The use of distortion product otoacoustic emissions in the estimation of hearing and sensory cell loss in noise-damaged cochleas

Bob Davis

Wei Qiu

Roger P. Hamernik

Auditory Research Laboratory

Plattsburgh State University of New York

107 Beaumont Hall

Plattsburgh, New York 12901

Bob Davis

Auditory Research Laboratory

Plattsburgh State University of New York

107 Beaumont Hall

101 Broad St.

Plattsburgh, New York 12901

TELEPHONE: (518) 564-7700

E-MAIL: Robert.Davis@plattsburgh.edu

1. Introduction

The distortion product otoacoustic emission (DPOAE), which is a consequence of normal nonlinear processes in the cochlea, has gained popularity as a clinical test for hearing screening and diagnostic purposes. Several studies have evaluated the clinical utility of DPOAE test performance to determine how well DPOAEs identify hearing loss in humans (Gorga et. al 1993; Kimberley et al., 1994; Gorga et al., 1996; Gorga et al., 1997; Attais et al., 2001; Boege and Janssen, 2002; Gorga et al., 2003) and in animal models (Canlon et al., 1993; Hamernik et al., 1996; Hofstetter et al., 1997; Le Calvez et al., 1998; Hamernik et al., 1998; Hamernik et al., 2000; Avan et al., 2001; Mills, 2003). In general, results have shown considerable variability in the distribution of response properties from normal ears as well as in those with damaged cochleas.

Attempts to refine the predictive power of the DPOAE in order to estimate behavioral thresholds in humans have been met with varying degrees of success (Kimberley et al., 1994; Gorga et al., 1996, 1997, 2003; Boege and Janssen, 2002). Overall, these studies utilized the DPOAE (e.g., level, SNR, threshold) to make a dichotomous decision as to whether hearing was normal or impaired. The large variance of DPOAE levels found in human studies, however, did not seem to allow for an accurate prediction of the amount of hearing loss despite good statistical correlations (Gorga et al., 1993; Gorga et al., 1996, 1997; Le Calvez et al., 1998).

Evidence from experiments in animal models on the potential value of DPOAEs as a sensitive indicator of hearing threshold or OHC loss have also been inconclusive. The few studies that have attempted to correlate DPOAEs with histopathology in animals have been conflicting (Brown et al., 1989; Canlon et al., 1993; Subramaniam et al., 1995; Hamernik et al.,1996; Le Calvez et al., 1998; Hamernik and Qiu, 2000; Harding et al., 2002). Several studies for instance have reported generally weak correlations between DPOAE's and either pure tone thresholds or OHC loss (Canlon et al., 1993; Subramaniam et al., 1994; Emmerich et al., 2000), while good correspondence between DPOAE change and OHC loss has been reported by e.g. Hofstetter et al. (1997) and Hamernik and Qiu (2000). The inconsistent relations between the DPOAE and OHC loss may be attributed, in part, to the inability to easily quantify other

morphological changes (e.g. stereocilia defects, altered tip links) over the entire extent of the basilar membrane in large numbers of animals, or to changes in the endocochlear potential which may affect the function of cells that are present. This report presents the results of a population study on the relations among OHC loss, PTS and the DPOAE in an effort to resolve some of the ambiguity that exists in the literature on the use of the DPOAE in: 1) predicting the amount of PTS or OHC loss, 2) defining the specific PTS and OHC loss values which represent clear boundaries for predictive accuracy, and 3) determining the extent of overlap between normal and abnormal response distributions of the DPOAE as a function of the magnitude of PTS and OHC loss. This information may provide insight into the use of the DPOAE as a reliable metric in the assessment of auditory functioning in animals both before and following noise exposure, especially in cases where auditory thresholds or histological information cannot be easily obtained.

2. Materials and methods

DPOAEs, auditory evoked potentials (AEP), which were used to estimate hearing thresholds, and frequency-specific sensory cell population data were collected on a population of 187 chinchillas exposed to a variety of continuous noise for a period of 5 uninterrupted days. Data were acquired over a five-year period as part of a protocol to assess the effects of complex (non-Gaussian) noise environments on hearing.

