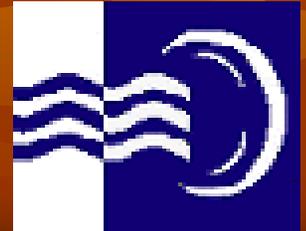


# Relationship Between Ototoxic Induced Behavioral Threshold Changes & DPOAE Changes

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# Collaborators & Acknowledgements

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Work supported by VA Rehabilitation R&D Service (grants  
C3213R, C4697R, and C4447K)

# Outline

- Learning Objectives
- Background
- Research Objectives
- Methods
- Results
- Conclusions and Clinical Implications
- Question and Answers

# Learner Outcomes

- Discuss benefits and limitations of distortion-product otoacoustic emissions (DPOAEs) as a screening test for ototoxicity
- List factors that appear to influence the ability of DPOAEs to detect ototoxic damage
- Discuss ways in which DPOAE sensitivity reported in this study may differ for other populations tested or when other DPOAE variables are used



# Background



# Symptoms of Ototoxicity

- Tinnitus
- Hearing loss
  - Usually permanent, high frequency
  - Can be progressive
  - Difficulty understanding speech in background noise
- Dizziness
  - Dysequilibrium, oscillopsia, vertigo

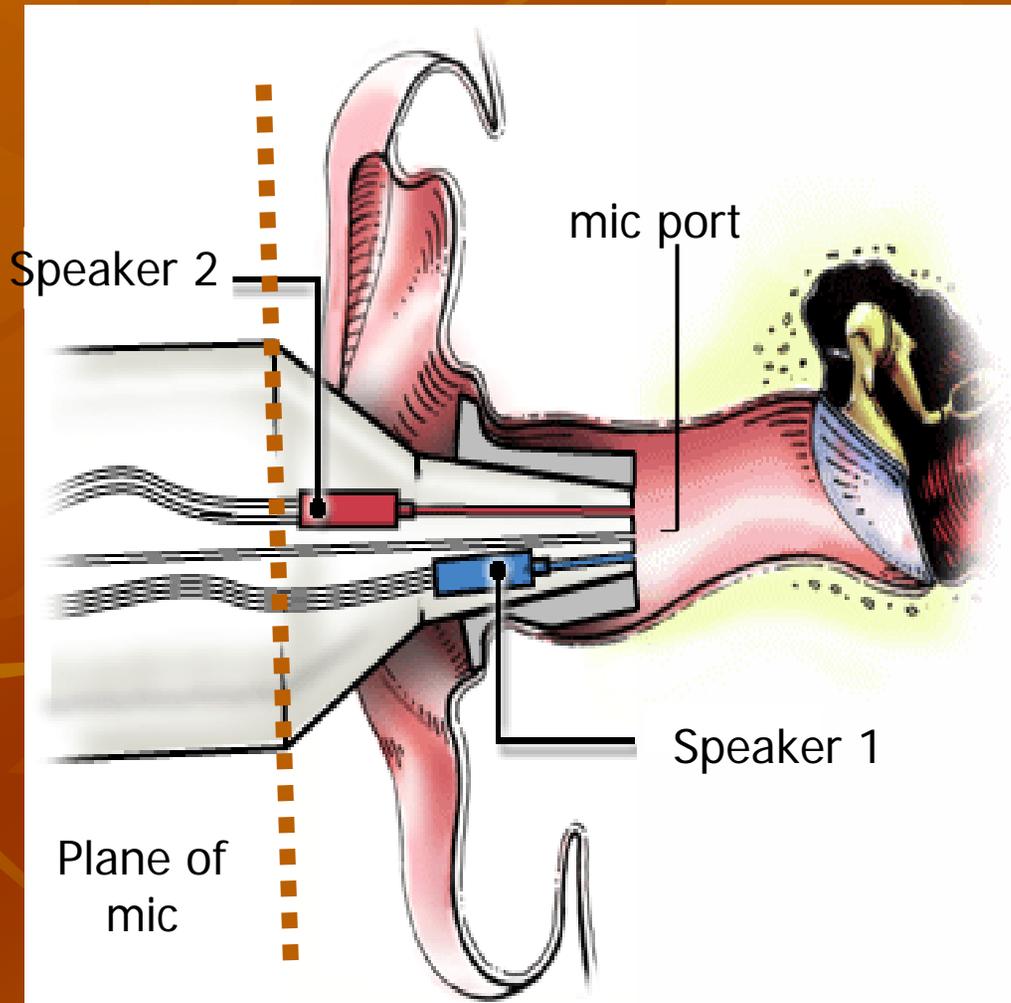
# Benefits of Monitoring

- Early detection may prevent hearing damage that requires rehabilitation
- If change observed, treatment modification can prevent further hearing loss; if no change observed, continued treatment warranted
- Ototoxicity monitoring program
  - educates patients, care givers and physicians about ototoxic symptoms raises awareness of synergistic effects of toxins and noise
  - ensures audiology work up and rehabilitation plan are implemented if and when appropriate

# DPOAE Measurement

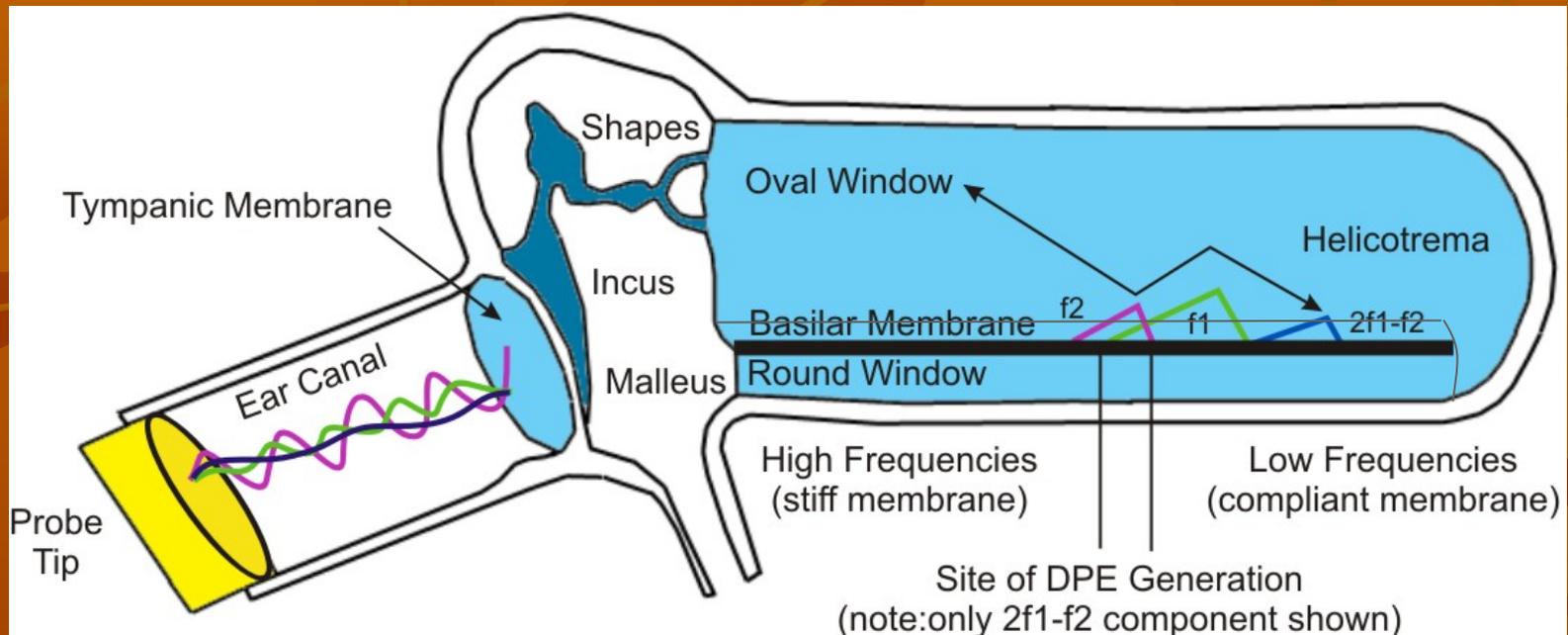
- Objective measure that tests functioning of outer hair cell (OHC) system
- OHC system must be normal for hearing to be normal
- OHCs typically affected by ototoxic drugs
- Hearing thresholds and OAEs also affected by ototoxic drugs

