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Kimberly J. Lavoie  
*Portland State University*

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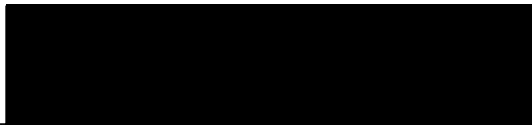
## THESIS APPROVAL

The abstract and thesis of Kimberly J. Lavoie for the Master of Science in Speech and Hearing Sciences were presented February 12, 2003, and accepted by the thesis committee and the department.

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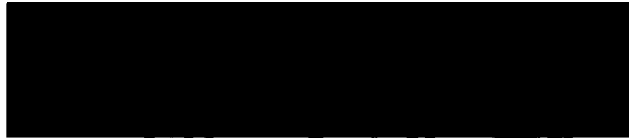
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## ABSTRACT

An abstract of the thesis of Kimberly J. Lavoie for the Master of Science in Speech and Hearing Sciences presented February 12, 2003.

Title: High frequency Pure Tone Audiometry and High Frequency Distortion Product Otoacoustic Emissions: A Correlational Analysis.

Previous studies show that pure tone thresholds are strongly correlated with distortion product otoacoustic emission amplitudes when evaluating the frequency range from 1 to 8 kHz (Avan & Bonfils, 1993). Little is known about correlations between these two measures at higher frequencies from 9-16 kHz. This study compared pure tone thresholds and distortion product otoacoustic emissions (DPOAEs) in this high frequency range for 29 normal hearing subjects ages 18-30. Pure tone thresholds were obtained at 250-16 kHz and distortion product otoacoustic emissions (DPOAE) 2,211-17,675 were measured in the same ears. DPOAE amplitudes were measured using a constant F1/F2 ratio of 1.2, with F2 values ranging from 2,211-17,675 Hz. Data obtained from 50 ears showed a decline in DPOAE amplitude with increasing frequency of the F1 and F2 primary stimulus tones. Behavioral thresholds demonstrated an increase with increasing frequency of the pure tone stimulus. Pearson r- correlation analysis demonstrated a weak relationship between measures. Further investigation revealed that equipment variables prevented accurate readings.

HIGH FREQUENCY PURE TONE AUDIOMETRY AND HIGH  
FREQUENCY DISTORTION PRODUCT OTOACOUSTIC EMISSIONS:  
A CORRELATIONAL ANALYSIS

by

KIMBERLY J. LAVOIE

A thesis submitted in partial fulfillment of the  
requirements for the degree of

MASTER OF SCIENCE  
in  
SPEECH AND HEARING SCIENCES

Portland State University  
2003

## DEDICATION

I would like to dedicate my thesis in loving memory of my father, Richard F. Lodeski.

He inspired me to persevere, and to keep perspective.

## ACKNOWLEDGEMENTS

As I acknowledge those who have helped me in this process, I would like to say that I am proud to complete the last masters thesis presented at Portland State University's Masters level program in Audiology. I would like to thank Dr. Thomas Dolan for his guidance, Dr. Donald Plapinger and the Doernbecher CDRC audiologists for the use of their facilities, and for their time and patience. I would like to thank Dr. Nancy Doolittle for educating me on the importance of monitoring the auditory system in patients undergoing cancer treatment protocols. I would also like to extend many thanks to my friends and family for their support.

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## High frequency pure tone audiometry and high frequency DPOAE's

Current methods of obtaining auditory thresholds include both behavioral and physiological measurements of hearing sensitivity. Standard behavioral hearing tests include pure tone audiometry, measuring pure tone thresholds from 250-8000 Hz. Researchers have discovered that information about hearing sensitivity at frequencies beyond this standard range may provide valuable information for clinical and research applications (Fausti, Frey, Erickson, Rappaport, & Cleary, 1979). One application of high frequency audiometry is for early detection of ototoxic damage (Dreschler, Hulst, Tange, & Urbanus, 1989).

A standard physiological method of obtaining audiometric information is through the use of otoacoustic emissions. Otoacoustic emissions are an indirect physical measurement of the outer hair cell function of the cochlea, and are not dependent on a behavioral response (Hall, 2000). There are four types of otoacoustic emissions: Spontaneous (SOAE), Stimulus Frequency (SFOAE), Transient (TEOAE), and Distortion Product otoacoustic emissions (DPOAE). Two types, transient, and distortion product otoacoustic emissions, are applied clinically (Hall, 2000). An example of the application of otoacoustic emissions is monitoring for the ototoxic effects of medications (Stavroulaki, Apostopoulos, Segas, Tsakanikos, & Adamopoulos, 2001).

Several medications prescribed are known to cause auditory and vestibular dysfunction. Categories of ototoxic medications may include anti-inflammatory drugs, amino glycoside antibiotics, loop diuretics, antimalarials, chemotherapeutic agents, and ototopical medications (Jordan & Roland, 2000).

The effects of medications are thought to be expressed throughout many areas of the auditory system. Areas affected may include the outer hair cells in the mid turn and basal turn organ of Corti, and neurons in the spiral ganglion (Gabaizadeh et al., 1997). The stria vascularis may also demonstrate severe degenerative changes (Hulst, Dreschler, and Urbanus, 1988). At the cellular level, it is theorized that medications can result in an increase of intracellular calcium, thereby adversely affecting cell membranes, and ultimately resulting in magnesium deficiency (Cevette, Drew, Webb and Marion, 2000).

Ototoxic damage to the auditory system may manifest itself clinically as an initial bilateral high frequency sensorineural hearing loss, which may progress to a loss in sensitivity at all frequencies (Jerger & Jerger, 1981). This dysfunction is most often identified through the application of pure tone audiometry.

Many studies have evaluated changes in the auditory system with pure tone audiometry in patients using ototoxic medications. In one such study measuring from 250-8000 Hz for patients undergoing carboplatin chemotherapy administered in conjunction with osmotic opening of the blood-brain barrier, post treatment auditory threshold shifts were identified at 4000 and 8000 Hz (Doolittle et al., 2001). This identification of changes in auditory thresholds supported the need for prospective

monitoring of frequencies higher than 8000 Hz for patients enrolled in platinum based chemotherapy clinical trials.

When comparing the detectability for ototoxic damage between low frequency and high frequency pure tone audiometry, a 1989 study by Dreschler et al. (1989) found that 34-77% of ears with ototoxic damage were discovered in an earlier stage when using high frequency audiometry. This study also concluded high frequency damage is present earlier than low frequency damage, with 12000 and 14000 Hz being the best test frequencies for the detection of ototoxicity (Dreschler et al., 1989).

Conventional and high frequency pure tone audiometry have been applied in case studies of patients receiving cisplatin chemotherapy (Fausti, Schechter, Rappaport, Frey & Mass, 1984). Significant changes in consecutive high frequency thresholds were revealed in eight of thirteen patients. When comparing low and high frequency audiometric configurations, it was found that the magnitude of change was greater in the high frequency range of 8000 Hz- 20000 Hz (Fausti et al., 1984)

Many studies have not only applied conventional audiometry to the evaluation of patients using ototoxic medications, but have added otoacoustic emissions to their regimen as well. Because the presence of an evoked otoacoustic emission is correlated with normal to near normal hearing thresholds, emissions can reflect the state of the cochlea (Avan & Bonfils, 1993). As objective indicators of auditory function, emissions are not affected by extraneous influences; such as inattentiveness (Lonsbury-Martin, Whitehead, & Martin, 1991) therefore medically compromised patients can provide reliable responses despite their state of health.

In a 1998 study of 12 children with a mean age of 7.8 years, transient evoked otoacoustic emissions (TEOAE's) from 1000-5000 Hz were measured and compared to behavioral thresholds before and after a cisplatin chemotherapy regimen (Allen et al., 1998). Consistent with the literature (Doolittle et al., 2001), hearing loss of greater than 25 dB HL occurred in 81% of participants in this study at levels higher than 4000 Hz. When TEOAE reproducibility was compared with pure tone thresholds, it was found that the emission amplitudes correlated highly with pure tone audiometry findings.

When comparing TEOAE's, DPOAE's and pure tone audiometry in a pediatric oncology population undergoing cisplatin chemotherapy (Stavroulaki et al., 2001) it was found that distortion product DP grams (a method of profiling distortion product frequency analysis) are a more sensitive indicator of cochlear dysfunction than TEOAE's. This study further revealed statistically significant reductions in the DP gram amplitudes in patient's ears with normal pure tone thresholds at 3000 Hz. The authors concluded that DPOAE's are more sensitive than TEOAE's and/or pure tone audiometry as ototoxicity screening tools.