2.1 Surgical preparation

All animals were made monaural by the surgical destruction of the left cochlea and an AEP-recording electrode was implanted into the left inferior colliculus. Details of the AEP procedures and surgery can be found in Ahroon et al. (1993). Briefly, each animal was anesthetized [IM injection of ketamine (35 mg/kg body weight) and xylazine (1 mg/kg body weight)] and made monaural by the surgical destruction of the left cochlea. A bipolar, platinum EEG electrode, with electrode lengths of 7.5 mm (probe) and 2.5 mm (ground)

was implanted into the region of the inferior colliculus under stereotaxic control for single-ended recordings of the AEP (Henderson et al., 1973; Salvi et al., 1982). A xylazine reversing agent [yohimbine (2 mg/kg body weight IM] was administered after the surgical procedure. The animals were allowed to recover for at least two weeks before AEP and DPOAE testing began.

2.2 Threshold testing:

The animals were awake during testing and restrained in a yoke-like apparatus to maintain the animal's head in a fixed position within the calibrated sound field (Blakeslee et al., 1978). AEPs were collected to 20 ms pure-tone bursts with 5 ms rise/fall times, presented at a rate of 10/s. A general purpose computer was used to acquire the AEP data and control the frequency, intensity, and timing of the stimulus. The electrical signal from the implanted electrode was amplified (50,000x), filtered (30 to 3000 Hz), and sampled using an analog-to-digital (12-bit resolution) converter at 20,000 samples/s (50 μs period) over 500 points to obtain a 25 ms sampling window. Each digitized waveform was analyzed for large amplitude artifacts, and if present, the sample was rejected from the average and another sample taken. Averaged AEPs were obtained from 250 presentations of the 20 ms signal. Each waveform was stored to be used in threshold determination following the completion of the test stimulus intensity series.

Thresholds were estimated from each tone-burst intensity series using 5 dB steps at octave intervals from 0.5 to 16 kHz. Threshold was determined to be one half step size (2.5 dB) below the lowest intensity that showed a response consistent with the responses seen at higher intensities. The average of at least three separate threshold determinations at each frequency obtained on different days was used to define the preexposure audiogram. Following a 30 d postexposure recovery period, thresholds were measured again on three different days and averaged to establish the animal's PTS. PTS was defined as the difference between the 30 d post- and preexposure audiograms.

2.3 Cubic distortion product otoacoustic emissions:

Cubic distortion products ($2f_1$-f_2) were measured in the ear canal of the awake but restrained animal with the Etymotic ER-10C instrument using CUBeDIS (v2.40) software. DPOAEs were measured at 32 points per octave. The following parameters were used in collecting the DPOAEs: 1.0 kHz ≤ f_2 ≤ 10 kHz, where f_2 was the higher frequency primary tone; f_2/f_1 = 1.22. The level (L_1) of the f_1 primary tone was 65 dB with L_1=L_2 +10 dB and the averaging time was constant at 2 s. All DPOAE data were plotted as a function of f_2. The same number of DP-grams (DPOAE level versus f_2) were collected and at approximately the same times during the experimental sequence as the AEP audiograms. The average of the three pre- and three 30 d post-treatment DPOAE measurements was used to establish permanent treatment effects.

To prepare scatter plots and DPOAE cumulative distributions for use in estimating correlations among DPOAE measures and other variables, the DPOAE data collected over each 1/3 octave band centered on the audiometric test frequencies (1.0, 2.0, 4.0, and 8.0 kHz) was averaged to produce a single DPOAE datum point corresponding to the 1.0, 2.0, 4.0 and 8.0 kHz AEP test frequencies. DPOAE correlations with OHC loss and AEP determined PTS were performed for the following three sets of DPOAE data: 1) postexposure DPOAE level, 2) Δ DPOAE (pre- minus postexposure level), and 3) SNR (postexposure DPOAE/noise floor level difference).

