and evaluating boron uptake from various carrier molecules. Given the large number of boron compounds being synthesized and needing evaluation as to their usefulness for NCT, the *in vitro* technique described here is simple and advantageous for initial compound screening. In addition to sparing animal lives, it is both time and cost effective and utilizes much smaller quantities of test compound than are required for an *in vivo* assay.

A boronated porphyrin (BOPP) evaluated by the above procedure shows an uptake and retention ~20 times that of sulfhydryl boron hydride monomer (BSH); the latter compound is currently being used clinically for NCT in Japan and is anticipated for use in clinical trials in the United States. If the advantages demonstrated by BOPP in these *in vitro* studies are validated in animal experiments, BOPP should be considered for clinical application.

INTRODUCTION

NCT[3] is a binary system in which boron is transported to tumor, and an external neutron beam is used to deliver thermal neutrons to produce the $^{10}B(n,\alpha)^7Li$ reaction. The short range of the high linear energy transfer (LET) reaction products (~10 μm, or one cell diameter) results in a severe dependency of the biological efficacy (ability to kill cells) on boron microlocalization. For a typical cell, it is calculated that ~10 times more boron is needed if it is located extracellularly, as opposed to intracellularly (1, 2).

One of the major problems remaining in the evaluation of various compounds for NCT is the need to determine intracellular *versus* extracellular distribution of boron (3, 4). Current analytical procedures, including neutron activation analysis by prompt-γ emission (5), inductively coupled plasma-atomic emission spectroscopy (6), and track-etching techniques (7), do not have resolutions requisite for measurement of intracellular distribution. Thus, this important parameter has been unavailable for compound evaluation.

The *in vitro* procedure described here was developed mainly to provide information regarding boron location within cells. However, use of the procedure also allows the measurement of compound uptake and retention (binding) and the determination of biological efficacy by the evaluation of survival curves obtained following irradiation of boronated and nonboronated control cells with thermal neutrons. Concomitantly, an indication of compound toxicity can be obtained from the plating efficiency of unirradiated control cells. Briefly, cells are grown for one mitotic cell cycle in the presence of the boron-containing compounds to be tested and then irradiated in the presence of the same compound; similar irradiations are then carried out after a thorough washing of the cells and suspension in boron-free media. Biological response is then compared to that obtained after irradiation of cells in known amounts of boric acid ($H_3{}^{10}BO_3$), in which a homogeneous intra- and extracellular distribution is assumed. A comparison of results indicates whether the test compound is taken into the cell, whether it is retained (binds) despite washings, and how much is present in terms of known amounts of $H_3{}^{10}BO_3$ (boric acid equivalents). Gross (average) amounts of ^{10}B retained in washed cells can then be determined by the prompt-γ method (5). The evaluation of biological efficacy in terms of boric acid equivalents in addition to the quantification of the average cellular boron content can then, in principle, indicate the intracellular (or extracellular) distribution. The analysis utilizes Monte-Carlo calculations of nuclear dose as a function of boron location as described by Gabel *et al.* (1).

This procedure was used to determine the uptake, retention, distribution, biological efficacy, and toxicity of a boronated natural porphyrin synthesized by one of us (S. B. K.). Also, information bearing on the mechanism of porphyrin incorporation was obtained by measuring uptake as a function of duration of exposure to the drug. Porphyrins are expected to be a particularly effective vehicle for boron transport; they have been suggested for NCT since they are known to be taken up avidly by all tumors investigated to date, to have long-term retention in tumors, and to have a singularly large boron-carrying capacity (8, 9).

In addition, BSH and BSSB were evaluated. BSH has been used in Japan to treat >100 patients with brain tumors with NCT and has been proposed for further clinical trials by a number of groups in the United States and Europe (3, 4). BSSB has been shown to have better uptake and retention in tumors

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[3] The abbreviations used are: NCT, neutron capture therapy; BSH, monomer form of $Na_2B_{12}H_{11}SH$; BSSB, dimer form of $Na_2B_{12}H_{11}SH$; BOPP, hematoporphyrin-like polyol porphyrin; PBS, phosphate-buffered saline; BMRR, Brookha-

effective than BSH in the treatment of animal tumors (11–14).