DPOAE's have thus been shown to be a useful objective test in screening for ototoxic medications, and high frequency pure tone audiometry has been shown to be an effective behavioral method of evaluating auditory function in ototoxicity monitoring. To date there have been no studies examining the correlation high frequency behavioral pure tone thresholds and high frequency otoacoustic emissions. Exploring the relationship between these two measurements in a normal hearing

population might prove useful for establishing baselines to measure the high frequency threshold changes that patients may encounter with ototoxic medications. The purpose of this study is to evaluate the relationship between high frequency pure tone audiometric thresholds, and high frequency DPOAE amplitudes. Behavioral thresholds will be measured at test frequencies from 250-16,000 Hz in a group of normal hearing persons. High frequency DPOAE's will be obtained in this same group from 1810 - 17675.

## REVIEW OF THE LITERATURE

### High Frequency pure tone audiometry

In 1979, a system for evaluating auditory thresholds from 8000-20000 Hz was developed to evaluate changes in high frequency hearing sensitivity due to ototoxic agents and noise exposure (Fausti et al., 1979). This system employs the use of a high output, low noise amplifier/filter for high fidelity, and an earphone that includes a ceramic diaphragm to provide a relatively flat response from 8000-20000 Hz (Fausti, Rappaport, Schechter, & Frey, 1982).

This system for evaluating hearing sensitivity includes obtaining threshold information in the conventional frequencies from 250-8000 Hz by applying the standard audiometric procedure of Hughson-Westlake technique in 5 dB increments. Second, high frequency thresholds are then obtained from 8000-20000 Hz, using a 2 dB bracketing technique (Fausti et al., 1984).

When recruiting participants to assess this high frequency measurement system, a survey evaluating frequencies above 12000 Hz found applicants to have highly variable hearing sensitivity on average, with medical history not accounting for the differences in hearing thresholds. The 21 participants from this survey demonstrated mean thresholds from 500-12000 Hz to be less than or equal to 20 dB SPL, rising slightly to 35 dB SPL at 17000 Hz, then increasing to 82 dB SPL at 20000 Hz (Fausti et al., 1979).

Application of this high frequency system discovered participants to have a progressive sloping response from 8000-20000 Hz. Mean between test differences for

high frequency thresholds revealed no variations in thresholds greater than 4 dB (Fausti et al., 1979). Hulst et al. (1985) performed a similar with results consistent with Fausti et.al. In evaluating 180 audiograms, standard deviation of repeated measurements was found to be within 4.3 dB HL from 250-20000 Hz.

#### Sites of ototoxic damage

The exact mechanisms affected by cisplatin are not known (Allen et al., 1998) however; outer hair cell degeneration is a consistently reported side effect of patients undergoing cisplatin chemotherapy. Research evaluating the mechanisms involved in cisplatin ototoxicity on outer hair cells (e.g., McAlpine & Brownstone, 1990) suggests the ototoxic effects of cisplatin specifically disrupt the mechano-electrical transduction process of the outer hair cells. This causes a reduction in hair cell receptor current and thus subsequent hearing loss (McAlpine et al., 1990).

In comparing which frequencies are damaged by cisplatin ototoxicity, McAlpine et al. (1990) discovered that “there are no differences in the susceptibility of high and low frequency regions of the cochlea, but that the higher frequency regions are more permeable to cisplatin.” Studies evaluating the audiometric configuration of cisplatin ototoxicity demonstrate these effects in that the first area of the cochlea to suffer hearing loss is the high frequency region (Fausti et al., 1984; Dreschler, Hulst, Tange & Urbanus, 1985).

Other areas reportedly affected by ototoxic agents are the mid turn, and basal turn organ of Corti and the spiral ganglion. In animal studies analyzing the otoprotective effects of D-methionine, (Gabaizadeh et al., 1997) researchers exposed



the midturn, basal turn organ of Corti and whole spiral ganglion samples of Wistar rat pups to cisplatin. When applying a concentration of 6  $\mu\text{g}/\text{ml}$  of cisplatin without an otoprotectant, damage to the spiral ganglion resulted in no survival of auditory neurons. Exposing midturn and basal turn organ of Corti samples to 4  $\mu\text{g}/\text{ml}$  resulted in significantly lower hair cell densities than when compared to unexposed samples, and stereocilia bundle indices were reduced significantly for both outer and inner hair cells (Gabaizadeh et al., 1997).

#### Cisplatin and carboplatin chemotherapy agents

Cisplatin is a potent antineoplastic agent effective against a variety of tumors (McAlpine et al., 1990). Cisplatin has exhibited a broad spectrum of activity against epithelial cancers and has become the “foundation of curative regimens for testicular and ovarian cancers”. It has also demonstrated significant activity against cancers of the head and neck, esophagus, lung, bladder, cervix, and endometrium (Go et al., 1999).

Various toxic side effects have been observed after cisplatin treatment, including severe renal, neurologic, cytotoxic and emetogenic effects (Go et al. 1999). Other associated side effects may also include myelosuppression, gastrointestinal dysfunction, ototoxicity, and vestibulotoxicity (Hulst et al., 1988).

In 1981 carboplatin, an analog of cisplatin was introduced to circumvent some of the toxicities of cisplatin. Both are platinum complexes, but their compounds differ in that cisplatin contains two chloride “leaving” groups and carboplatin has a cyclobutane group (Go et al., 1999). Because carboplatin and cisplatin share a similar

structure, they undergo the same chemical reactions and both target DNA as their major cytotoxic target. Concentration of the two drugs vary however, in that carboplatin requires 10 times higher drug concentration and longer incubation time to induce the same degree of change on DNA (Go et al., 1999).

It has been revealed that carboplatin displays less nephrotoxicity, ototoxicity, and neurotoxicity than cisplatin (as cited in Neuwelt et al., 1998; Go et al., 1999). Renal impairment is rare under carboplatin chemotherapy, except at extremely high doses (Hulst et al., 1988) and carboplatin nausea and vomiting are less severe and frequent as compared to cisplatin (Go et al., 1999).

It is believed that carboplatin and cisplatin may have different sites of damage to the auditory system. It has been established that carboplatin exerts toxic effects on inner hair cell function, whereas cisplatin's effects are exhibited on outer hair cell function (Hoffstetter, Ding, Powers, & Salvi, 1997). These findings may have a significant impact on threshold monitoring, in that DPOAE's are independent of inner hair cell function (Hall, 2000). DPOAE's rely on functional outer hair cells for auditory threshold monitoring. According to Hall (2000), clinical protocols in monitoring for carboplatin ototoxicity should include measures of inner hair cell function such as pure tone audiometry or auditory brain stem response.

#### Use of otoprotectants

Due to the nephrotoxic, neurotoxic, myelosuppressive, and ototoxic mechanisms of cisplatin chemotherapy (Go et al., 1999) researchers have evaluated the effects of using chemoprotectants in combination with platinum chemotherapy agents

in clinical and pre-clinical settings (Neuwelt et al., 1996; Gabaizadeh et al., 1997; Neuwelt et al., 1998; Campbell et al. 1998; Doolittle et al, 2001). A potential chemoprotectant against carboplatin-induced ototoxicity is delayed high dose sodium thiosulfate (STS). STS is effective as an otoprotectant when carboplatin is administered in conjunction with osmotic opening of the blood-brain barrier (Doolittle et al., 2001). Agents that may provide protection against cisplatin-induced ototoxicity may include D-methionine (Campbell et. al, 1997). The mechanism of STS protection against carboplatin ototoxicity is unclear. It is currently theorized that the cochlea may act similar to the kidney to concentrate STS in the perilymph or endolymph. High concentrations of STS may act to inactivate carboplatin at the site of cochlear damage (Neuwelt et al. 1996). This inactivation is thought to occur through the chemical reaction of the thiol binding to the electrophile platinum, thus rendering the platinum inactive (Neuwelt et al., 1998, Doolittle et al, 2001).

Animal studies evaluating carboplatin ototoxicity in a guinea pig model demonstrated protection when STS was given up to eight hours subsequent to carboplatin (Neuwelt et al., 1996). Determination of the effect of STS on carboplatin induced ototoxicity was by electrophysiological measurements and cochlear hair cell count (Neuwelt et al., 1996).

Studies evaluating the efficacy of high dose STS in patients with malignant brain tumors, noted what appeared to be a preservation of hearing (Neuwelt et al., 1998). In Neuwelt et al.'s study (1998), twenty nine patients ranging from 2-63 years of age treated with carboplatin followed by one dose of STS, were compared to a

historical group of 19 patients treated with carboplatin that did not receive STS.

Patients with excellent baseline hearing (thresholds < 20 dB HL in the frequency range of 250-8000 Hz) showed little change in high frequency thresholds with a mean loss of  $8 \pm 5.6$  dB after the first carboplatin followed by STS treatment. In comparison, patients in the (no STS) historical group with excellent baseline hearing thresholds, demonstrated a mean hearing loss of  $30.0 \pm 8.4$  dB after the first carboplatin treatment (Neuwelt et al., 1998).