2.4 Histology

Following the last AEP or DPOAE test protocol, each animal was euthanized under anesthesia and the right auditory bulla removed and opened to gain access to the cochlea for perfusion. Fixation solution consisting of 2.5% glutaraldehyde in veronal acetate buffer (final pH=7.3; 605 mOs) was perfused through the cochlea. After 12 h of fixation the cochlea was postfixed in 1% OsO_4 in veronal acetate buffer. Surface preparation mounts of the entire organ of Corti were prepared and IHC and OHC populations, computed over 0.24 mm lengths of the basilar membrane, were plotted as a function of frequency and location using the frequency-place

map of Eldredge et al. (1981). Sensory cell population data were analyzed as group averages taken over 1/3 octave band lengths of the cochlea centered on the AEP test frequencies.

3. Results

The group mean (N = 187) preexposure DPOAE level for L_1 = 65 dB SPL is shown in Fig. 1. Each datum point in this figure was obtained by averaging the DPOAEs collected in each 1/3 octave band centered on the indicated frequencies. The mean DPOAE level varied between 21 dB at the lower frequencies to about 31 dB (6 < s.d. < 10 dB) at the higher frequencies with the largest DPOAE levels occurring between 4 and 8 kHz. These results are consistent with those reported by Hamernik et al., (2000) and Eddins et al., (1999) in the chinchilla.

A selected example of the results from a group of animals (N = 11) exposed to a continuous non-Gaussian noise at 100 dB(A) for 5 consecutive days is shown in Fig. 2. The permanent changes in DPOAE level, AEP thresholds, and the profile of IHC and OHC loss for this exposure were consistent in showing changes that reflect the effects of sensory cell loss on indices of auditory functioning. In this example, larger amounts of OHC loss are associated with slightly more PTS at 2 and 4 kHz and slightly greater reductions in DPOAE level in the 4 to 8 kHz range. It is from data sets such as this that the subsequent figures were derived. Bars in any of the figures indicate standard errors (s.e.) of the mean. When no bar is shown the s.e. was less than the size of the datum symbol.

Fig's. 3 and 4 show cumulative distributions of DPOAE levels from the population of subjects before noise exposure (N =187) compared with those having varying amounts of PTS (Fig. 3) and OHC loss (Fig. 4). The cumulative distributions were computed after separating animals into bins based upon the amount of PTS or OHC loss the animal had at a given frequency and then calculating a percentile rank for all animals in that particular bin at that frequency. In each figure, the frequency-specific noise floor amplitudes for the total population of

187 ears before and after noise exposure are also shown. Noise levels were very similar in both the pre and postexposure group. The data in Fig's. 3 and 4 may be used as a guide to determining the predictive hit rate for the DPOAE for various levels of PTS and OHC loss in noise-exposed ears and the corresponding false alarm rate from the preexposure distribution. Conversely, the preexposure DPOAE distribution can serve as criterion for the hit rate and the PTS and OHC loss DPOAE distributions for the false alarm rate. As expected, the postexposure DPOAE distributions shift to the left as the amount of PTS or OHC loss increases, i.e., the hit rate increases systematically as the amount of PTS and OHC loss increases. From these cumulative distribution curves it is clear that as PTS and OHC loss increases, there is less error in correctly identifying an ear that falls into one of the PTS and OHC loss categories without incorrectly identifying some percentage of normal ears as impaired. The data shown in Fig's. 3 and 4 suggest that a postexposure DPOAE level of $\leq$ 10 dB SPL for L_1= 65 dB SPL represents a criterion value for the chinchilla that can serve as an indication of significant PTS ($\geq$ 35 dB) or OHC loss ($\geq$ 50%).

Fig' 7 shows OHC loss and PTS data. Table 1 lists the index of determination (r^2) obtained from a nonlinear regression for five sets of data as follows: 1) postexposure DPOAE level versus PTS and OHC loss; 2) Δ DPOAE (pre- minus postexposure level) versus PTS and OHC loss; 3) SNR (postexposure DPOAE/noise floor level difference) versus PTS and OHC loss; 4) OHC loss versus PTS, and (5) PTS versus OHC loss. The solid line in Figs. 5 through 7 shows the result of the nonlinear regression on the individual animal data.