Our comparison of BSH and BSSB with the porphyrin, using this system, indicates that BSSB is taken up and bound more effectively than BSH and that the porphyrin is at least 4 times more effective than BSSB.

MATERIALS AND METHODS

Boronated Porphyrins. We have synthesized and characterized an unusual tetracarborane carboxylic acid ester of BOPP, with low toxicity, in which high aqueous solubility was achieved by two propionic acid side chains (15, 16). The 95% ^{10}B-enriched potassium salt of the compound has a molecular weight of 1363, so that the molecule is 29.3% boron by weight.

$Na_2B_{12}H_{11}SH$ and $Na_4B_{24}H_{22}S_2$. These compounds 95% enriched in ^{10}B were purchased from the Callery Chemical Co., Callery, PA.

Preirradiation Cell Procedures. V-79 Chinese hamster cells in logarithmic growth were propagated in Dulbecco's modified Eagle's media (Gibco, Grand Island, NY) supplemented with 10% fetal bovine serum (Hyclone Laboratories, Logan, UT), 1% penicillin-streptomycin-fungisone (Gibco), and 2.0 mM L-glutamine (Gibco). BSH, BSSB, boric acid (H_3BO_3), or BOPP were added to the growth medium at a ^{10}B concentration of ~30 ppm for each experiment. After 12 h, the boronated medium was aspirated from above the cell monolayer.

Washing Procedures. Cells which were to be irradiated in a boron-containing medium ("ambient" experiments) were processed with reagents (PBS, trypsin) containing 30 ppm ^{10}B from the experimental compound. In the experiments using BOPP, the cells did not survive trypsinization when the trypsin contained 30 ppm ^{10}B of BOPP (cause unknown); therefore, BOPP was excluded from the trypsinization procedure. Cells were suspended in boron-containing medium (30 ppm ^{10}B) in preparation for irradiation. In the "washed" experiments, every effort was made to remove unbound boron prior to irradiation in boron-free growth medium. Cells which were to be irradiated in a boron-free environment were washed 3 times with PBS, trypsinized, and harvested with boron-free reagents prior to suspension and irradiated in boron-free medium.

Cell Irradiations. Cells were irradiated in suspension in growth medium at a population density of 3.0×10^5 cells/ml. Irradiations were carried out at the thermal neutron beam port of the BMRR within 1–2 h following suspension in growth medium. The thermal neutron fluence rate at the center of the sample (1.5-ml Eppendorf microfuge tubes) was 2.8×10^{11} n cm^{-2} min^{-1}. Beam parameters are summarized in Table 1. The irradiation apparatus is described in Ref. 17.

Survival Assay. Cells were plated for undisturbed colony growth for 5–6 days. Colonies were then washed with PBS, fixed with buffered formalin, and stained with Giemsa, prior to optoelectronic counting with an Artec colony counter.

Survival Curve Analysis. Data were analyzed on the basis of D_0s obtained from the linear portion of the survival curves. Curves were fitted with the multihit formula (18):

$$S = 1 - [1 - \exp(-D/D_0)]^n,$$

Table 1 *Dose rates for cell irradiations at the BMRR*
Power level = 1 MW, thermal neutron flux density = 2.8×10^{11} n/(cm^2 − min)

Component	cGy/min	cGy × RBE /min[a]	% of total effective dose rate
Fast neutrons	13	26	68
γ	6	6	16
$^{14}N(n,p)^{14}C$	3.1	6.2	16
Total	22.6	38.2	100
$^{10}B(n,\alpha)^7Li$[b]	2.4C[c]		

[a] A relative biological effect (RBE) of 2 is assumed for fast neutrons and the $^{14}N(n,p)^{14}C$ reaction (21).
[b] Dose rate for $H_3{}^{10}BO_3$; a uniform extra- and intracellular distribution is

and D_0s were obtained from this fit, where S is survival, D is dose, and n is extrapolation number.