# DPOAE Measurement



*Drawing by S. Blatrix from "promenade around the cochlea" EDU website [www.cochlea.org](http://www.cochlea.org) by Rémy Pujol et al., INSERM and University Montpellier 1*

# DPOAE Measurement



- Nonlinear interaction between stimulus frequencies generates intermodulation distortion at  $2f_1 - f_2$
- This “distortion emission” is emitted from the  $f_2$  place
- Elicits a “reflection emission” from the  $2f_1 - f_2$  place
- DPOAE distortion & reflection sites  $\sim \frac{1}{2}$  octave apart

# DPOAE Measurement

- DPOAEs arise by a combination of coherent linear reflection & nonlinear distortion, from sources near  $f_2$  and near  $f_{dp}$  ( $2f_1 - f_2$ )
- **Nonlinear Distortion** –  
Due to nonlinearities acting as sources of cochlear traveling waves
- **Linear Reflection** –  
Due to coherent reflection of traveling wave from random impedance perturbations

# DPOAE Measurement

## ■ DP-gram

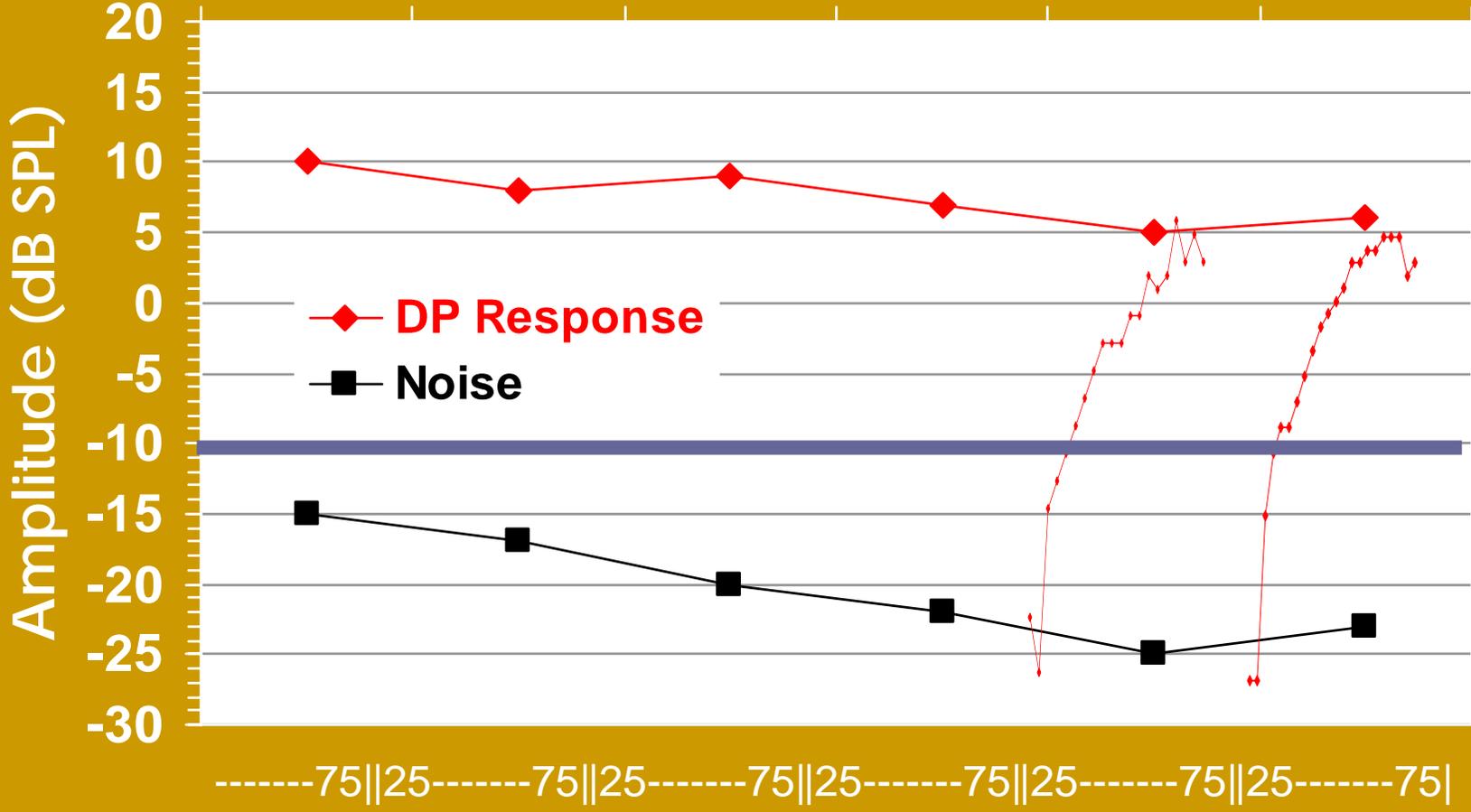
- Plot DPOAE level as a function of  $f_2$  frequency, while primary levels are held constant
- Uses moderate level, e.g., L1, L2 in dB SPL = 65, 65 or 65,59
- $f_2$  is varied in small frequency steps

## ■ Input/output (I/O) function

- Plot DPOAE level as a function of primary level, while primary frequency held constant

# f2 Frequency (Hz)

1414      2000      3000      4000      6000      8000



# Sensitivity: DPOAE

DPOAEs more effective than audiometry?

- In young subjects, DPOAEs sensitivity greater than conventional audiometric testing (AMG: Katbamna et al., 1999; Stavroulaki et al., 2002; Mulheran & Degg, 1997; CDDP: Stavroulaki et al., 2001).
- In adults, DPOAE sensitivity greater than CA testing, but similar to ultra-high frequency testing ( $> 8000$  Hz). Fewer subjects could be monitored using UHF testing (Ress et al., 1999).

# Sensitivity: DPOAE

Ress, Sridhar, Balkany, Waxman, Stagner, Lonsbury-Martin, *Otolaryngology-Head and Neck Surg*, 1999

- Adult cancer patients treated with cisplatin
  - hearing in CA range  $\leq 70$  dB HL
- DP-grams,  $f_2$  0.8-8 kHz,  $L_1=L_2=75$  dB SPL
- DP change  $\geq 5$  dB at 2 consecutive frequencies

	CA	UHF	DPOAE
Ears at baseline	52/65 (80%)	35/65 (54%)	53/65 (82%)
Ears changed	34/52 (65%)	26/35 (74%)	40/53 (75%)

*DPOAEs appear to be sensitive to pre-clinical changes or to hearing loss at frequencies higher than the DPOAE test frequencies used*