Examination of Table 1 shows that the r^2 coefficients for the regression of OHC loss on PTS are greater than each of the three OHC/DPOAE correlations (i.e., post DPOAE level, Δ DPOAE, and SNR) at all frequencies except at 8 kHz where they are similar. The r^2 coefficients for the prediction of PTS from OHC loss values are generally greater than the three PTS/DPOAE correlations at the low frequencies (1.0 and 2.0 kHz) while the prediction of PTS from DPOAE measures is better at 4.0 and 8.0 kHz. The r^2 coefficients for all three sets of PTS/DPOAE correlations were also greater than those of the corresponding three OHC/DPOAE correlations at each test frequency, especially for frequencies above 1.0 kHz. Correlations were typically lowest

between any set of DPOAE level measurements at 1.0 kHz, as a result of the higher noise levels at the lower frequencies.

In an attempt to establish postexposure DPOAE levels which reflect an ear with abnormal thresholds conservatively defined as PTS > 5 dB and DPOAEs for cochleas having OHC loss > 5% in the 1/3 octave band centered on the selected AEP test frequency, the 5^{th} percentile of the distribution of preexposure DPOAE levels was established and used as a strict criterion for normal emissions. The objective of this exercise was to determine the extent to which the classification of auditory status, based upon post DPOAE level measures, agrees with the classification based on PTS and OHC loss. The post DPOAE level was selected for this analysis since higher correlations for this variable than for either the Δ DPOAE or SNR variables were found for the PTS/DPOAE relation (Table 1). The 5^{th} percentile of the preexposure (normal subjects) data, shown as a vertical line in the scatter plots of Fig's. 5 and 6, yields two possible categories for all post DPOAE level measurements. The post DPOAE response amplitudes to the left of the 5^{th} percentile line were classified as abnormal because so few normal ears produced responses this weak. The post DPOAE values to the left of the line are, therefore, unlikely to occur in a normal ear. The individual data points falling to the right of the vertical line represent post DPOAE values within the range of normal preexposure subjects for each test frequency. In this analysis, the normal audiometric and histological status of the cochlea was arbitrarily established at a criterion of PTS $\leq$ 5 dB and OHC loss $\leq$ 5% and a horizontal line was drawn to identify these levels in Figs. 5 and 6, respectively. With the data divided according to these two criteria in each scatter plot, the sensitivity (proportion of abnormal ears that are correctly identified by the post DPOAE measurement) and specificity (proportion of normal ears that are correctly identified by post DPOAE measurement) of the post DPOAE level for the PTS and OHC measurements at each test frequency was calculated. The results are presented in Table 2 for both the PTS and OHC loss data.

The results indicate that the post DPOAE level measurements can identify, with reasonable accuracy, normal hearing subjects (PTS $\leq$ 5 dB) at all test frequencies, as well as animals with noise-induced PTS > 5 dB, for frequencies above 1 kHz. For example at 8 kHz, the

post DPOAE correctly identified 80% (specificity) of the normal hearing and 75% (sensitivity) of the animals with a noise-induced loss. The poorer performance (i.e., sensitivity) at 1.0 kHz is, at least in part, due to the relatively high noise levels for this frequency which reduced the signal level and resulted in a larger number of ears with little to no PTS having abnormal post DPOAE levels. Since the correlation between PTS and OHC loss (Fig. 7) across the test frequencies was good (r^2 = 0.50 to 0.69), it was not surprising to see similar results for the sensitivity and specificity measures for both the PTS/post DPOAE level and OHC loss/post DPOAE level data (Table 2). Overall, the use of a strict criterion indicates that the post DPOAE level is more reliable at telling us correctly when an ear is normal (PTS $\leq$ 5 dB or OHC loss $\leq$ 5%) than at identifying an abnormal ear (PTS > 5 dB or OHC loss > 5%) for frequencies of 1 and 2 kHz.