Evaluation of Experimental Compounds in $H_3{}^{10}BO_3$ Equivalents. The radiation response of cells containing boron compounds with unknown distributions was evaluated relative to the response obtained with known amounts of ^{10}B from $H_3{}^{10}BO_3$; it is assumed that $H_3{}^{10}BO_3$ distribution is uniform and homogeneous throughout the cells in suspension. For experiments described here, V-79 cells were grown in the presence of $H_3{}^{10}BO_3$ in concentrations of 15 and 30 μg ^{10}B/g of growth medium. Survival curves for $H_3{}^{10}BO_3$ are shown in Fig. 1. If one evaluates the slope of the survival curve in the linear portion when plotted on semilog paper, the inverse of the slope is the dose (D_0) in terms of time, neutron fluence, or absorbed dose that it takes to reduce survival by a factor of "*e*" (*i.e.*, by 63%). D_0 is expressed in units of time throughout this paper, as the latter is the most basic parameter. Conversion to absorbed dose, biologically effective dose, fluence of thermal neutrons, etc. can be carried out directly using data in Table 1. D_0 in rad or cGy is equal to the sum of the mixed field dose components in cGy/min (as given in Table 1), multiplied by irradiation time in min. The slope itself will be a linear function of boron concentration, *i.e.*, $-1/D_0 = a + 2.4C$, where a is the contribution from the sum of components other than ^{10}B in rad/min (*i.e.*, the "background" radiation) and C is the fractional concentration of ^{10}B from $H_3{}^{10}BO_3$ (see Table 1). A plot of $1/D_0$ *versus* ^{10}B content provides a graph with 1 dependent variable from which the response of a compound with unknown concentration and distribution can be evaluated in terms of an equivalent amount of ^{10}B from $H_3{}^{10}BO_3$ (Fig. 2) (17, 19). Thus, if the negative inverse of D_0 for any survival experiment is evaluated from Fig. 2, the boron response in terms of an equivalent concentration of $H_3{}^{10}BO_3$ in μg ^{10}B/g can be obtained (boric acid equivalents) free of effects from contaminating radiations.

Boron Analysis by Prompt-γ Neutron Activation Analysis. Unless otherwise noted, the growth medium in each experiment was prepared with a boron concentration calculated to be 30 μg ^{10}B/g. This was verified by analyzing 0.5 ml of media from each experiment by the prompt-γ technique at the BMRR facility (5). For analysis of ^{10}B in cells, ~10^8 cells (~0.1 g) were grown in boronated growth media and then washed, pelletized, and analyzed by prompt-γ. This technique is capable of measuring 0.5 ppm ^{10}B with ~15% accuracy in 200 s.

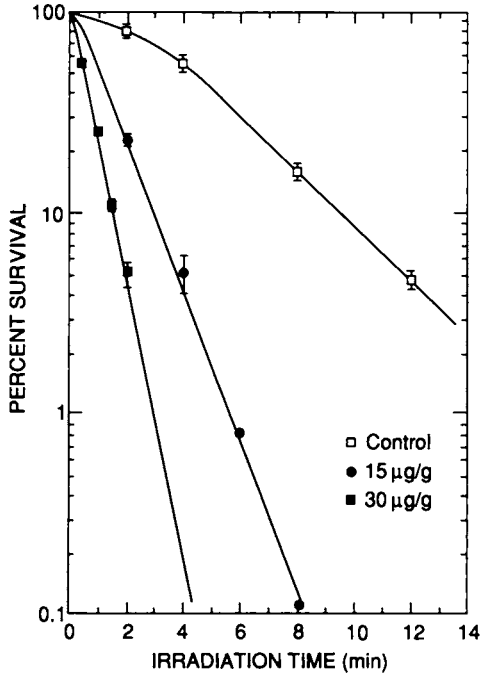

Fig. 1. Survival curves for V-79 Chinese hamster cells incubated for 12 h in the presence of 15 and 30 μg ^{10}B/ml of growth medium from $^3H^{10}BO_3$ and