This 1998 study further demonstrated that 50% of patients with impaired baseline hearing (thresholds > 20 dB HL in the frequency range of 250-8000 Hz) developed an additional 20 dB threshold shift, despite treatment with one dose of STS (Neuwelt et al. 1998). Because of this finding, the treatment regimen was altered. Patients with impaired baseline hearing thereafter received a second dose of STS, 6 hours following carboplatin treatment (Doolittle et al., 2001).

In a more recent study, audiologic data from patients who received STS two (or two and six) hours after carboplatin, and patients who received STS four (or four and eight) hours after carboplatin, were compared with the historical (no STS) group. Spearman rank correlation coefficients showed decreased rates of ototoxicity, with greater decay in STS (Doolittle et al., 2001).

### Otoacoustic Emissions

Otoacoustic emissions (OAE's) are the result of biomechanical activity associated with normally functioning outer hair cells. This motility produces a signal within the cochlea that is transmitted through the middle ear and ossicles. The signal is

then measured with a microphone inserted into the ear canal (Gelfand, 1997). Because OAEs can reflect the state of the cochlea, they are applied clinically to provide an objective measure of auditory sensitivity (Hall, 2000). There are two general categories of otoacoustic emissions, spontaneous and evoked.

Spontaneous otoacoustic emissions (SOAEs) are emissions that occur in the absence of external stimuli. They consist of energies at one or more frequencies emitted by the normal ear (Hall, 2000). SOAEs are most commonly detected in the 1000-2000 Hz region where reverse transmission through the middle ear is most efficient (Kemp, 1986). Clinical application of SOAEs are limited, as they can be detected in only 50% of ears with normal hearing, with a genetic preference for females, they have variable amplitudes over time, and frequencies at which they occur are limited (Lonsbury-Martin et al., 1991).

Evoked otoacoustic emissions are emissions that occur in response to presentation of an acoustic stimulus. These emissions can be further categorized into three subtypes according to the stimuli used to elicit them. Transient evoked emissions (TEOAEs) are elicited by a click, or toneburst; stimulus frequency (SFOAEs) are evoked by a single continuous pure tone; and acoustic distortion products (DPOAEs) are generated in response to two continuous pure tones separated using a prescribed frequency difference (Lonsbury-Martin et al., 1991).

SFOAEs are emissions that are evoked using a constant pure tone stimulus presented at a low intensity level swept or changed slowly across a region of frequencies (Hall, 2000). SFOAEs are more difficult to analyze than other types of

emissions, because it is necessary to separate the SFOAE from the stimulus tone that is simultaneously present in the ear canal, and is larger than the emission (Lonsbury-Martin et.al. 1991). There are currently no available devices for recording SFOAEs; therefore they are the least studied experimentally, and clinically (Hall, 2000).

TEOAEs are acoustical signals emitted by outer hair cells of the cochlea on presentation of transient stimuli, such as clicks, or tone bursts (Ferguson, Smith, Davis, & Lutman, 2000). TEOAE's are a waveform that is generated in the cochlea, and detected in the ear canal several milliseconds following presentation of a stimulus (Gelfand, 1997). The average latency, or time between waveforms is typically 5-20 milliseconds; time averages tend to decrease with increase in OAE frequency. Spectral analysis of these waveforms can provide frequency specific information across the frequency region from 0-5000 Hz (Gelfand, 1997).

Click evoked emissions, such as TEOAE's are thought to reflect the presence of outer hair cell function of the cochlea. When sensitivity tuning of the inner ear is impaired within a certain frequency range, spectral components of the TEOAE within that same frequency range are expected to be altered (Avan, Elbez, & Bonfils, 1997). This phenomenon supports the clinical utility of TEOAEs in monitoring the state of the cochlea in areas such as newborn infant hearing screening and ototoxicity monitoring (Allen et al, 1998).

DPOAEs are emissions that are elicited by the simultaneous presentation of two pure tones, called primaries, closely spaced in frequency. The two primaries activate the cochlea in the same region of the basilar membrane, but due to nonlinear

properties of a healthy cochlea, a third combination tone is generated in the frequency region where the two primary frequencies overlap. This is combination tone called an acoustic distortion product (Hall, 2000).

The strongest DPOAE in human ears occurs at the cubic difference frequency,  $2f_1 - f_2$ , in which  $f_1$  represents the lower frequency stimulus, and  $f_2$  represents the higher frequency primary (Lonsbury-Martin et al., 1991). DPOAE amplitudes may vary with the level of the primary tones, as an increase in level of the primaries results in an increase emission size (Gelfand, 1997).

Research supports that DPOAE amplitudes provide information as to the frequency specificity of the cochlea (Avan et al, 1993; Moulin, Bera & Collet, 1994). When analyzing DPOAE amplitudes elicited by low frequency primaries, researchers have found significant correlations with auditory thresholds at the mean frequencies of the primary tones.

DPOAEs can be measured using two methods; a DPOAE audiogram, which shows DPOAE amplitude as a function of the geometric mean (generation site) of the two frequencies, or an input/output function, which measures DPOAE amplitude as a function of stimulus level at a given frequency (Lonsbury-Martin, et al, 1991).

Because of their high sensitivity, reliability, and objectivity, DPOAEs are used routinely as a measure of hearing sensitivity not only for patients using ototoxic medications, but for patients unable to perform behavioral testing, newborn and infant testing, testing persons with multiple disabilities, and malingers (Stavroulaki et al, 2001).

## METHODS

### Participants

Twenty nine students from Portland State University volunteered to participate in this study. To be eligible for inclusion, participants were between 18-30 years of age at the time of enrollment in this study. Participants had normal hearing sensitivity at audiometric test frequencies from 250-8000 Hz. Criteria for exclusion from this study included hearing thresholds above 20 dB HL from 250-8000 Hz, the absence of otoacoustic emissions from 2000-16000 Hz, or history of significant ear disease or significant noise exposure.

Volunteers were recruited by flyers posted in hallways at Portland State University, and by announcement in Speech and Hearing science classrooms. Volunteers were instructed to register for participation by e-mail or phone.

### Materials/Instrumentation

Testing was performed at the Children's Developmental Rehabilitation Center (CDRC) at Doernbecher Children's Hospital. Following a brief otoscopic evaluation, tympanometry was performed using a Grason-Stadler GSI 33 middle ear acoustic analyzer. Middle ear assessment was made using a Grason-Stadler GSI single use silicon probe tip, with a 226 Hz probe tone. Following tympanometry, DPOAE's were measured in a double walled acoustic chamber at CDRC to ensure an adequately low noise floor. An Etymotic Research (ER 2) transducer was used to obtain DPOAE's. An Intelligent Hearing Systems Smart OAE program was used to acquire emissions from 1810-17675 Hz.



A daily biological calibration of the audiometer was performed to ensure adequate output before testing began. An exhaustive calibration was performed on the audiometer prior to the initiation of the study. DPOAE calibration in a 1 cc coupler was performed to confirm adequate transducer linearity prior to data collection. No significant 2F1-F2 components at any of the primary frequency combinations. The DPOAE microphone was calibrated using a within the ear approach measurements on each individual prior to obtaining measurements, according to the manufacturers recommendations.

L2 and L1 levels were set to 65 dB and 55 dB SPL. The F1/F2 ratio was set at the default setting of 1.2 (Hall, 2001).

Table 1. F1 and F2 primary stimulus tones

<u>Frequency combination</u>	<u>F1, Hz</u>	<u>F2, Hz</u>
1	1810	2211
2	2152	2631
3	2563	3120
4	3042	3717
5	3619	4421
6	4304	5253
7	5125	6250
8	6094	7434
9	7238	8832
10	8617	10505

(Table 1 continued)

11	10241	12500
12	12178	14858
13	14486	17675

All audiometric testing was conducted within an Acoustic Systems double walled acoustic chamber. Pure tone thresholds were obtained using an Interacoustics AC 40 clinical audiometer. Thresholds were obtained from 250 through 8000 Hz under TDH 39P headphones. High frequency thresholds from 9000-20000 Hz were obtained using Sennheiser HDA 200 headphones. Using a technique introduced by Fausti et al. (1984), standard audiologic techniques were employed to obtain thresholds from 250-8000 Hz, and a modified Hughson-Westlake technique in 2 dB increments were used to obtain pure tone thresholds from 8000- 20000 Hz.

## RESULTS

High frequency DPOAEs and pure tone thresholds were collected from 29 participants. This yielded information on these two types of measurements from a total of 50 ears.

Examples of DPOAE amplitudes recorded from one subject are given in figure 1A. Each plot shows amplitude of sound recorded in the ear canal as a function of frequency. Two tones were presented to this subject's ears. The F1 primary was presented at 1810 Hz, stimulating at a level of 65 dB SPL. The F2 primary was presented at 2211 Hz. The amplitude of the F2 stimulus was 55 dB SPL. These two tones resulted in a distortion product at a frequency of  $2F_1 - F_2$ , which in this case was 1409 Hz. The measured amplitude was 16 dB SPL.