Table 3 illustrates the percentage of ears in which the post DPOAE level correctly identified a normal post exposure ear (i.e. fell above the 5th percentile of the normal preexposure distribution) and various abnormal (i.e. fell below the 5th percentile of the normal preexposure distribution) PTS and OHC loss conditions. Using the strict 5% criteria, the post DPOAE level correctly identified over 90% of all ears with PTS above 30 dB. In contrast, the post DPOAE level correctly identified 70 to 95% of the cochleas with OHC loss greater than 40% and 82-100% with OHC loss in excess of 60% across the test frequencies. These data indicate that the probability for the post DPOAE level to predict PTS of $\leq$ 5 dB or > 30 dB and OHC loss of $\leq$ 5% at 1 and 2 kHz or > 40% is high. Between these limit extremes, however, the probability of correctly predicting the amount of PTS or OHC loss is dramatically reduced. Similar conclusions could be drawn from the cumulative distributions shown in Fig's. 3 and 4.

5. Discussion

The purpose of the preceding analysis was to assess the effectiveness of the DPOAE in distinguishing between normal ears and ears with various amounts of noise-induced PTS and OHC loss in the chinchilla. The finding of a good correspondence would lend support for the use of this relatively quick, non-invasive measure of auditory function as an alternative to other forms

of assessing auditory function in animals. In general, the presence of overlapping cumulative distributions (Fig's. 3 and 4) and high variability (Fig's. 5 and 6) in the emission responses as a function of PTS and OHC loss makes it difficult to adequately predict hearing and sensory cell loss from emission measurements alone. The results of the present study are similar to those found in humans (Gorga et al., 1996, 1997, 2000; Stover et al., 1996). That is, there was a large range of emission responses for a given hearing level and a large range of hearing loss for a given DPOAE level.

Results from the chinchilla indicate that the DPOAE level can accurately identify normal ears (i.e., PTS $\leq$ 5 dB) and ears with PTS > 30 dB or OHC loss > 40% in a given 1/3 octave band. For the range of pathology between these two extremes the DPOAE is a much less reliable predictor. Given the dependence of the DPOAE on OHC function, and that PTS of ~40 dB are typically associated with near complete loss of OHCs (Schuknecht, 1953; Hamernik et al., 1989), it is not surprising to see the DPOAE cumulative distributions for the PTS data (Fig. 3) and OHC loss data (Fig. 4) show that the DPOAE is reliable in its ability to differentiate between normal hearing function and ears with significant PTS ($\geq$ 35 dB) and OHC loss ($\geq$ 50%). Since the OHC system is the source of the DPOAE, less variability in the DPOAE response would be expected in cochleas with complete to near complete loss of OHCs. This result indicates that the probability of correctly identifying an ear with PTS $\geq$ 35 dB (or OHC loss $\geq$ 50%) without also identifying an ear with less or no PTS (or OHC loss) is very high for low DPOAE levels ($\leq$ 10 dB SPL). Thus, at an L_1=65 dB SPL this DPOAE level may be used as test criteria which reflects an amount of PTS that equates with significant PTS and OHC loss in noise-exposed chinchillas.

The variability of DPOAE levels from noise-exposed chinchillas in our study was very similar to the variability reported in the DPOAE level measures obtained from normal and abnormal hearing humans by Gorga et al., 1996, 1997). The scatter plots shown in Fig. 5, for instance, show that the range of post DPOAE level for no or relatively little PTS ($\leq$ 5 dB) can range from about 0 to 30 dB, while animals showing very low DPOAE levels ($\leq$ 5 dB SPL) can have a PTS that varies over the range of 0 to 50 dB. Similarly, in Fig. 6, the range of post

DPOAE levels for no or very small OHC losses (≤ 5%) can be over 40 dB, while animals showing very low post DPOAE levels

(≤ 5 dB) can have OHC losses that vary from 0 to 100%. In humans, Gorga et al., (1996) reported that the range of DPOAE amplitude for normal hearing thresholds (0 to 20 dB HL) can be up to 40 dB SPL while DPOAE levels of ≤ 15 dB SPL were associated with a 40 dB range of hearing levels. The variability inherent in these results both for the chinchilla and human illustrates the limitation of DPOAE levels to accurately predict the amount of PTS and OHC loss in individual subjects following noise-exposure.