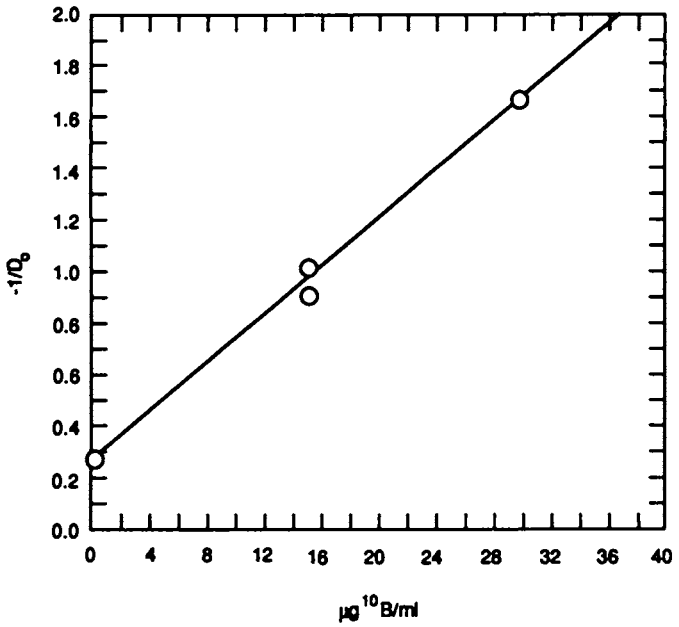

Fig. 2. Slope of survival curves represented by Fig. 1, plotted *versus* boron content in growth medium. Data point at 0 boron content is the average of 11 control curves.

RESULTS

Experimental conditions and measured parameters for each individual experiment are summarized in Table 2. Representative survival curves are shown in Figs. 1, 3, 4, and 5. Values for boric acid equivalents were obtained from the average of replicate experiments (Table 3).

BSH. Survival curves for BSH are shown in Fig. 3; data from individual experiments are given in Table 2. Averaged values of D_0 are summarized in Table 3, in units of time of irradiation at a reactor power of 1 MW. Actual doses can be obtained from Table 1. The biological response of BSH can be expressed in boric acid equivalents as obtained from Fig. 2; these data are also summarized in Table 3. It is apparent that (*a*) most of the BSH is easily washed out because the radiation response is equivalent to only 0.5 μg ^{10}B/g (boric acid equivalents = 0.5 μg ^{10}B/g) and (*b*) even under ambient conditions (*i.e.*, irradiation in the presence of 30 ppm ^{10}B from BSH) most of the boron is excluded from the cell (response in boric acid equivalents = 9.5 μg ^{10}B/g).

BSSB. Results with the dimer are shown in Fig. 4. Average D_0s and boric acid equivalents are recorded in Table 3. As with BSH, it is apparent that most of the compound is washed out and that most of the boron is excluded from the cell. However, it is clear that BSSB has better retention and uptake relative to BSH.

BOPP. Survival curves for BOPP are given in Fig. 5. It is obvious that the biological efficacy of BOPP is significantly greater than that of the sulfhydryl boron hydrides. In terms of boric acid equivalents (Table 3), it is evident that in experiments with cells maintained under ambient conditions, the effective boron concentration is greater than the equilibrium concentration (*i.e.*, BOPP is concentrated in cells) and that under washed conditions, retention is ~4 and ~20 times greater than that obtained with BSSB and BSH, respectively.

To gain further insight into the mechanisms of porphyrin uptake, washed experiments similar to those shown in Fig. 5 were carried out, but the time of exposure to the drug was varied from 1–18.5 h. Biological efficacy in terms of boric acid equivalents is summarized in Table 4 and plotted in Fig. 6 after normalization to 30 ppm ^{10}B in the growth medium (*i.e.*, boric acid equivalents were adjusted to reflect linearly projected uptake for cells grown in 30 ppm ^{10}B/g growth medium). Following an initial rapid uptake of ~3 μg ^{10}B/g within the first hour, accumulation is seen to progress linearly at a rate of ~1 μg ^{10}B/g/h. In one experiment boron concentration in growth medium was deliberately reduced to 2.3 μg ^{10}B/g. Normalization to 30 μg ^{10}B/g showed that response was proportional to boron content in media (○, Fig. 6), thus showing an absence of saturation effects at the higher boron concentrations.

Survival curves were also obtained following 12 h growth in BOPP and subsequent irradiation with ^{137}Cs γ-rays at 50 rad/h. No radiation sensitization (dose enhancement) was observed for BOPP with the 661 keV photons (data not shown).