Figure 1B is a graph of an acoustic distortion product generated with higher frequency primaries on the same subject. The F1 primary was presented at 5125 Hz at a level of 65 dB SPL. The F2 stimulus was presented at 6250 Hz. The F2 intensity was 55 dB SPL. When using 5125 and 6250 as the two primaries, this resulted in a  $2F_1 - F_2$  frequency of 4001 Hz. The amplitude of the DPOAE was 8 dB SPL. As the stimulus frequency increases above 2000 Hz, the distortion product amplitudes are expected to reduce (Hall, 2000). The difference between the amplitude of the DPOAE between figures 1 and 2 was 8 dB.

Fig 1A

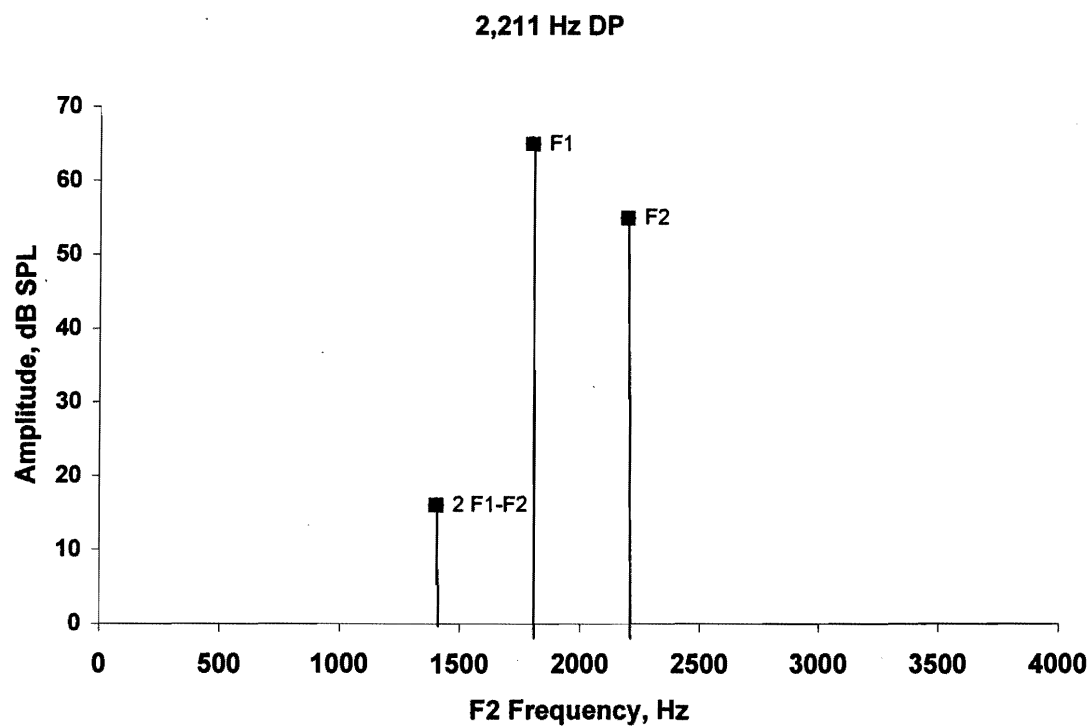


Fig 1A. DP amplitude as a function of F2 frequency. This demonstrates the relationship between the F1 and F2 primaries and the resulting 2F1-F2 DPOAE in a low frequency region for one subject.

Fig 1B

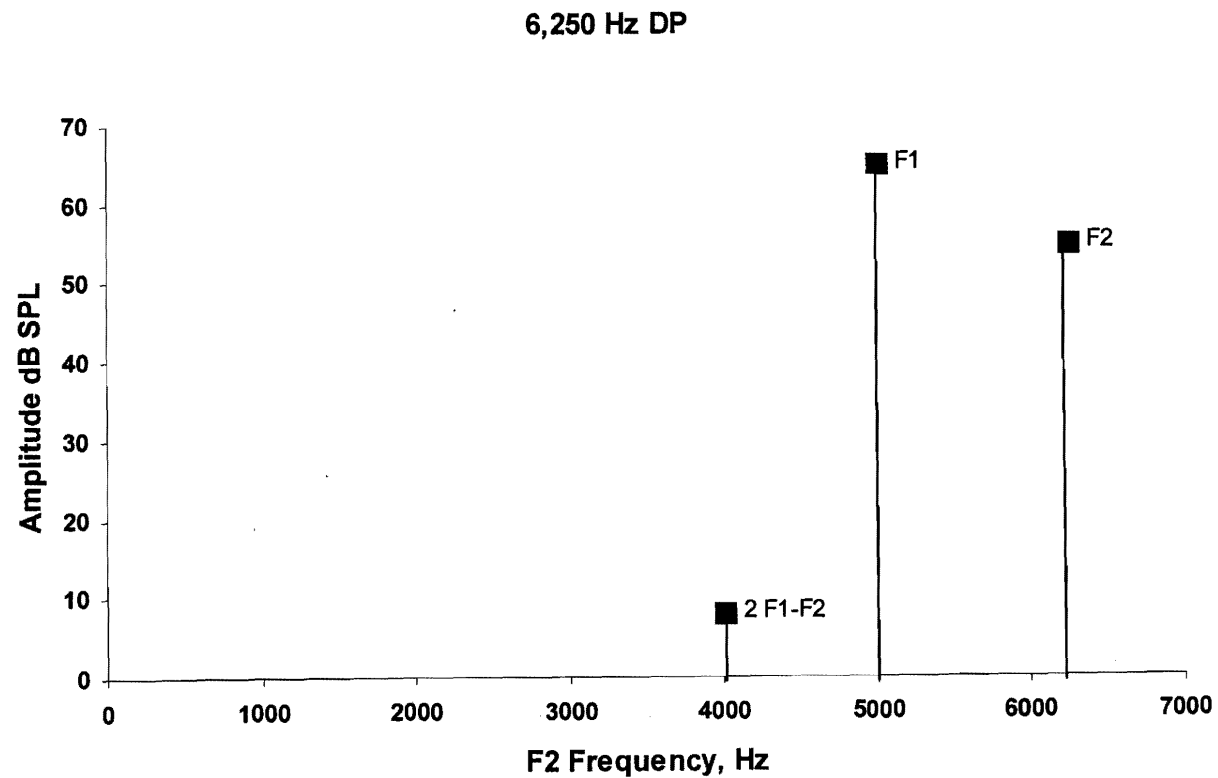


Fig 1B. DP amplitude as a function of F2 frequency. This demonstrates the relationship between the F1 and F2 primaries and the resulting 2F1-F2 DPOAE in a mid frequency region for one subject.

Figure 1C is a graph of an acoustic distortion product at the high frequency region (base) of the basilar membrane. The F1 primary was presented at 12178 Hz. The amplitude was 65 dB SPL. The F2 primary was presented at 14858 Hz, with an intensity level of 55 dB SPL. When using 12178 and 14858 as the two primaries, this resulted in a  $2F_1-F_2$  frequency of 9498 Hz, with an amplitude of 2 dB SPL.

Figure 2 gives  $2F_1-F_2$  distortion product amplitude as a function of F2 frequency for one subject. Thirteen DPOAE combinations were measured with F2 frequencies from 2211 to 17675 Hz. The frequency ratio of F2 to F1 for each of the primaries was 1.22. This plot shows all DP emissions measured for all primaries presented to each ear. The shaded area on the graph represents the noise floor during testing. This measure varied with each subject, but in this case was below -10 dB SPL. As demonstrated in figure 2, distortion product amplitude tend to decrease with increasing frequency.

In Figure 3 distortion product amplitude is plotted as a function of F2 Frequency for all subjects. As with the individual data in Fig. 2, the group data in Fig. 3 tend to show a decline in DP level with increasing frequency. The mean amplitude from 2211-3717 Hz was 5.7 dB SPL, the mean amplitude from 4421-8832 Hz was 1.4 dB SPL, and the mean amplitude from 10505-17675 Hz was -1 dB SPL. The amplitude range throughout the frequency spectrum from 2211 to 17675 Hz was an average of 27 dB SPL from 2211-3717 Hz, an average range of 27 dB SPL from 4421-8832 Hz, and an average range of 32 dB SPL from 10505-17675 Hz. Thus amplitude variability appears to be similar across frequencies.