A comparison of the cumulative distribution functions obtained from the population (N = 187) of normal prexposure chinchillas in this study and the distributions from normal hearing humans (N = 107) obtained by Gorga et al., (1996) at several f_2 frequencies shown in Fig. 8 illustrates the parallel behavior of the population DPOAE data between the two species. The cumulative distributions differ by a frequency dependent constant; the constant increases with increasing frequency. This result, along with the high hit rates in the cumulative distribution for the most severe PTS (≥ 35 dB) (Fig. 3) and OHC loss (≥ 50%) (Fig. 4) in the chinchilla, suggests that one might consider using the postexposure DPOAE chinchilla data to estimate the amount of OHC loss in humans.

6. Conclusions

Based on the analysis of DPOAE, PTS and OHC losses in noise-exposed chinchillas the results presented show the following: 1) The considerable variability of individual post DPOAE level values for PTS between 5 and 30 dB and for OHC loss between 5 and 40%, results in a broad region of “uncertainty” making it difficult, in the chinchilla model, to use the post DPOAE level with confidence to predict the magnitude of PTS or OHC loss within these limits in individual subjects, 2) the postexposure DPOAE level can be used with reasonable confidence to determine if the status of auditory functioning is either normal (i.e., ≤ 5 dB PTS) or abnormal (> 30 dB PTS or > 40% OHC loss) in noise-exposed chinchillas, 3) the cumulative distributions of DPOAE

amplitudes in normal and noise-exposed ears indicate that there is a systematic relation between test performance (i.e., hit rate) and the amount of PTS and OHC loss, and can be used to assign a level of confidence to these categories for an individual noise-exposed ear, and 4) the possible existence of subtle OHC abnormalities not revealed by averaging OHC losses may have accounted for the lower specificity values for OHC loss ($\leq$ 5%) than for PTS ($\leq$ 5 dB), as well as the weaker correlations for OHC loss/DPOAE than for PTS/DPOAE.

Acknowledgments

This work was supported by grant 1-R01-OH02317 from the national Institute for Occupational Safety and Health. The able technical assistance of Tomas Lewis, George A. Turrentine, Ann Johnson and Dianne Fresch is greatly appreciated. In conducting the research described in this study, the investigators adhered to the “Guide for the Care and Use of laboratory Animals,” prepared by the Committee on Care and Use of laboratory Animals of the Institute of Laboratory Animal Resources, National Research Council [DHHS Publication No. (NIH) 86-23, revised 198

References

Ahroon, W.A., Hamernik, R.P., Davis, R.I., 1993. Complex noise exposures: An energy analysis. J. Acoust. Soc. Am. 93, 997-1006.

Attias, J., Horovitz, G., El-Hatib, N., Nageris,, B. 2001. Detection and clinical diagnosis of noise-induced hearing loss by otoacoustic emissions. In: Henderson, D., Prasher, D., Kopke, R., Salvi, R., Hamernik, R.P. (Eds.). Noise Induced Hearing Loss:Basic Mechanisms, Prevention and Control. Noise Research Networks Publications, London, pp. 429-441.

Avan, P., Bonfils, P., Mom, T., 2001. Correlations among distortion product otoacoustic emissions, thresholds and sensory cell impairment. In: Henderson, D., Prasaher, D., Kopke, R., Salvi, R., Hamernik, R.P (Eds.) Noise Induced Hearing Loss: Basic Mechanisms, Prevention and Control. Noise Research Networks Publications, London, pp. 411-427.

Blakeslee, E.A., Hynson, K., Hamernik,R.P., Henderson, D. 1978., Asymptotic threshold shift in chinchillas exposed to impulse noise. J. Acoust. Soc. Am. 63, 876-882.

Boerge. P, and Janssen T. 2002. Pure-tone threshold estimation from extrapolated distortion product otoacoustic emission I/O-functions in normal and cochlear hearing loss ears. J. Acoust. Soc. Am. 111, 1810-1818.

Brown, A.M., McDowell, B., Forge, A. 1989, Acoustic distortion products can be used to monitor the effects of chronic gentamicin treatment. Hear Res. 42, 143-156.