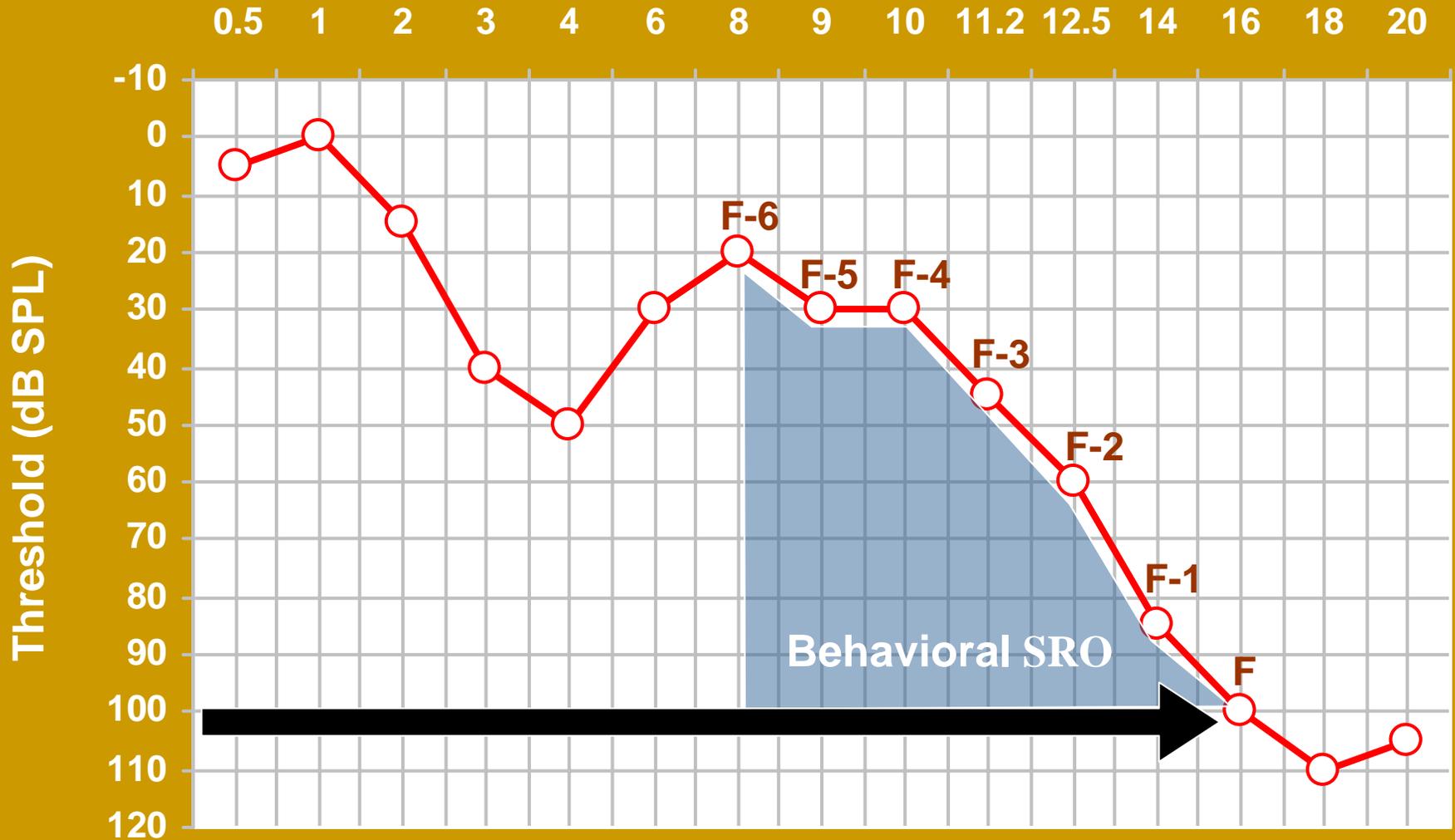
# Specificity: DPOAEs

*FP rates of ~5% for DPOAE level changes of 5-6 dB*

- Standard error of measurement difference (SEM)
  - Typically 2 X SEM is about 5 dB for f2 from 1-4 kHz (Franklin et al. 1992; Beattie et al., 2003)
- Average amplitude difference plus 2 SD
  - 6 dB for most frequencies from 1-6 kHz (Roede et al., 1993)
- Cumulative distributions
  - Our preliminary data show > 95% of ears had test-retest change of 6 dB or less for frequencies from 1 -10,000 Hz
- Future studies - ROC curves

Behavioral Measurement:  
*Individualized Sensitive  
Range for Ototoxicity  
(SRO)*

# Example SRO



# Sensitivity: SRO 1/6<sup>th</sup> Octave

	<b>Total (Ears)</b>	<b>Hit</b>	<b>Miss</b>	<b>Initial Change on SRO</b>
<b>AMG</b>	54	46	8	85%
<b>Cisplatin</b>	226	207	19	92%
<b>Carboplatin</b>	59	50	9	85%
<b>Total</b>	339	303	36	89%

Fausti SA, Helt WJ, Phillips DS, Gordon JS, Bratt GW, Sugiura KM, Noffsinger D: Early detection of ototoxicity using 1/6th-octave steps. *J Am Acad Audiol* 14(8):444-50, 2003.

# SRO Principle

- Thresholds  $> 100$  dB SPL remain unchanged
- Early changes seen within **one octave** below the highest audible frequency
- Range for each individual is **unique** and specific to their hearing configuration

*A sensitive range for ototoxicity (SRO) is the uppermost frequency with a threshold  $\leq 100$  dB SPL and 6 lower consecutive frequencies in  $1/6^{\text{th}}$  octave steps*

# ASHA 1994 Guidelines: Criteria for Audiometric Threshold Change

- 20 dB change at any 1 test frequency
- 10 dB change at any 2 adjacent test frequencies
- Loss of responses (as little as 5 dB change) at 3 consecutive frequencies, where responses were previously obtained close to the limit of the audiometer
- Changes confirmed by repeat testing

# Specificity: HF in Booth

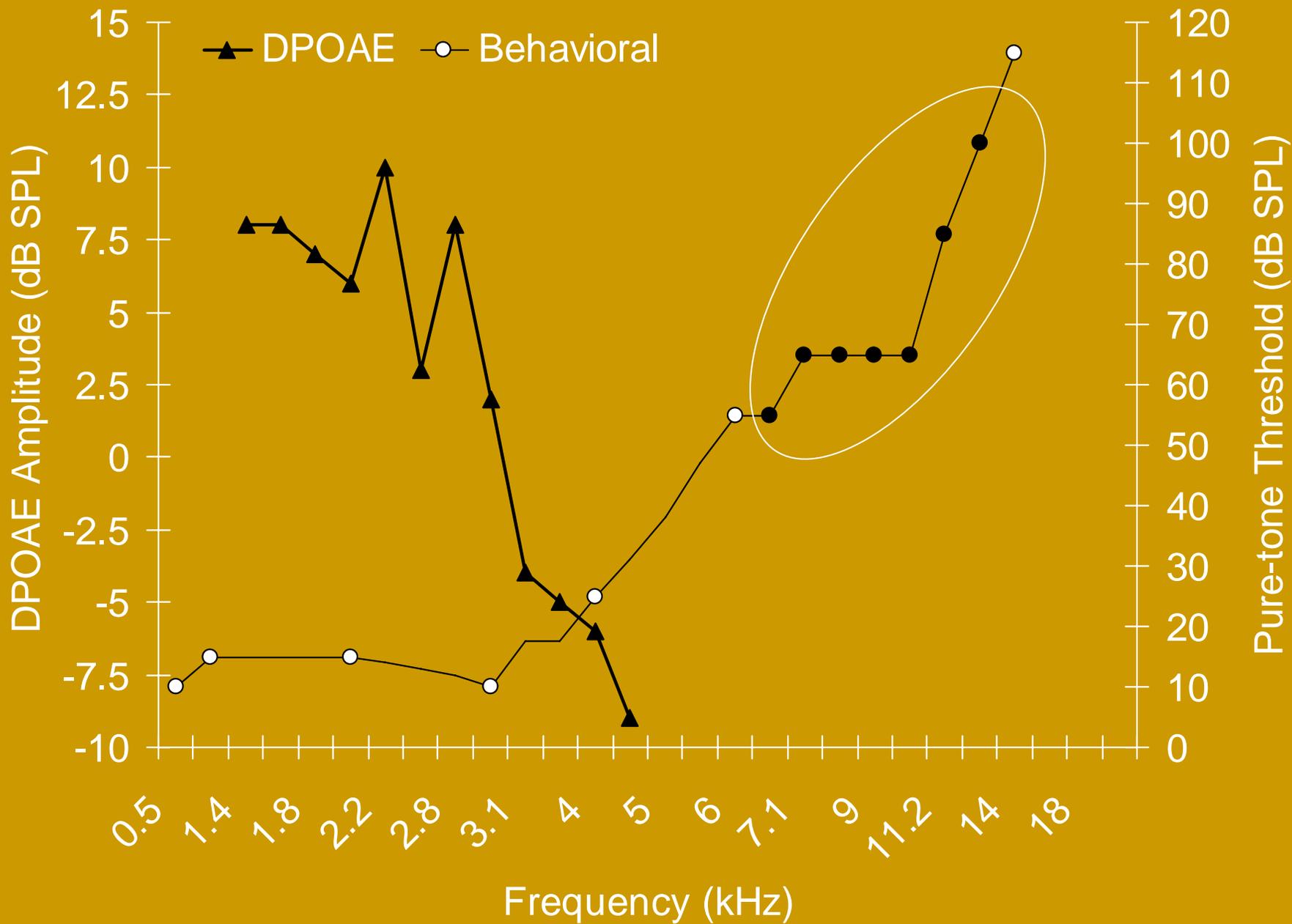
Sound Booth False Positive rate, using ASHA Criteria			
	$\geq 20$ dB at 1 Frequency	$\geq 10$ dB at 2 consecutive frequencies	Frequency Range
<b>Koss PRO/4X*</b>	0%	0%	2, 5-16 kHz
<b>ER-4B*</b>	0%	0%	2, 5-16 kHz
<b>Sennheiser HAD 200**</b>	0%	2%	8-16 kHz

\*Gordon JS, Phillips DS, Helt WJ, Fausti SA: The evaluation of insert earphones for high-frequency bedside ototoxicity monitoring. *JRR&D*, under review.