DISCUSSION

Evaluation of Boron Distribution. If actual boron concentration within or on the cell is measured for an "unknown" compound, an evaluation of its location can be made if calculations are available giving biological efficacy as a function of cellular location. This procedure has been followed for the "washed" experiments. It is possible to grow large amounts of cells (~100 mg, or ~10^8 cells), and following removal of surrounding media and thorough washing, to measure ^{10}B retained in cells by prompt-γ analysis.

Monte-Carlo calculations have shown that for a hamster V-70 cell (with a spherical volume of ~1150 μm^3 and a centrally

Table 2 *Experimental conditions and measured parameters for individual experiments used in preparing Fig. 2 and Table 3*

Experimental parameters and status during irradiation	Compounds evaluated								
	$H_3{}^{10}BO_3$		BSH		BSSB		BOPP		
Boron concentration in growth media (μg ^{10}B/g)									
Ambient[a]	13.8	14.8	28.1	27.9	28.0	27.5	30.2	30.7	
Ambient	29.5	30.0							
Washed[b]			40.8	24.6	27.5	28.7	28.2	25.7	26.5
Plating efficiency (%)									
Ambient	51.0	65.0	64.0	88.0	60.0	76.0	65.0	77.0	
Ambient	55.0	65.0							
Washed			81.0	82.0	69.0	99.0	81.0	72.0	83.0
D_0 (min)									
Ambient	0.95	1.1	1.35	1.45	1.2	1.1	0.55	0.40	
Ambient	0.60	0.60							
Washed			3.4	3.6	2.2	2.4	1.2	1.1	1.4

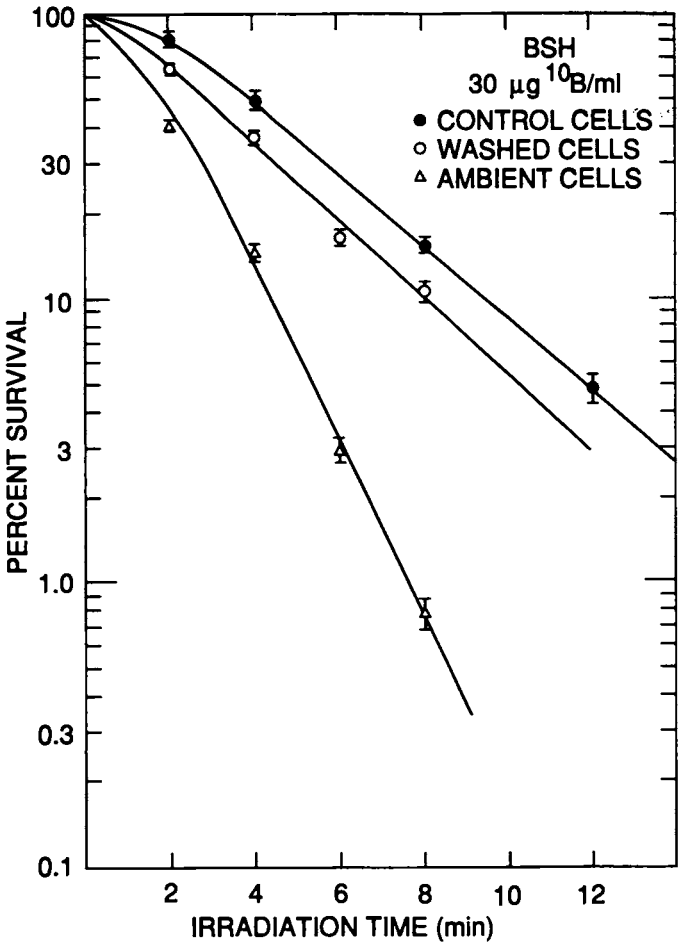

Fig. 3. Survival curves for V-79 Chinese hamster cells incubated for 12 h in the presence of ~30 μg ^{10}B/ml of growth medium from BSH. Cells were then irradiated at the thermal neutron beam of the BMRR either in the presence of BSH (ambient cells) or in boron-free growth medium (washed cells).