Fig 1C

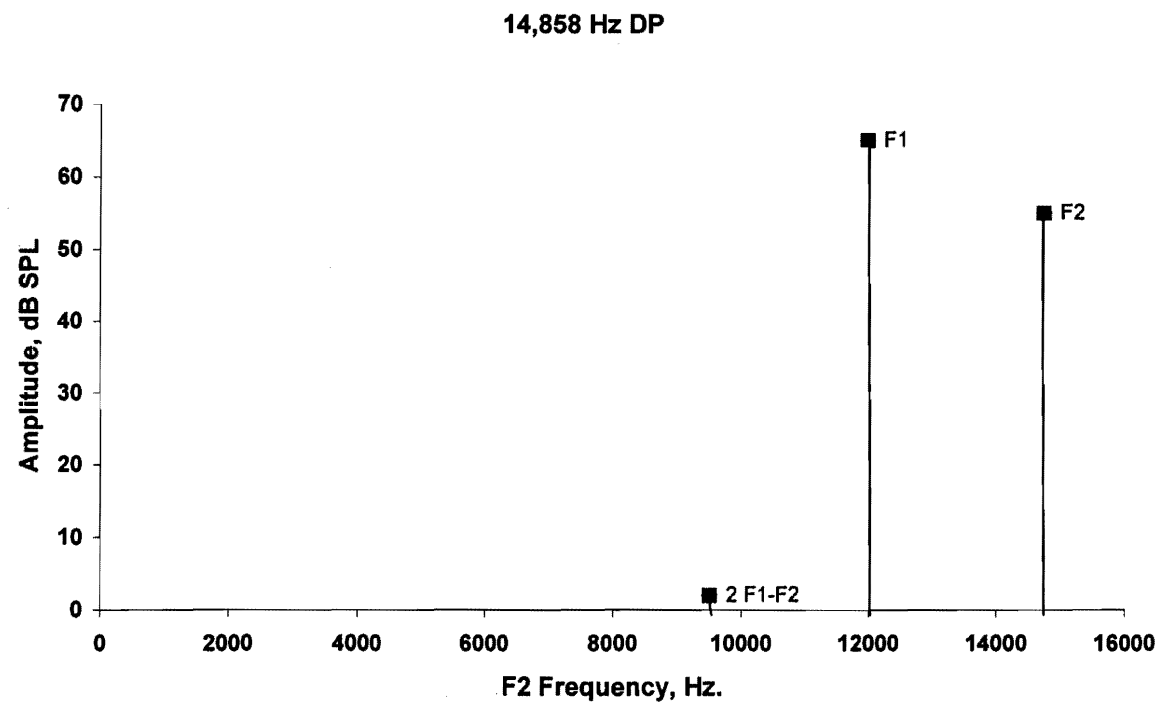


Fig 1C. DP amplitude as a function of F2 frequency. This demonstrates the relationship between the F1 and F2 primaries and the resulting 2F1-F2 DPOAE in a high frequency region for one subject.

Fig 2

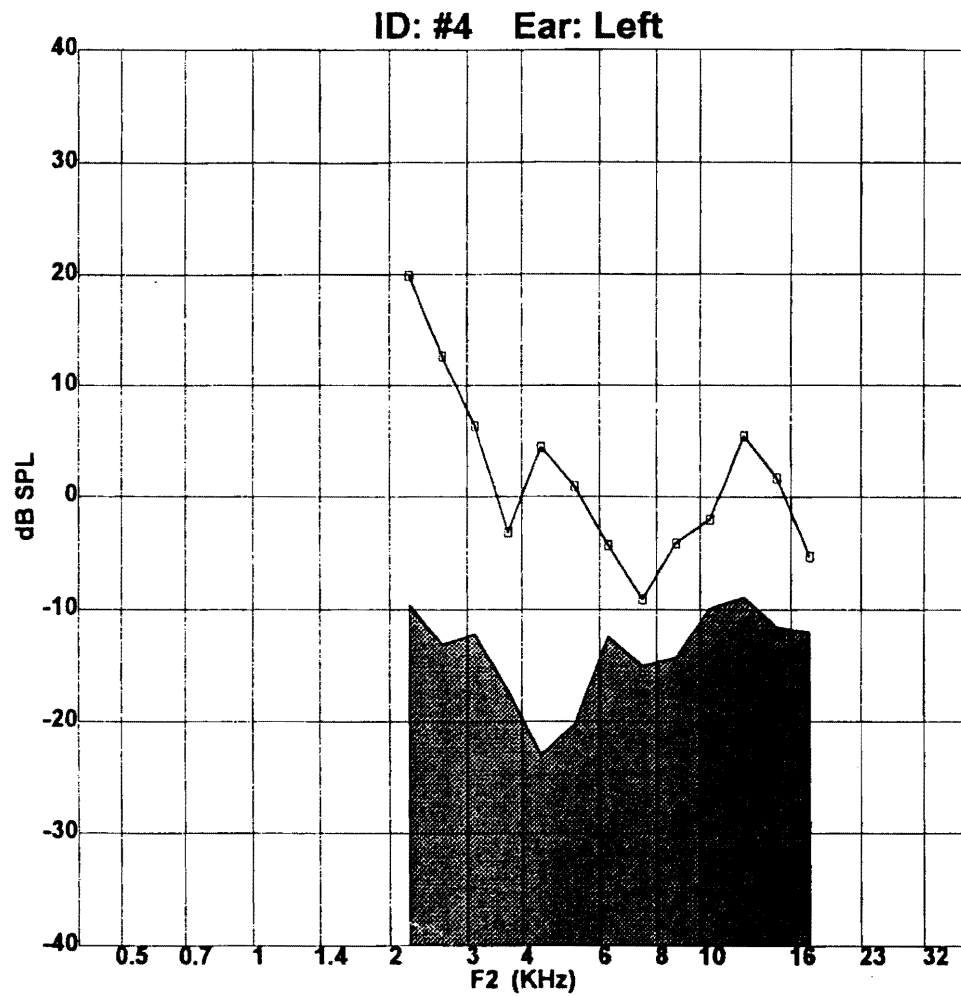


Fig 2. Distortion product amplitude as a function of F2 frequency in kHz. The noise floor across the frequency spectrum is depicted by the shaded area. These data are from one ear.



Fig 3

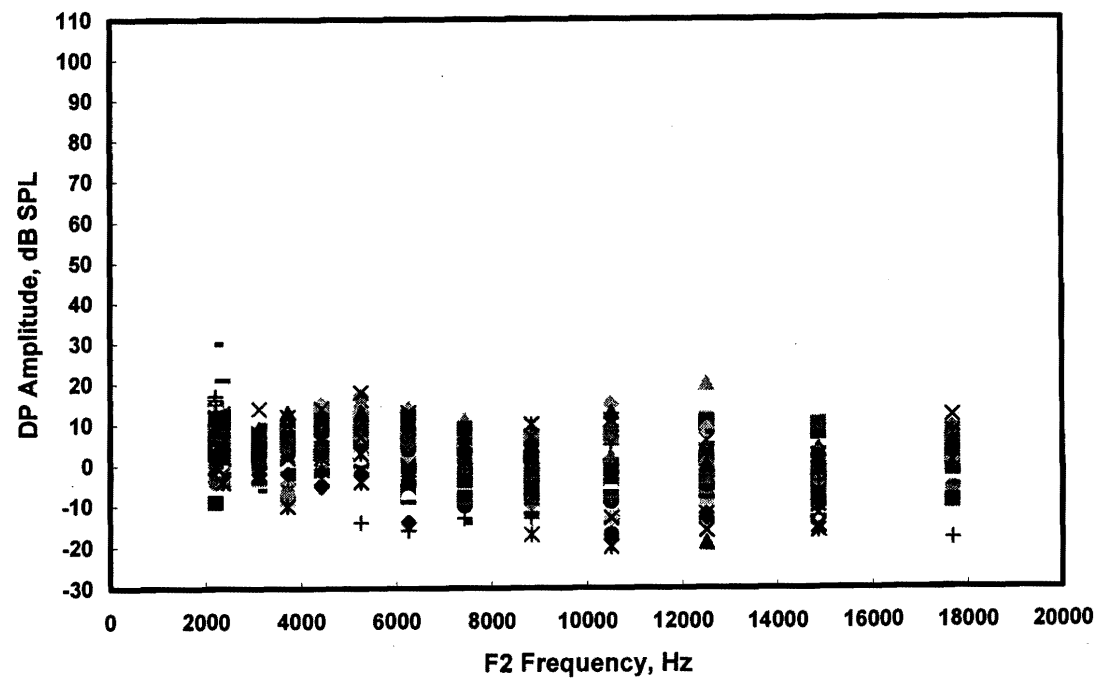


Fig 3. DP amplitude in dB SPL as a function of F2 frequency across subjects

Behavioral thresholds are given in Figure 4 where pure tone thresholds are plotted as a function of frequency for all subjects. The most notable effect here is the increase in pure tone thresholds with increasing frequency. Mean thresholds from 250-3000 Hz were 7 dB HL. Mean thresholds from 4000-9000 Hz were 18 dB HL, and 32 dB HL from 10000-16000 Hz. A range of 17 dB was found in thresholds from 250-3000 Hz, a 37 dB range from 4000-9000 Hz, and a 70 dB range was illustrated from 10000 to 16000 Hz. Thus thresholds have the greatest variability in the high frequencies.