\*\*Frank T: High-Frequency (8 to 16 kHz) reference thresholds and intrasubject threshold variability relative to ototoxicity criteria using Sennheiser HAD 200 earphone. *Ear & Hearing* 22 (2): 161-168, 2001.

# Sensitivity: DPOAE vs Audiometry

- Would sensitivity to ototoxicity be improved by making behavioral (& DPOAE) measurements at frequencies higher than typically measured?
- What is the most effective ototoxicity screening test if pre-exposure hearing limits measurable DPOAE f2 range?



# Research Objectives

- 1) How well do DPOAEs predict ototoxic hearing changes near each subjects' high-frequency hearing limit?
- 2) Is DPOAE sensitivity related to:
  - type of drug administered
  - magnitude of behavioral threshold changes
  - pre-exposure hearing
  - Pre-exposure DPOAEs
- 3) Can we predict which patients will be good candidates for monitoring using DPOAEs

# Methods

## Control Subjects:

- 4 non-exposed subjects (8 ears) tested at least 4 times over a period of 2 to 7 months
- Received more than 3 days of specified non-ototoxic medications
- Had mild to moderate high-frequency hearing loss
- Used to verify that test-retest differences in DPOAE level were consistent with previous reports in laboratory subjects, and to determine criteria for DPOAE change

# Methods

- Drug-exposed Subjects:
  - 53 exposed subjects (90 ears) with demonstrated ototoxic hearing change based on behavioral monitoring of the SRO
  - Mean age 59 years (range 46 – 82 years)
  - Could have any degree of hearing loss
- Received at least one chemotherapeutic treatment of cisplatin or carboplatin
- Received more than 3 days of specified antibiotic medications

# Methods

- Normal middle ear function based on 226 tympanometry
- No history of retrocochlear or Meniere's disease
- Able to respond reliably to behavioral testing

# Methods

- Behavioral method included pure tone threshold testing from .5-20 kHz
- Determined individual's SRO
  - Virtual Corporation Model 320 audiometer (V320)
  - TDH-50P earphones in MX-41/AR cushions were used for testing 0.5 and 1 kHz thresholds.
  - Koss Pro/4X Plus earphones, modified to improve signal-to-noise ratio at high frequencies was used for high frequency testing (2 – 20 kHz)

# Methods

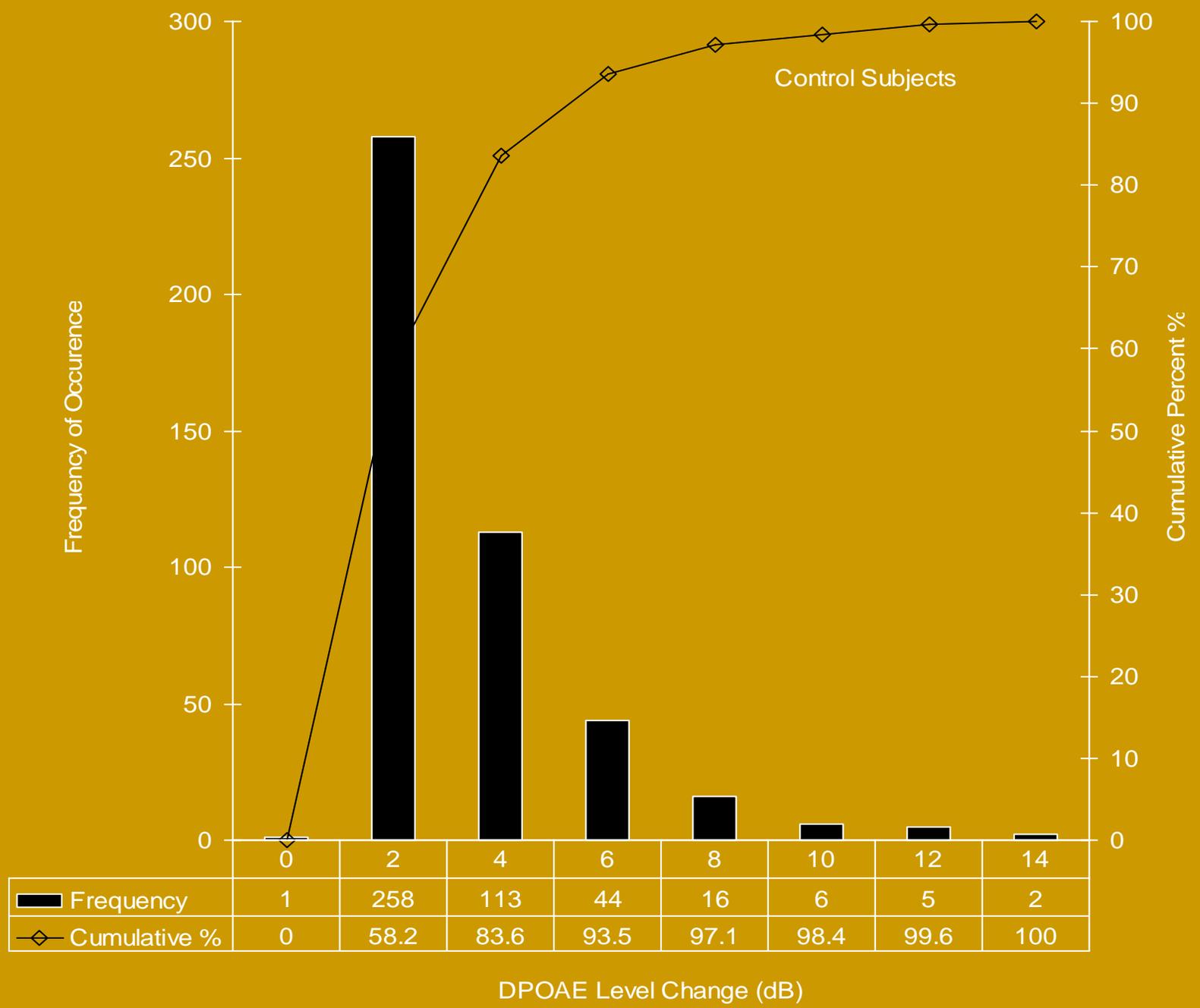
- DPOAE testing
  - Intelligent Hearing Systems SmartDPOAE, modified by manufacturer to enhance high-frequency measurements
  - $f_2$  varied 0.8-8 kHz;  $f_2/f_1=1.22$ ; L1, L2=65, 59
- Criteria for inclusion of DPOAE data
  - Level  $\geq -10$ dB SPL; SNR  $\geq 6$  dB
- Criteria for Change in DPOAE level
  - 4 dB amplitude change or loss of response at *two* consecutive frequencies
  - Changes could be outside the region of frequencies showing behavioral changes
  - Changes could occur before, together with, or after behavioral changes