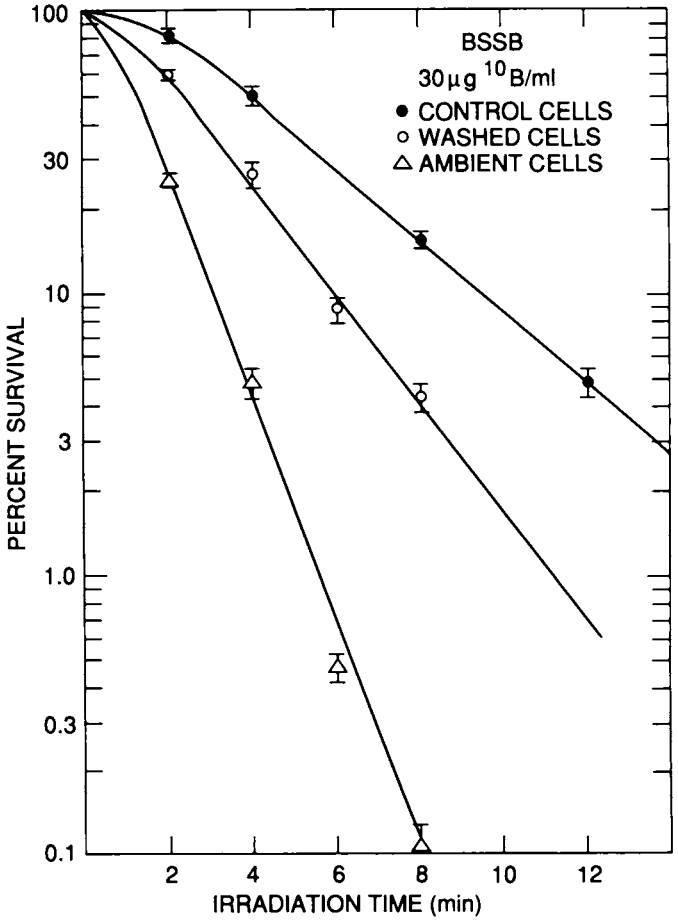

Fig. 4. Survival curves for V-79 Chinese hamster cells incubated for 12 h in the presence of ~30 μg ^{10}B/ml of growth medium from BSSB. Cells were then irradiated at the thermal neutron beam of the BMRR either in the presence of BSSB (ambient cells) or in boron-free growth medium (washed cells).

Table 3 *Response of V-79 cells to thermal neutron irradiation following growth for 12 h (1 cell cycle time) in the presence of 30 μg ^{10}B/g growth medium from various compounds*

Compound	D_0 (min)		Boric acid equivalents (μg/g)		Measured B Content for washed cells (μg/g)
	Washed[a]	Ambient	Washed	Ambient	
BSH	3.5	1.4	0.5	9.5	
BSSB	2.3	1.2	3.0	12.0	6.2
BOPP	1.2	0.5	12.0	41.0	28.0

[a] Conditions for individual experiments are given in Table 2.

located nuclear volume of 230 μm^3) in suspension in $H_3{}^{10}BO_3$ (ambient experiments) ~10% of the dose would be expected to come from external ^{10}B, while ~45% of the dose would come from ^{10}B in the cytoplasm and 45% from the nucleus (details given in Ref. 1). Similarly, for washed experiments, boron attached to the cell membrane will be only ~10% as effective the same quantity of ^{10}B uniformly distributed intracellularly.

Uptake, Retention, Distribution and Biological Efficacy. A comparison of measured parameters from individual and average experiments in Tables 2 and 3, respectively, demonstrates that the experimental error observed in replicate experiments is much less than the differences obtained when experimental conditions (*i.e.*, compound, status during irradiation) are changed.

An evaluation of boric acid equivalents in Table 3 indicates that BSH and BSSB are to a significant extent excluded from grown and irradiated in the presence of 30 μg ^{10}B/g of growth medium, the biological efficacy was equivalent to only 9.5 and 12 μg ^{10}B/g of uniformly distributed boron for BSH and BSSB, respectively. These results are in agreement with the finding that BSH is bound to albumin *in vivo* and that the albumin molecule, because of its size and charge, remains extracellular (20). Perhaps most striking was the finding that, of the small amounts of sulfhydryl boron hydrides which were bound, BSSB retention was significantly higher than BSH. The higher uptake of BSSB *in vitro* correlates well with the observations that BSSB uptake and retention is greater than BSH *in vivo* and that BSSB is more efficient than BSH in the treatment of small animal tumors (11–14). The results showing that 6.2 μg ^{10}BSS^{10}B/g cell produced a response equivalent to 3.0 μg ^{10}B of $H_3{}^{10}BO_3$ is consistent with the hypothesis that BSSB distribution is primarily intracytoplasmic.