The relationship between behavioral thresholds and DPOAE amplitude between subjects was explored by conducting a Pearson  $r$  correlation analysis at each frequency. The results of this analysis are given in Table 2. A negative relationship between variables was found in 10 of the 14 bivariate correlations. The Pearson  $r$ -values had a range of  $-.032$  to  $-.46$ . The remaining 4 correlations had a positive value, with a range of  $.06$  to  $.18$  indicating a weak positive correlation for these measures.

Two of the bivariate correlations, 12000 and 14000 Hz were found to be significant at the  $.05$  level. One frequency, 4000 Hz, was found to be significant at the  $.01$  level, with an  $r$ -value =  $-.461$ , indicating a moderate negative correlation.

Table 2 displays the analysis of bivariate correlations for each frequency, including the Pearson- $r$  correlation value and significance:

Fig 4

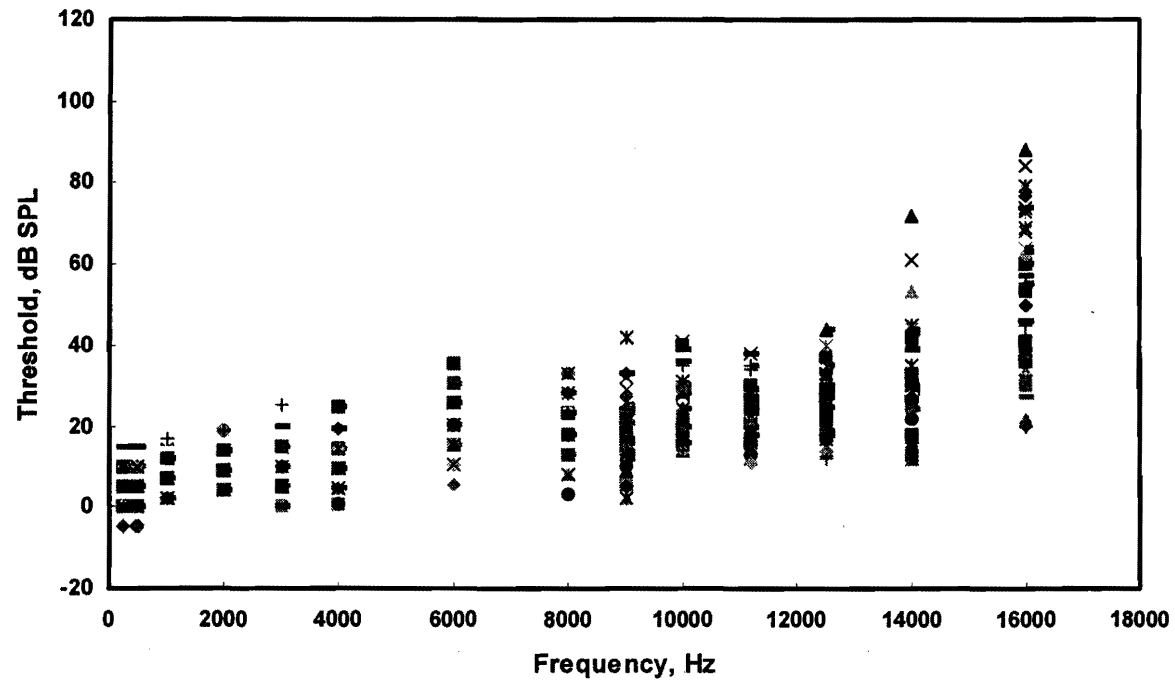


Table 2. Pearson r correlation analysis

<u>Frequency</u>	<u>Pearson r</u>	<u>Significance (2-tailed)</u>
PT 2000 DP 2361	-.18	.217
PT 3000 DP 3171	-.099	.499
PT 4000 DP 4421	-.461	.001
PT 6000 DP 6250	-.195	.180
PT 8000 DP 8832	-.118	.420
PT 9000 DP 10505	.183	.208
PT 10000 DP 10505	.067	.646
PT 11200 DP 10505	-.035	.812
PT 12500 DP 12500	-.302	.035
PT 14000 DP14858	-.358	.012
PT 16000 DP 14858	-.282	.049
PT 16000 DP17675	.086	.558

The scatter plots in figure 5A, 5B, and 5C illustrate the relationship between the objective and subjective measurements of hearing sensitivity for all subjects at the three frequencies with high correlation. If the variables are correlated as suspected, a diffuse clustering of data points spread around a downward sloping pattern is expected.

Figure 5A is a scatter plot that displays 4000 Hz pure tone thresholds as a function of 4421 Hz DPOAE amplitudes. Each data point on the graph represents a subject response. Figure 5B is a scatter plot that displays the relationships of the 12500 Hz pure tone thresholds and 12500 Hz DPOAE amplitudes in all subjects. Figure 5C is a scatter plot that displays 14858 DPOAE amplitudes and 14000 Hz pure tone thresholds in all subjects. The correlations between the two measures therefore appear to be weak.

Fig 5A

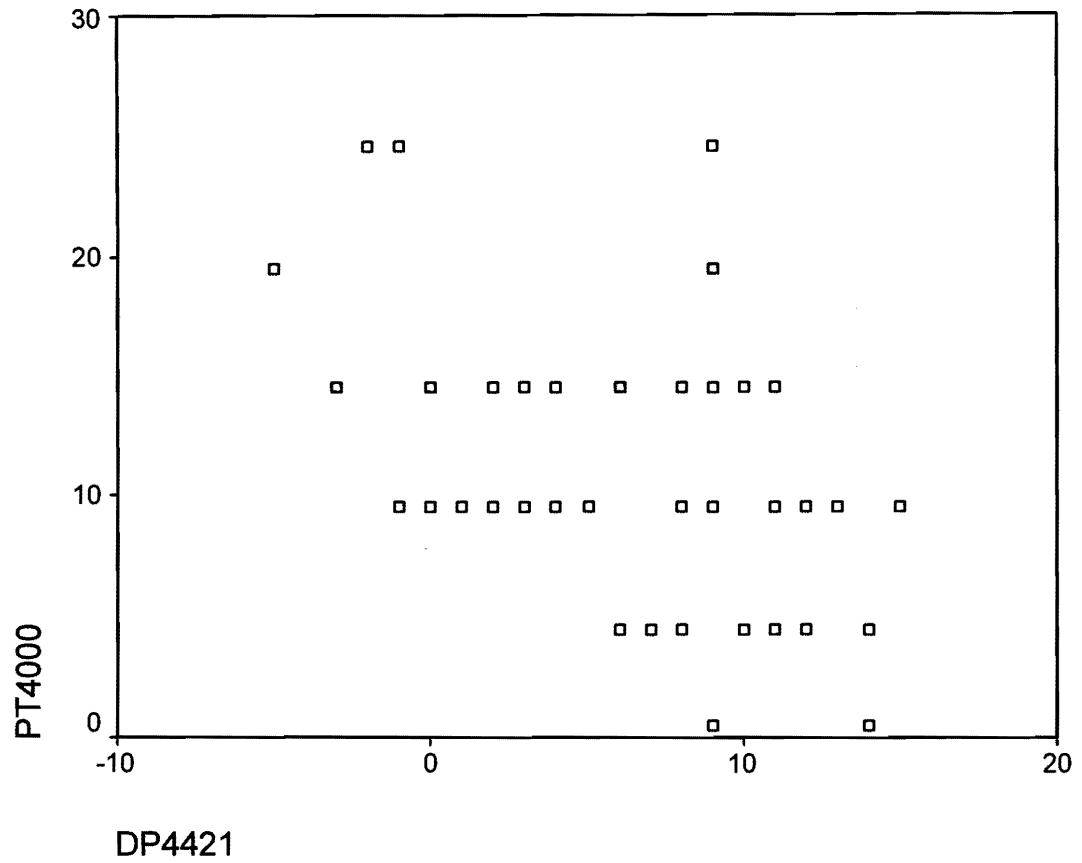


Fig 5A. A scatter plot illustrating the relationship between 4,000 Hz pure tone and DP amplitude for an F2 frequency of 4,000 Hz across subjects. A dispersed pattern of data points is revealed.