# Results



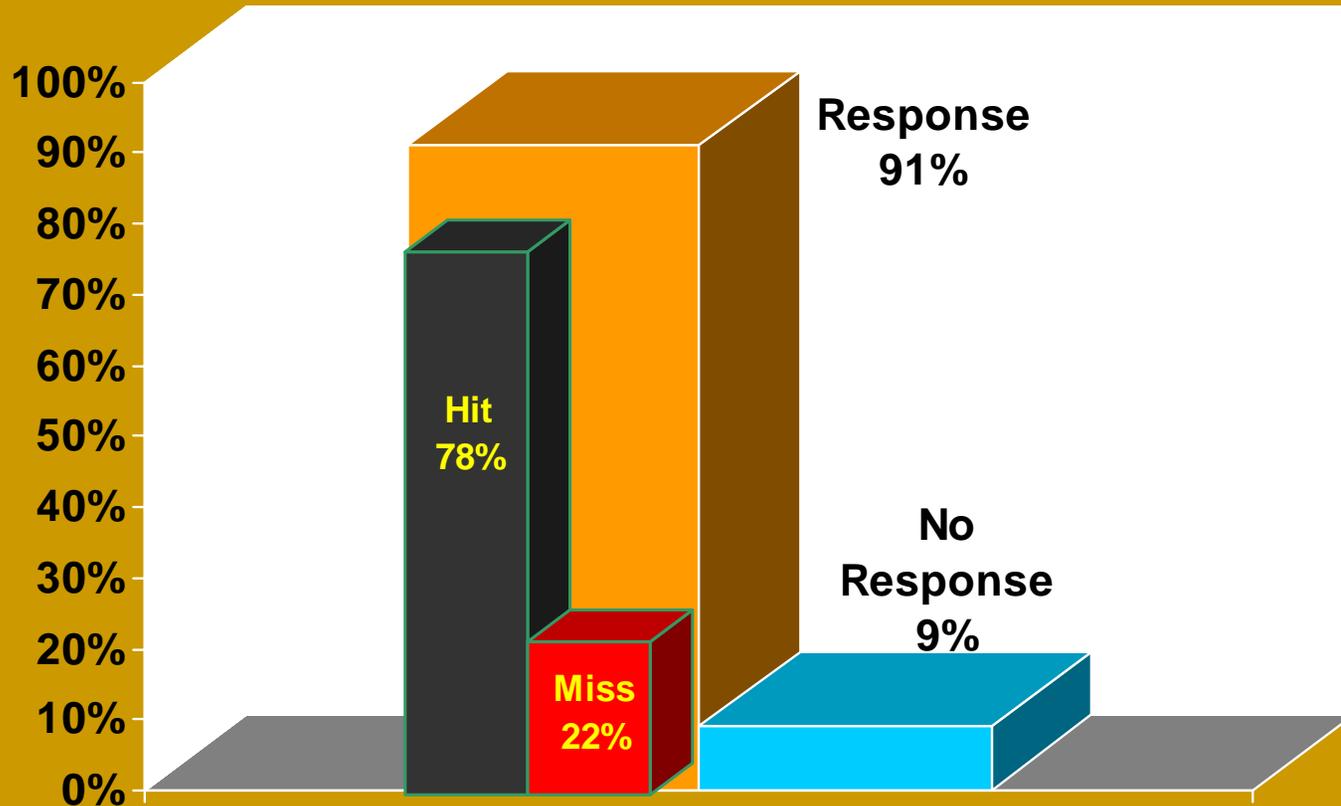
Figure 1



# Results

- DPOAE level change  $\geq 6$  dB at a single frequency yielded a false positive rate of  $\sim 6\%$ , consistent with previous reports for healthy young subjects (e.g., Beattie, Kenworthy and Luna, 2003; Franklin, McCoy, Martin & Lonsbury-Marti, 1992; Roede, Harris, Probst, & Xu, 1993)
- 6 dB shift in DPOAE level is large and such level changes tend not to occur at adjacent frequencies (Dreisbach, Long, & Lees, 2006)
- Of 409 potential occurrences, DPOAE levels shifts  $\geq 4$  dB at adjacent  $f_2$  frequencies were only observed 5% (21/409) of the time

# OAE Sensitivity



**DPOAE Response to Ototoxic Hearing Loss**

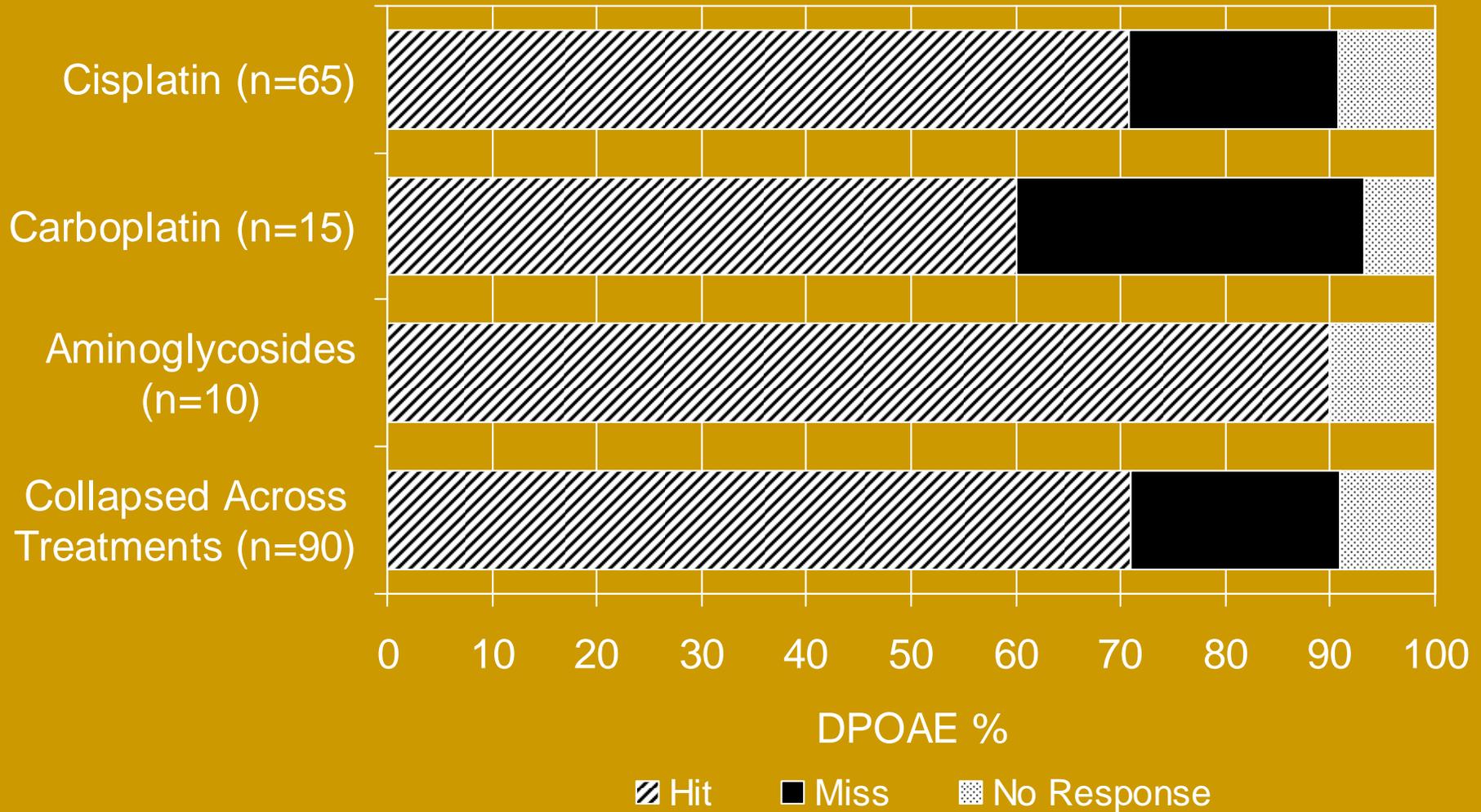
**Hit: N = 64**    **Miss: N = 18**    **No Response: N = 8**

# Results

How well do DPOAEs predict ototoxic hearing changes near each subjects' high-frequency hearing limit?

- Less well than in studies in children and young adults with normal hearing
- Hit rate (78%) was comparable to hit rate found by Ress et al., 1999 (75%) in adults with some pre-exposure hearing loss
- DPOAEs were measurable in a greater number of subjects in our study (91%) compared with Ress study (82%)