The evaluation of BOPP in terms of boric acid equivalents shows clearly that BOPP is ~4 times more effective than BSH or BSSB. The actual boron content of 28 μg ^{10}B/g of washed cells which produced damage equivalent to 12.0 μg/g of $H_3{}^{10}BO_3$ is also indicative of a cytoplasmic location; however, the greater intracellular concentration and retention of BOPP accounts for its increased biological efficacy.

The linear accumulation of BOPP during the 18-h period investigated is significantly different from the rapid diffusion processes characteristic of H_3BO_3, BSH, and BSSB (Table 3 and Refs. 10, 11, 20, and 22). The linear accumulation and

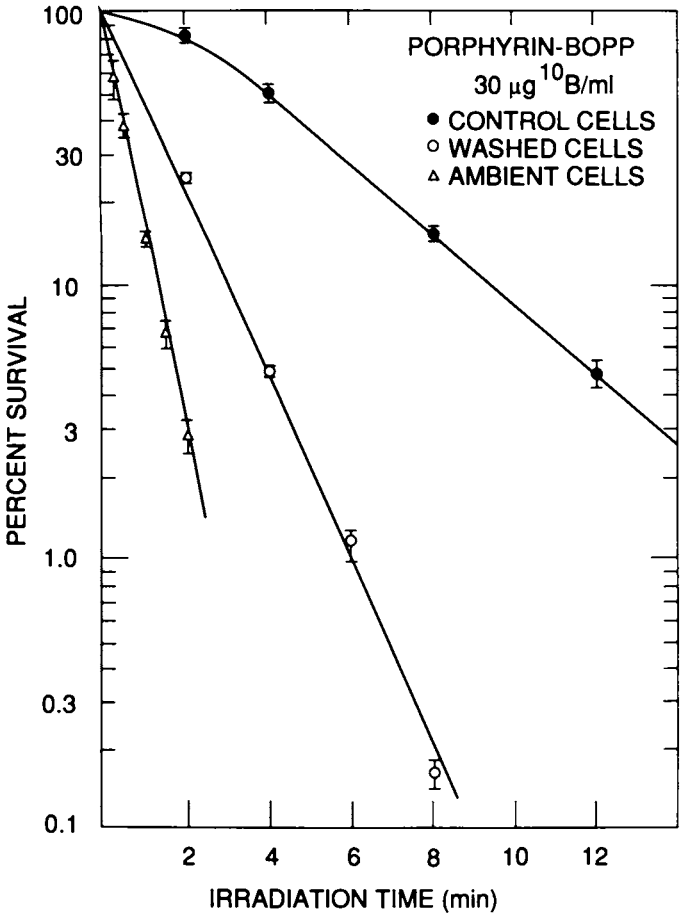

Fig. 5. Survival curves for V-79 Chinese hamster cells incubated for 12 h in the presence of ~30 μg ^{10}B/ml of growth medium from BOPP. Cells were then irradiated at the thermal neutron beam of the BMRR either in the presence of BOPP (ambient cells) or in boron-free growth medium (washed cells).