Fig 5B

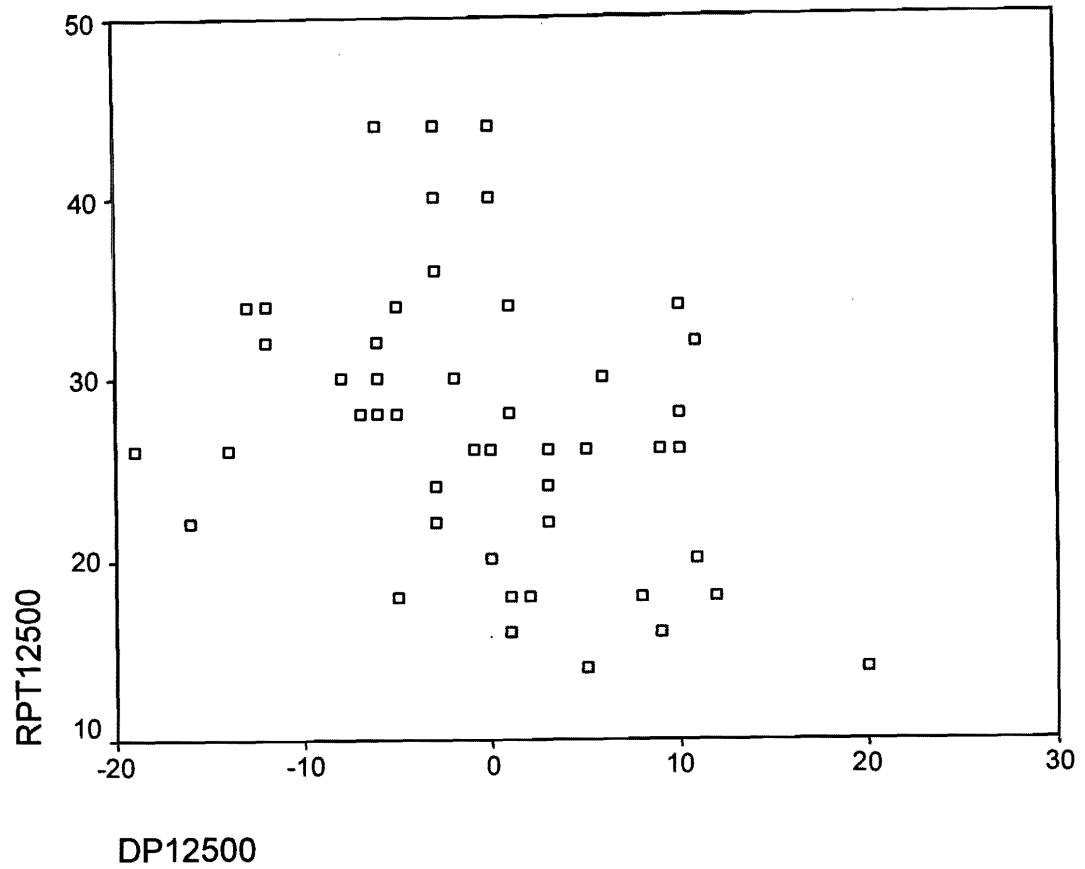


Fig 5B. A scatter plot illustrating the relationship between 12,500 Hz pure tone and DP amplitude for an F2 frequency of 12,500 Hz across subjects. A dispersed pattern of data points is revealed

Fig 5C

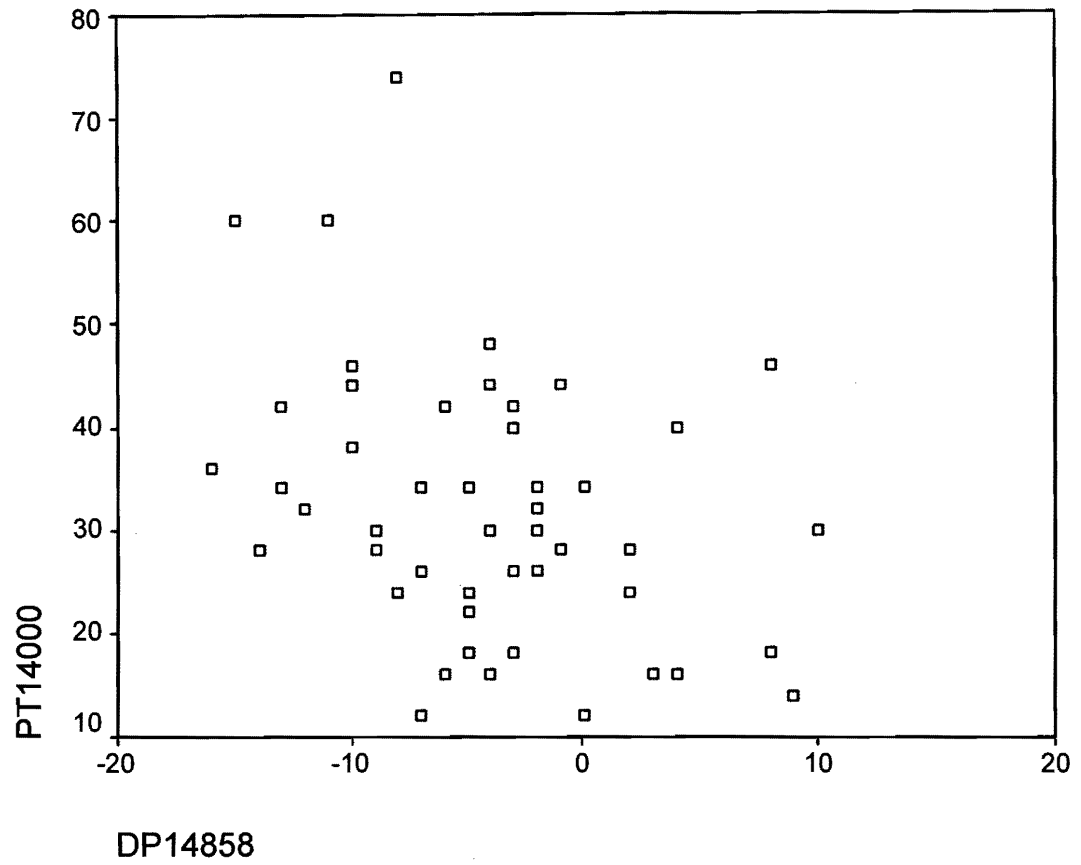


Fig 5C A scatter plot illustrating the relationship between 14,000 Hz pure tone and DP amplitude for an F2 frequency of 14,858 Hz across subjects. A dispersed pattern of data points is revealed



## DISCUSSION

The aim of this study was to evaluate relationship between High frequency pure tone thresholds and High frequency DPOAE's. Data obtained from 50 ears showed a decline in DPOAE amplitude with increasing frequencies of the primaries. This trend is consistent with the findings, as stimulus frequency increases above 2000 Hz, a progressive reduction of DP amplitude for higher frequency stimuli were recorded when the  $f_1/f_2$  ratio is kept at 1.22 (Hall, 2000). The present study indicates that the decline continues to F2 values as high as 17,675 Hz. Our data also demonstrated an increase in behavioral thresholds with increasing frequency. This is consistent with the findings of Fausti et al., 1979, who showed that thresholds for normal hearing individuals increase with test tone frequencies from 8000-20000 Hz.

The literature has established significant correlations between DPOAEs and pure tone audiometry when evaluating the frequency range from 250-8000 Hz (Avan et.al, 1993; Moulin, Bera & Collet, 1994). Our data show a relatively poor correlation between the two types of measures within this range of frequencies and for frequencies above 8000 Hz. Possible reasons for the discrepancy in our findings are discussed below.

An inherent problem with behavioral pure tone thresholds, is the fact that they are a subjective measurement at risk to variability. When performing a Pearson  $r$  correlation analysis between repeated measures, all thresholds were found to have a high statistical significance, with an  $r$ -value of at least .905 for all frequencies tested from 9000 through 16000 Hz. This indicates a high level of reproducibility between

repeated measures. The range of high frequency thresholds was found to be within the clinically acceptable range of  $\pm 10$  dB SPL for repeated thresholds (Frank et.al., 1991).

It is therefore unlikely that the low correlation was due to poor reliability of our behavioral thresholds.

Repeated measures were not performed on OAEs because they are generally not subject to patient variability, so an evaluation of equipment was performed. The Intelligent Hearing Systems (IHS) is the only commercially available device capable of measuring high frequency DPOAEs for a clinical setting. There are currently no ANSI standards for high frequency measurements, so protocols and calibrations were performed using the manufacturer's recommendations with the software and probe tips recommended by IHS.

As outlined in the methods section, measurement of the transducer output using a 1 cc coupler was performed prior to data collection to evaluate stimulus purity. Emissions should not exist in a hard walled cavity if the transduction system is linear. We found that there were no significant distortion products that were generated by the transducer, so we therefore assumed that the system was linear. However, when a similar check was made following data collection, significant DPOAE amplitudes were recorded across the frequency spectrum from 2211 to 17675 Hz, with amplitudes ranging from -13 to 10 dB SPL. This suggests that at some point during data collection the system may have become nonlinear.