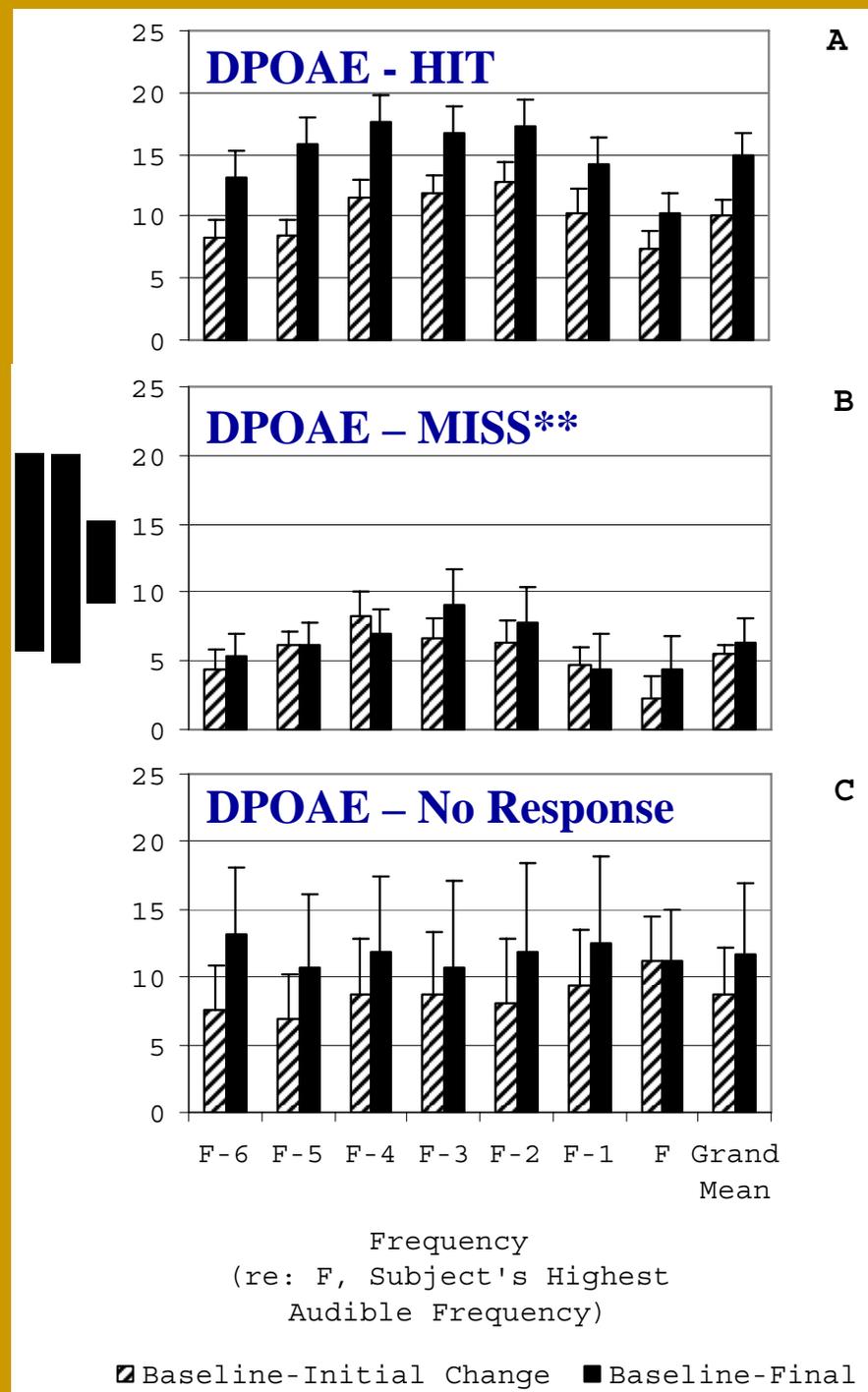
# No Effect of Drug Type



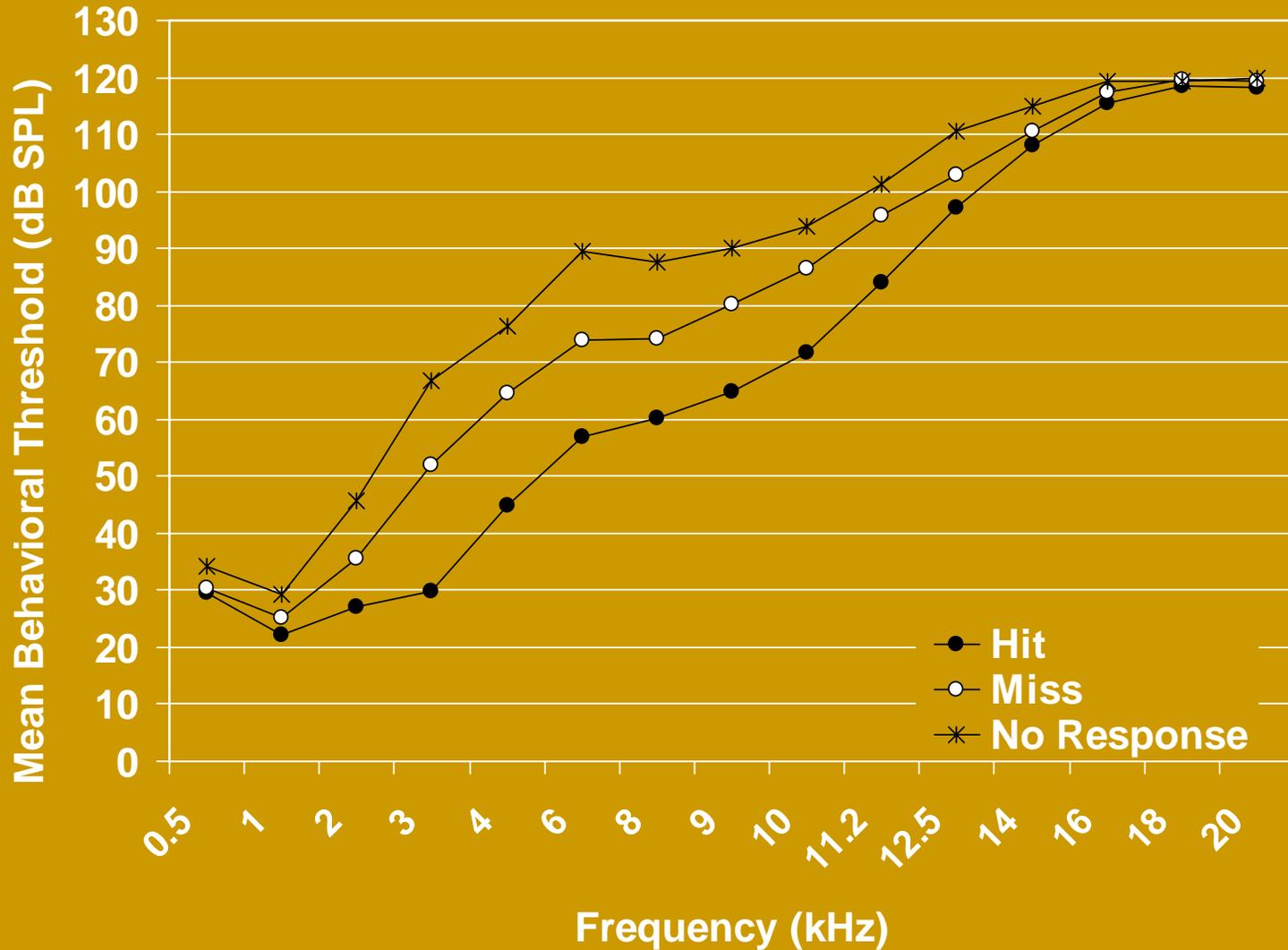
Yates corrected chi-square test=5.837, 2df,  $p$ -value=0.54