Brown, A. M. 1987, Acoustic distortion from rodent ears: A comparison of responses from rats, guinea pigs, and gerbils. Hear. Res. 31, 25-38.

Canlon, B., Marklund, K., Borg, E., 1993. Measures of auditory brain-stem responses, distortion product otoacoustic emissions, hair cell loss and forward masking tuning curves in the walzing guinea pig. J. Acoust. Soc. Am. 94, 3232-3243.

Eddins, A.C., Zuskov, M., Salvi, R., 1999. Changes in distortion product otoacoustic emissions during prolonged noise exposure. Hear. Res. 127, 119-128.

Eldredge, D.H., Miller, J.D., Bohne, B.A., 1981. A frequency-position map for the chinchilla cochlea. J. Acosut. Soc. Am. 69, 1091-1095.

Emmerich, E., Richter, F., Reinhold, U., Linss, V., Linss, W., 2000. Effects of industrial noise on distortion product otoacoustic emissions (DPOAEs) and hair cell loss of the cochlea – long term experiments in awake guinea pigs. Hear. Res. 148, 9-17.

Gorga, M.P., Neely, S.T., Dorn, P.A., Hoover, B., 2003. Further efforts to predict pure-tone thresholds from distortion product otoacoustic emission input/output functions. J. Acoust. Soc. Am. 113, 3275-3284.

Gorga, M.P., Nelson, K., Davis, T., Dorn, P.A., 2000. Distortion product otoacoustic emission test performance when both $2f_1$-f_2 and $2f_2$-f_1 are used to predict auditory status. J. Acoust. Soc. Am. 107, 2128-2135.

Gorga, M.P., Neely, S.T., Ohlrich, B., Hoover, B., Redner, J., and Peters, J., 1997. From laboratory to clinic: a large scale study of distortion product otoacoustic emissions in ears with normal hearing and hearing loss. Ear and Hearing 18, 440-455.

Gorga, M.P., Stover, L., and Neely, S.T., 1996. The use of cumulative distributions to determine critical values and levels of confidence for clinical distortion product otoacoustic emission measurements. J. Acoust. Soc. Am. 100, 968-977.

Gorga, M.P., Neely, S.T., Bergman, B.M., and Beauchaine K. L., 1993. A comparison of transient-evoked and distortion product otoacoustic emissions in normal-hearing and hearing-impaired subjects. J. Acoust. Soc. Am. 94, 2639-2648.

Hamernik, R.P., Patterson, J.H., Turrentine, G.A., Ahroon,W.A., 1989. The quantitative relation between sensory cell loss and hearing thresholds. Hear. Res. 38, 199-212.

Hamernik, R.P., Ahroon, W.A., Jock, J.M., Bennett, J.A., 1998. Noise-induced threshold shift dynamics measured with distortion-product otoacoustic emissions and auditory evoked potentials in chinchillas with inner hair cell deficient cochleas, Hear. Res . 118, 73-82.

Hamernik, R.P. and Qiu, W., 2000. Correlations among evoked potential thresholds, distortion product otoacoustic emissions and hair cell loss following various noise exposures in the chinchilla. Hear. Res. 150, 245-257.

Hamernik, R.P., Ahroon, W.A, and Lei, S.F., 1996. The cubic distortion product otoacoustic emissions from the normal and noise-damaged chinchilla cochlea. J. Acoust. Soc. Am. 100 (2), 1003-1012.

Hamernik, R.P., Qiu, W, and Davis, B., 2003. The effects of the amplitude distribution of equal energy exposures on noise-induced hearing loss: The kurtosis metric. J. Acoust. Soc. Am. 114, 386-395.

Harding, G.W., Bohne, B.A., Ahmad, M., 2002. DPOAE level shifts and ABR threshold shifts compared to detailed analysis of histopathological damage from noise. Hear. Res. 174, 158-171.

Henderson, D., Hamernik, R.P., Woodford, C., Sitler, R.W., Salvi, R., 1973. Evoked-response audibility curve of the chinchilla. J. Acoust. Soc. Am. 54, 1099-1101.

Hofstetter, P., Ding, D., Powers, N., Salvi, R.J., 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, Hear. Res. 112, 199-215.