Two possible explanations of this are standing waves and electrical interference. Standing waves are cancellations and reinforcements of sound waves due

to reflections or interactions between the stimulus and tympanic membrane (Siegel, 1994). Standing waves can be averaged into amplitude measurements, causing the response to be underestimated or overestimated in interpretation.

Even when a transducer is designed for optimal conditions, a strong input signal can drive a transducer to saturation. When saturation occurs, there will be distortion of the output waveform, so that it will not have the same shape as the input waveform (Gibilisco, 1993). However, our transducer output was only 65 dB SPL, while the standard output values are acceptable up to 75 dB SPL without driving the transducer into saturation. Therefore, transducer saturation was most likely not a factor.

Due to the fact that there was change in transducer output calibration measures between initiation and completion of the study, this most likely compromised our data accuracy. Since our Intelligent Hearing Systems equipment was producing artifacts, caution should be used that emissions measured are actual measurements and are not artifacts.

High frequency OAE equipment should come equipped with a fool proof method of calibration. It is recommended that future protocols include a daily coupler calibration in addition to an in-the-ear calibration measure before acquiring data on each subject.

High frequency DPOAE's and high frequency pure tone audiometry should be used in future studies to evaluate correlational relationships for use in ototoxicity monitoring with different age groups. With properly functioning equipment, this

research will provide valuable information to the medical and research communities.

Other investigations could include a correlational analysis on a hearing impaired population, without adjusting protocols performed in our study. DPOAEs would not be present with hearing thresholds poorer than 35 dB HL. Significant DPOAE amplitudes on this population would provide evidence as to the presence of standing waves or electrical interference.

## REFERENCES

- Allen, G.C., Tiu, C., Koike, K., Ritchey, K., Kurs-Lasky, M., & Wax, M.K. (1998). Transient-evoked otoacoustic emissions in children after cisplatin chemotherapy. Otolaryngology- Head and Neck Surgery 118 (5). 584-588.
- Avan, P., Bonfils, P. (1993). Frequency specificity of human distortion product otoacoustic emissions. Audiology 32 (12). 12-26.
- Avan, P., Elbez, M., & Bonfils, P. (1997). Click-evoked otoacoustic emissions and the influence of high frequency hearing losses in humans. Journal of the Acoustical Society of America 101,(5) Pt.1. 2771-2777.
- Brown, A.M., McDowell, B., Forge, A. (1989). Acoustic distortion products can be used to monitor the effects of chronic gentamicin treatment. Hearing Research 42. 143-156.
- Campbell, K.C.M., Rybak, L.P., Meech, R.P., & Hughes, L. (1998). D-methionine provides excellent protection from cisplatin ototoxicity in the rat. Hearing Research 102. 90-98
- Cevette, M.J., Drew, D., Webb, T.M., & Marion, M.S. (2000). Cisplatin ototoxicity, increased DPOAE amplitudes, and magnesium deficiency. Journal of the American Academy of Audiology 11. 323-329.
- Doolittle, N.D., Muldoon, L.L., Brummett, R.E., Tyson, R.M., Lacy, C., Bubalo, J.J., Kraemer, D.F., Heinrich, M.C., Henry, J.A., & Neuwelt, E.A. (2001). Delayed sodium thiosulfate as an otoprotectant against carboplatin-induced hearing loss in patients with malignant brain tumors. Clinical Cancer Research 7. 493-500.
- Dreschler, WA., Hulst, R.J.A.M., Tange, R.A., & Urbanus, N.A.M (1985). Role of high frequency audiometry in the early detection of ototoxicity. 387-395.
- Dreschler, WA., Hulst, R.J.A.M., Tange, R.A., & Urbanus, N.A.M (1989). Role of high frequency audiometry in the early detection of ototoxicity. Audiology 28. 211-220.
- Fausti, S.A., Frey, R.H., Erickson, D.A., Rappaport, B.Z., & Cleary, E.J. (1979) A system for evaluating auditory function from 8000-20,000 Hz. Journal of the Acoustical Society of America 66 (6). 1713-1718.

Fausti, S.A., Rappaport, B.Z., Schechter, M.A., & Frey R.H. (1982). An investigation of the validity of high -frequency audition. Journal of the Acoustical Society of America 71 (3). 646-649.

Fausti, S.A., Schechter, M.A., Rappaport, B.Z., Frey, R.H., & Mass, R.E. (1984). Early Detection of Cisplatin ototoxicity. Cancer 53. 224-231.

Ferguson, M.A., Smith, P.A., Davis, A.C., Lutman, M.E. (2000). Transient-evoked otoacoustic emissions in a representative population sample aged 18-25 years. Audiology 39. 125-134.

Frank, T., Dreisbach LE. (1991). Repeatability of high frequency thresholds. Ear and Hearing 12. 450-454.

Gabaizadeh, R., Staecker, H., Liu, W., Kopke, R., Malgrange, B., Lefebvre, P.P & Van De Water, T.R. (1997). Protection of both auditory hair cells and auditory neurons from cisplatin induced damage. Acta Otolaryngology (Stockholm) 117. 232-238.

Gibilisco, S (1993). Teach yourself electricity and electronics. Blue Ridge Summit, P.A., USA : McGraw-Hill/TAB books.

Go, R.S & Adjei, A.A. (1999). Review of the comparative pharmacology and clinical activity of cisplatin and carboplatin. Journal of Clinical Oncology 17 (1). 409-422.

Hall, J.W. (2000). Handbook of otoacoustic emissions. San Diego, CA.: Singular.

Hatzopoulos, S., Cheng, J., Grzanka, A., Martini, A. (2000) Time-frequency analyses of TEOAE recordings from normals and SNHL patients. Audiology 39. 1-12.

Hoffstetter, P., Ding, D., Powers, N., & Salvi, R. (1997). Quantitative relationship of carboplatin dose to magnitude of inner and outer hair cell loss and the reduction in distortion product otoacoustic emission amplitude in chinchillas. Hearing Research 112. 199-215.

Jerger, S., & Jerger, J. (1981). Auditory Disorders. Needham Heights, M.A.: Allyn & Bacon.

Jordan, J.A, & Roland, P.S., Edited by Roeser, R.J., Valente, M., & Hosford-Dunn, H. (2000). Audiology Diagnosis. New York, N.Y.: Thieme.

Kemp, D.T. (1986). Otoacoustic emissions, travelling waves and cochlear mechanisms. Hearing Research 22. 95-104

Lonsbury-Martin, B.L., Whitehead, M.L., Martin, G.K. (1991). Clinical applications of otoacoustic emissions. Journal of Speech and Hearing Research 34. 964-981.

Mauermann, M., & Uppenkamp, S. (1999). Evidence for the distortion product frequency place as a source of fine structure in humans. II. Fine structure for different shapes of cochlear hearing loss. Journal of the Acoustical Society of America 106 (6). 3484-3490.

McAlpine, D., & Johnstone, B.M. (1990). The Ototoxic mechanism of cisplatin. Hearing Research 47. 191-204.

Moulin, A., Bera, J.C., & Collet, L., (1994). Distortion product otoacoustic emissions and sensorineural hearing loss. Audiology 33. 305-326.

Neuwelt, E.A., Brummett, R.E, Remsen, L.G., Kroll, R.A., Pagel, M.A., McCormick, C.I., Giutjens, S., & Muldoon, L.L. (1996). In vitro and animal studies of sodium thiosulfate as a potential chemoprotectant against carboplatin-induced ototoxicity. Cancer Research 56. 706-709.

Neuwelt, E.A., Brummett, R.E., Doolittle, N.D., Muldoon, L.L., Kroll, R.A., Pagel, M.A., Dojan, R., Church, V., Remsen, L.G., & Bubalo, J.S. (1998). First evidence of otoprotection against carboplatin-induced hearing loss with a two-compartment system in patients with central nervous system malignancy using sodium thiosulfate. Journal of Pharmacology and Experimental Therapeutics 286 (1). 77-84.

Siegel, J. (1994). Ear canal standing waves and high frequency sound calibration using Otoacoustic emission probes. Journal of the Acoustical Society of America 95(5). 2589-2597.

Stavroulaki, P., Apostolopoulos, N., Segas, J., Tsakanikos, M., Adamopoulos, G. (2001). Evoked otoacoustic emissions- an approach for monitoring cisplatin induced ototoxicity in children. International Journal of Pediatric Otorhinolaryngology 59. 47-57.

van der Hulst, R.J.A.M, Dreschler, & W.A, Urbanus, N.A.M. (1988). High frequency audiometry in prospective clinical research of ototoxicity due to platinum derivatives. Annals of Otology, Rhinology, and Laryngology 97. 133-137.

Wetmore, S.J., Koike, K.J., & Bloomfield, S.M. (1997). Profound hearing loss from intervertebral artery cisplatin. Otolaryngology- Head and Neck Surgery 116 (2) 234-237.