# Magnitude of Behavioral Threshold Shifts

\*\*ANOVA  $p$ -value 0.027;  
Bonferroni  $p$ -value 0.025

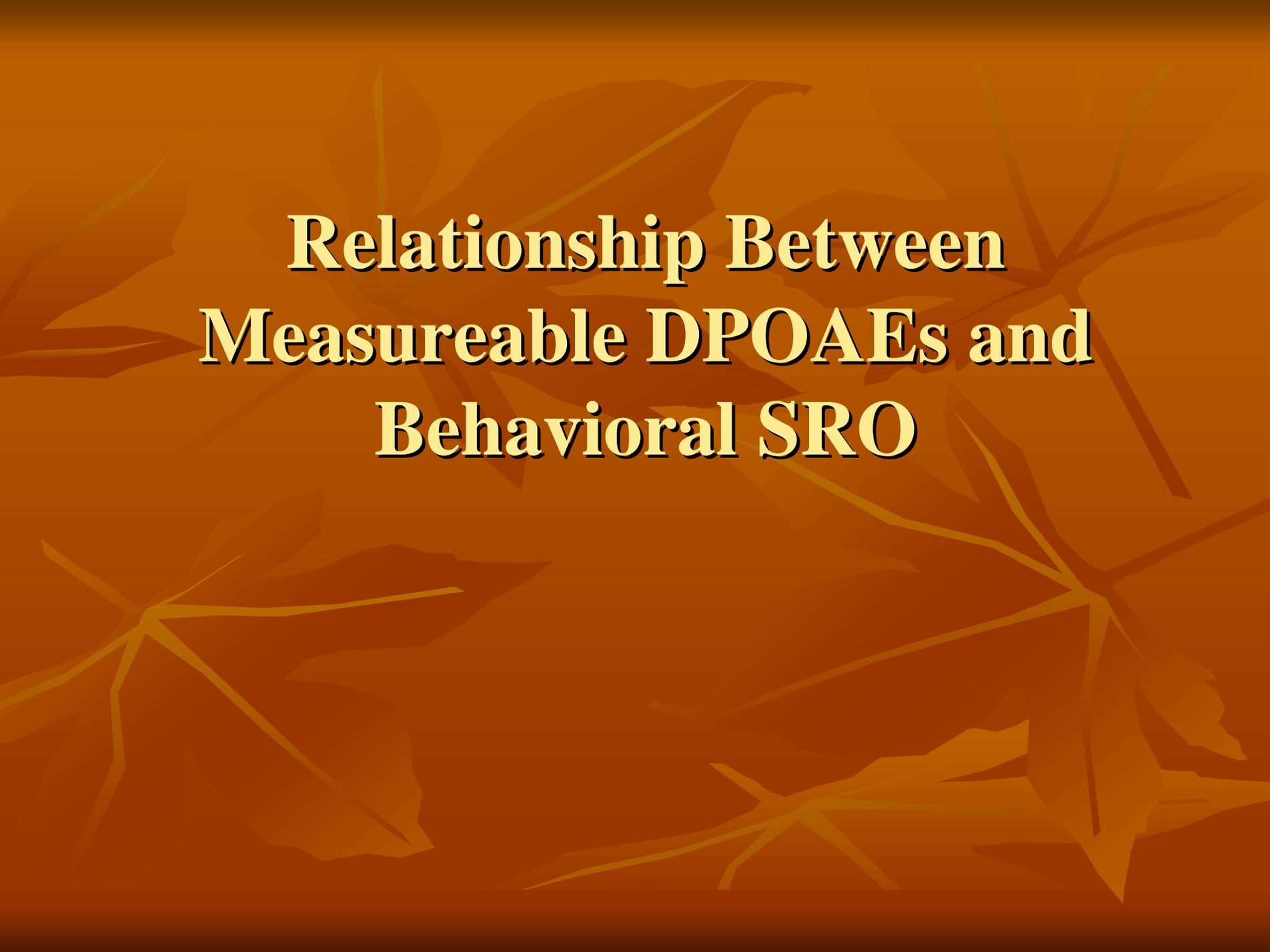


# Degree & Configuration of Pre-exposure Hearing Loss



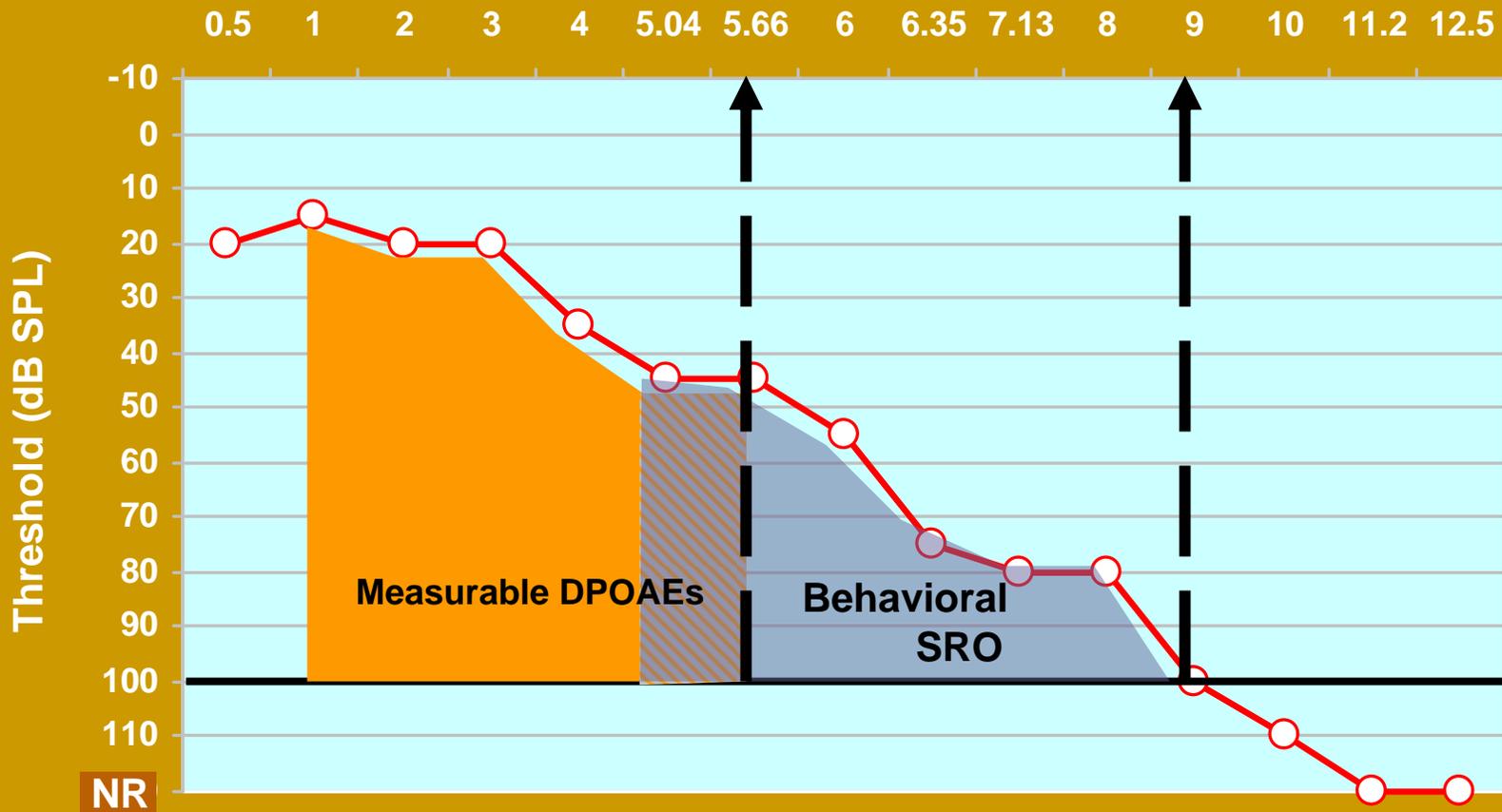
# Results

- High-frequency pure-tone average (hf-PTA) for 2, 4, and 6 kHz
  - ANOVA,  $F=11.965$ ,  $p\text{-value}=0.01$ , Bonferroni  $p\text{-value}<0.01$  (Hit vs Miss and Hit vs NR)
- Threshold level difference between SRO lowest and highest frequencies in dB
  - ANOVA,  $f=4.905$ ,  $p\text{-value}=0.01$ , Bonferroni  $p\text{-value}=0.015$  (Hit vs Miss),  $0.026$  (Hit vs NR)
- Behavioral high-frequency limit in Hz
  - Hit: 12.5 (3.6-20), Miss: 11.9 (4.5-14); NR: 10 (3.6-14) – not significantly different



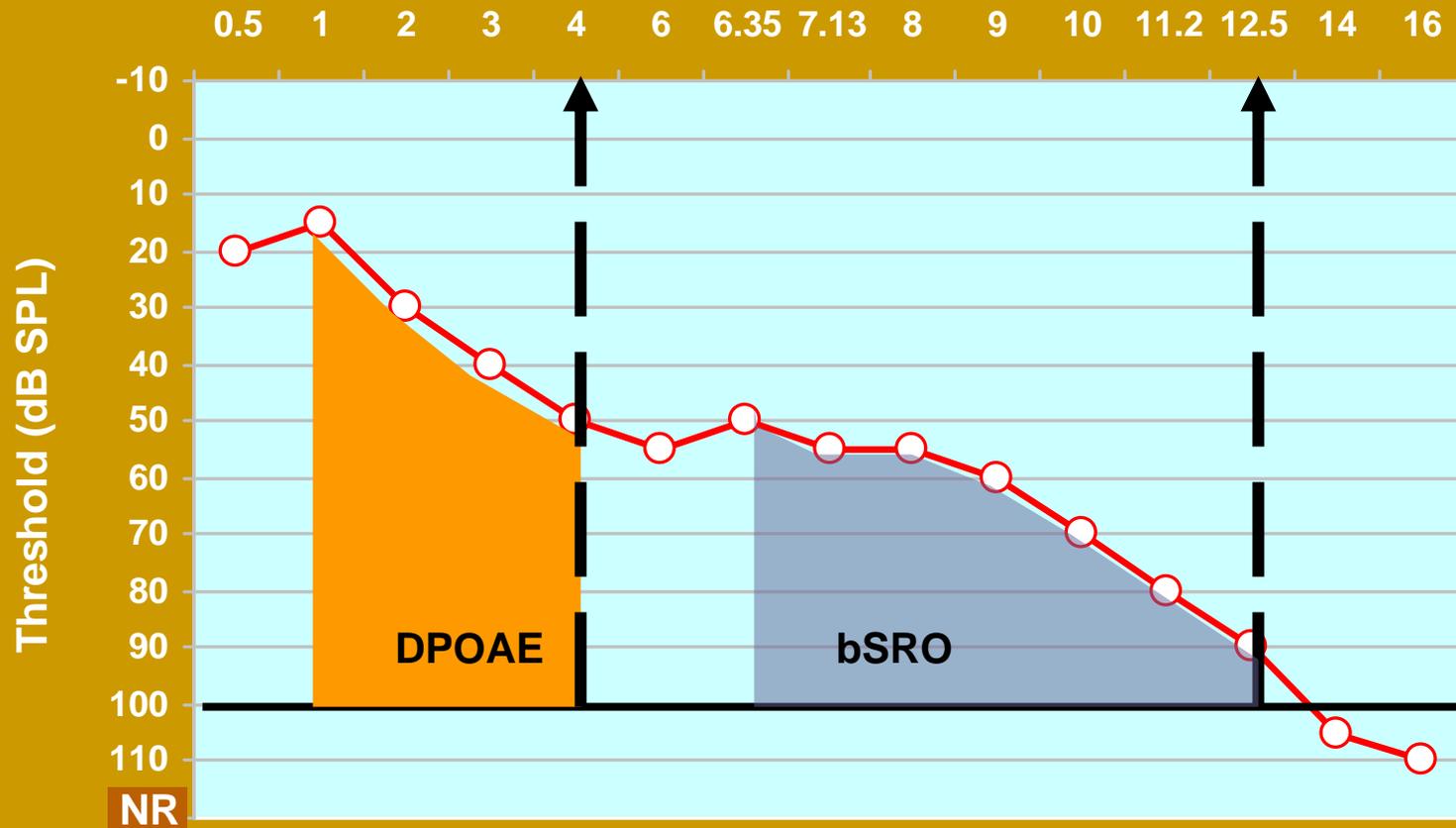
**Relationship Between  
Measurable DPOAEs and  
Behavioral SRO**