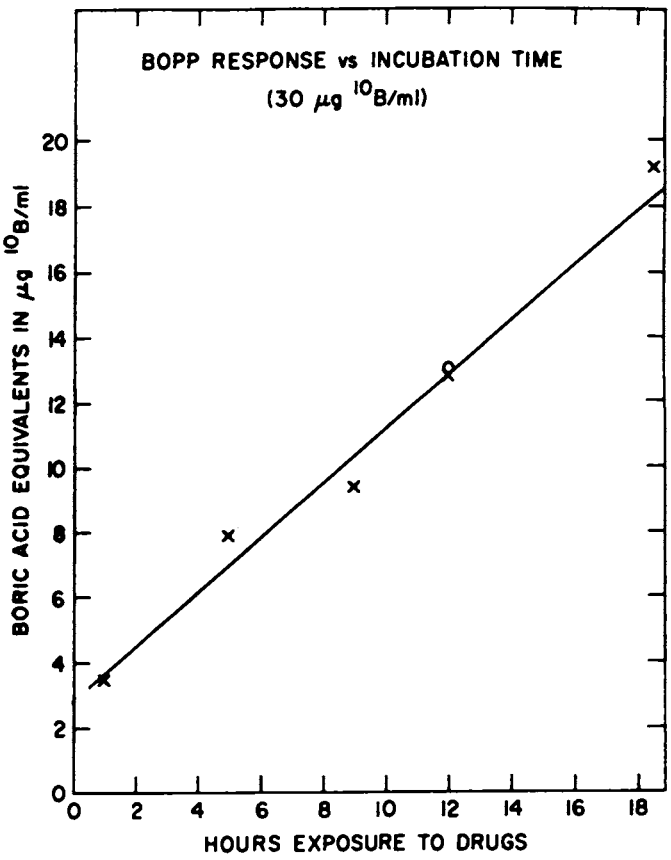

Fig. 6. The response of cells incubated for various times in ~30 μg ^{10}B/g/ml of growth medium from BOPP and then washed prior to irradiation in boron-free medium at the thermal neutron beam of the BMRR. Responses expressed in boric acid equivalents (*i.e.*, μg ^{10}B from $H_3{}^{10}BO_3$ which would give the same response). Data point marked with ○ was obtained with a boron concentration of 2.3 ppm and normalized to 30 ppm.

Table 4 *Biological efficacy of BOPP following exposure times of 1–20 h*

Boron concentrations in growth medium (μg ^{10}B/g)	Duration of exposure to BOPP (h)	D_0 (min)	Boric acid equivalents (μg ^{10}B/g)	Boric acid equivalents (normalized to 30 μg/g)
26.0	1	2.4	3.0	3.45
25.0	5	1.7	6.6	7.9
26.9	9	1.5	8.5	9.4
28.0	12	1.2	12.0	12.8
2.3	12	2.9	1.0	13.0
24.3	18.5	1.0	15.6	19.2

metabolic process and perhaps can be ascribed to a receptor-mediated mechanism (23, 24). The proportionality of uptake at both high (24–28 ppm) and low (2.3 ppm) boron concentrations indicates that, at the levels investigated here, saturation of the process has not occurred.

Porphyrins are known to be sensitizers to visible light, and this mechanism is the basis for photodynamic therapy (25). Similar sensitization has been noted for boronated porphyrins, so that these experiments have been protected from exposure to ambient light (shielded and manipulated under low intensity yellow light so that no reduction in plating efficiency was observed). As noted above, exposure of cells with BOPP to ^{137}Cs γ-rays showed no dose enhancement from BOPP; in addition, cells grown with 30 ppm BOPP with both natural and 95% ^{10}B enrichment showed a response proportional to ^{10}B shown). Thus, results presented here are attributed to the ^{10}B(n,α)^{7}Li reaction.

The above discussion illustrates that *in vitro* analysis is capable of revealing uptake mechanisms and relative biological efficacies for boronated biomolecules. This in turn makes it possible to predict and interpret data obtained *in vivo*. Clearly, however, *in vivo* studies will still be necessary in order to verify absolute and differential uptake in tumor and biological efficacy in the more complex and realistic animal tumor models.

Toxicity to Cells *in Vitro*. An indication of the toxicity of boron compounds can be obtained by comparing the PE of unboronated cells with the PE of unirradiated controls which were incubated for 12 h in the presence of the compound. Concentrations of boron used here (*i.e.*, 30 μg ^{10}B/g of growth medium) are typical of concentrations used *in vivo* (19, 21). The PE for nonboronated controls in these experiments was 72 ± 12 (SD) for a total of 11 curves. Boric acid showed a slight toxicity with an average PE of 59. The remaining compounds, BSH, BSSB, and BOPP, showed no evidence of toxicity for the times and concentrations used, as indicated in Table 2. This result is not surprising, because these compounds have been investigated in part because of their lack of debilitating toxicity. It is understood that *in vivo* toxicity is too complicated to be uniquely established by an *in vitro* test and that, ultimately, toxicity must be evaluated in animals. However, it should be noted that the majority of compounds synthesized for possible use in NCT cannot be successfully administered because of overt toxicity; this behavior is readily evidenced by a significant

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