# Example SRO Below 8 kHz

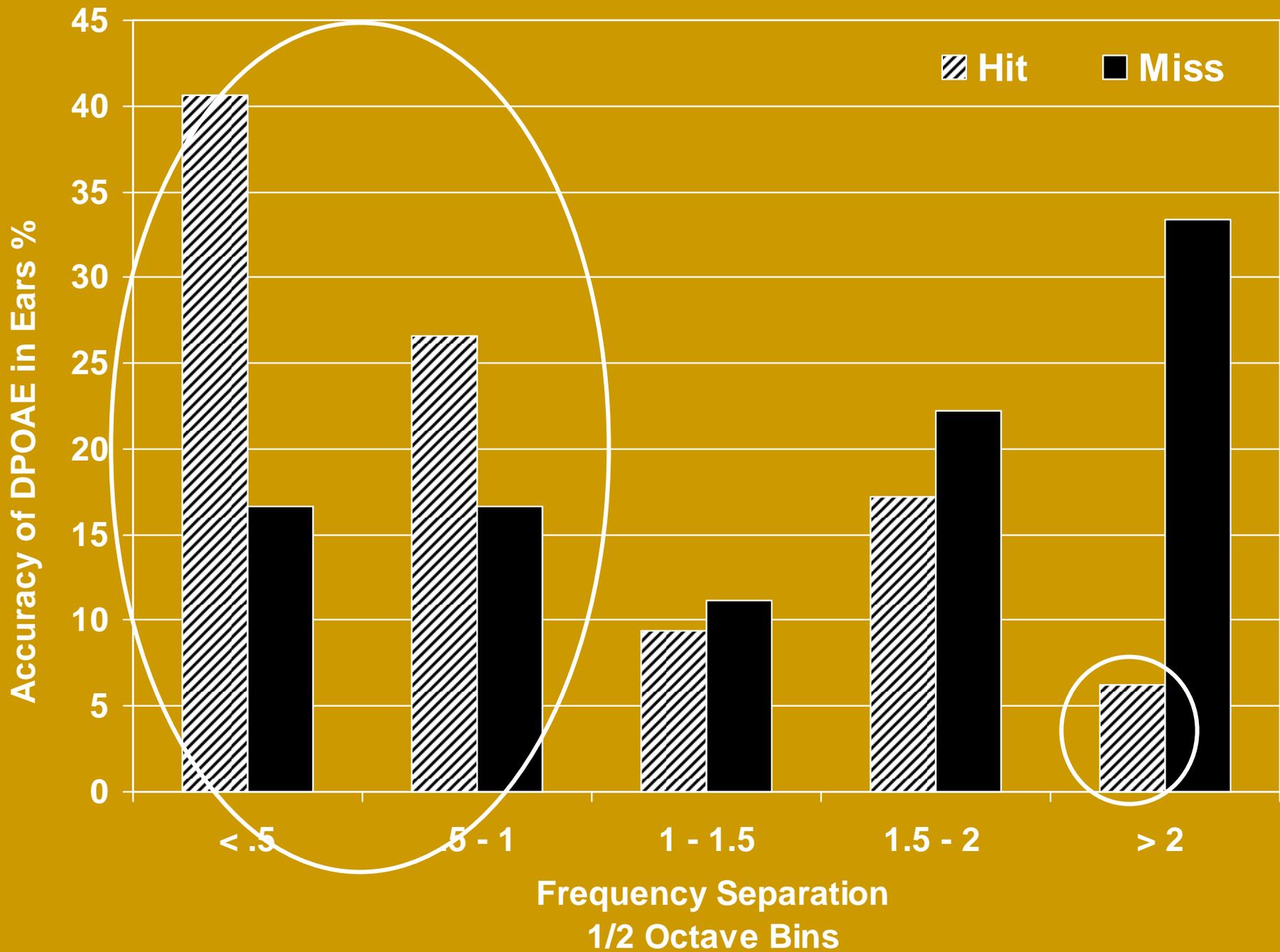


**bSRO Test Frequencies: 4.49 - 9 kHz**

# Example SRO Below 8 kHz



**bSRO Test Frequencies: 6.3 - 12.5 kHz**



# Results

- DPOAE-bSRO separation in fractions of an octave
  - Separation by 1 or more octaves was significantly associated with DPOAE sensitivity to ototoxic hearing change (Person chi-square,  $p$ -value 0.036)
  - Hit rate if DPOAE  $>$  2 octaves from SRO equal to false positive rate in control subjects
  - Odds of DPOAE hit if separation is 1-2 octave is 4 times the odds if separation is less than this

# Results

- DPOAE high-frequency limit in Hz
  - Ears in DPOAE Hit group more likely to have DPOAE hf-limit greater than 2.5 kHz compared to ears in Miss group (Chi-square=22.606, p-value<0.01)
  - Odds of DPOAE hit when DPOAE hf-limit was greater than 2.5 kHz were 15 times odds of DPOAE change when DPOAE hf-limit was less than 2.5 kHz

# Results

- Multiple logistic regression (backwards step-wise) was used to determine the best combination of predictors for DPOAE sensitivity to ototoxic change
  - Variables entered in had to be significant at  $p\text{-value}=0.25$
  - Variables dropped out if significance added to model was less than  $p\text{-value}=0.05$
  - All variables dropped out except DPOAE hf-limit

# Results

- Timing of DPOAE changes relative to behavioral changes
  - DPOAE before bSRO=33%
  - DPOAE concurrent with bSRO=33%
  - DPOAE after bSRO=34%
  - No variable examined gave insight into relative timing of changes observed using DPOAE and SRO techniques

# Conclusions

1. In adults with hearing loss, DPOAEs perform fairly well for detecting ototoxicity, but are less sensitive compared with behavioral testing near highest audible frequencies
2. Factors affecting DPOAE sensitivity were:
  1. magnitude of post-exposure threshold shifts
  2. degree and configuration of pre-exposure hearing loss
  3. frequency separation between DPOAEs & bSRO
  4. high-frequency limit of DPOAEs measurable at baseline
3. Magnitude of ototoxic hearing changes was similar for ears in which DPOAE detected ototoxicity compared with ears in which DPOAEs could not be measured
4. Further research needed to examine the relative timing of DPOAE and behavioral ototoxic changes

# Clinical Implications

- DPOAEs are a useful screening tool for ototoxicity even in ears with hearing loss
- DPOAE changes are associated with hearing changes at higher than the DPOAE test frequencies, consistent with results from previous studies (Arnold et al., 1999; Avan et al., 1993)
- If pre-exposure hearing limits DPOAE measurable frequency range to  $>$  an octave below patient's SRO and to frequencies below about 2.5 kHz, DPOAEs are less effective
- Behavioral hearing losses missed by DPOAEs were usually small (7 dB on average), but were as large as 34 dB

# Questions

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<http://www.ncrar.research.va.gov/>