Kimberley, B.P., Hernandi, I., Lee, A.M., Brown,D.K., 1994. Predicting pure tone thresholds in normal and hearing-impaired ears with distortion product emissions and age. Ear Hear. 15, 199-209.

Le Calvez, S., Avan, P., Gilain, L., and Romand, R., 1998. CD1 hearing-impaired mice. I: Distortion product otoacosutic emission levels, cochlear function and morphology, Hear Res. 120, 37-50.

Martin, G.K., Jassir, D., Stagner, B.B., and Lonsbury-Martin, B.L., 1998. Effects of loop diuretics on the suppression tuning of disrotion-product otoacoustic emissions in rabbits. J. Acoust. Soc. Am. 104, 972-983.

Mills, D., 2003. Differential responses to acoustic damage and furosimide in auditory brainstem and otoacoustic emission measures. J. Acoust. Soc. Am. 113, 914-924.

Salvi, R.J., Ahroon, W.A., Perry, J.W., Gunnarson, A.D., Henderson, D., 1982. Comparison of psychophysical and evoked-potential tuning curves in the chinchilla.

Am. J. Otolaryngol. 3, 408-416.

Schuknecht, H.F., 1953. Lesions of the organ of corti. Trans. Am. Acad. Opthal. Otolaryng. 57, 366-383.

Stover, L., Gorga, M.P., Neely, S.T., 1996. Toward optimizing the clinical utility of distortion product otoacoustic emission measurements. J. Acoust. Soc. Am. 100, 956-967.

Subramaniam, M., Salvi, R.J., Sponger, V.P., Henderson, D., Powers, N.L., 1994. Changes in distortion product otoacoustic emissions and outer hair cells following interrupted noise exposures. Hear. Res. 74, 204-216.

Table 1

Index of determination (r^2) derived from the scatter plots of individual animal PTS and OHC loss data for three DPOAE variables [postexposure DPOAE level, pre- minus postexposure DPOAE level (ΔDPOAE), and postexposure DPOAE/noise floor difference (SNR)] at each test frequency (kHz).

PTS vs kHz	Post DPOAE	Δ DPOAE	SNR
1	0.37	0.32	0.25
2	0.63	0.54	0.58
4	0.65	0.57	0.64
8	0.79	0.74	0.72

OHC vs. kHz	Post DPOAE	Δ DPOAE	SNR
1	0.31	0.29	0.23
2	0.50	0.42	0.51
4	0.49	0.39	0.53
8	0.59	0.53	0.59

	OHC vs. PTS	PTS vs. OHC
kHz		
1	0.45	0.44
2	0.66	0.62
4	0.61	0.58
8	0.59	0.58

Table 2

Sensitivity and specificity values (percent) for PTS and OHC loss at each test frequency for the post exposure DPOAE level variable at L_1 = 65 dB SPL. The criterion for a normal auditory system was set at: PTS $\leq$ 5 dB and OHC loss $\leq$ 5%.

	PTS		OHC	
	Sensitivity	Specificity	Sensitivity	Specificity
kHz				
1	36	93	36	84
2	61	88	68	83
4	67	70	74	66
8	75	80	74	49
Mean	60	83	63	71
s.d.	17	10	18	17

Table 3

The probability for the post DPOAE level to correctly predict (in percent) the presence of a normal ($\leq$ 5 dB PTS and $\leq$ 5% OHC loss) or an abnormal ear using the 5th percentile of the normal preexposure distribution for different PTS and OHC loss criteria at the L_1 = 65 dB SPL primary level.

	PTS		
	Normal	Abnormal	
	PTS $\leq$5 dB	5 < PTS $\leq$ 30 dB	PTS > 30 dB
kHz			
1	93	24	92
2	88	32	96
4	70	40	95
8	80	53	99

	OHC loss			
	Normal	Abnormal		
	OHC loss $\leq$ 5%	5% < OHC loss $\leq$ 40%	OHC loss > 40%	OHC loss > 60%
kHz				
1	84	22	70	82
2	83	45	89	92
4	66	32	90	92
8	49	49	95	100

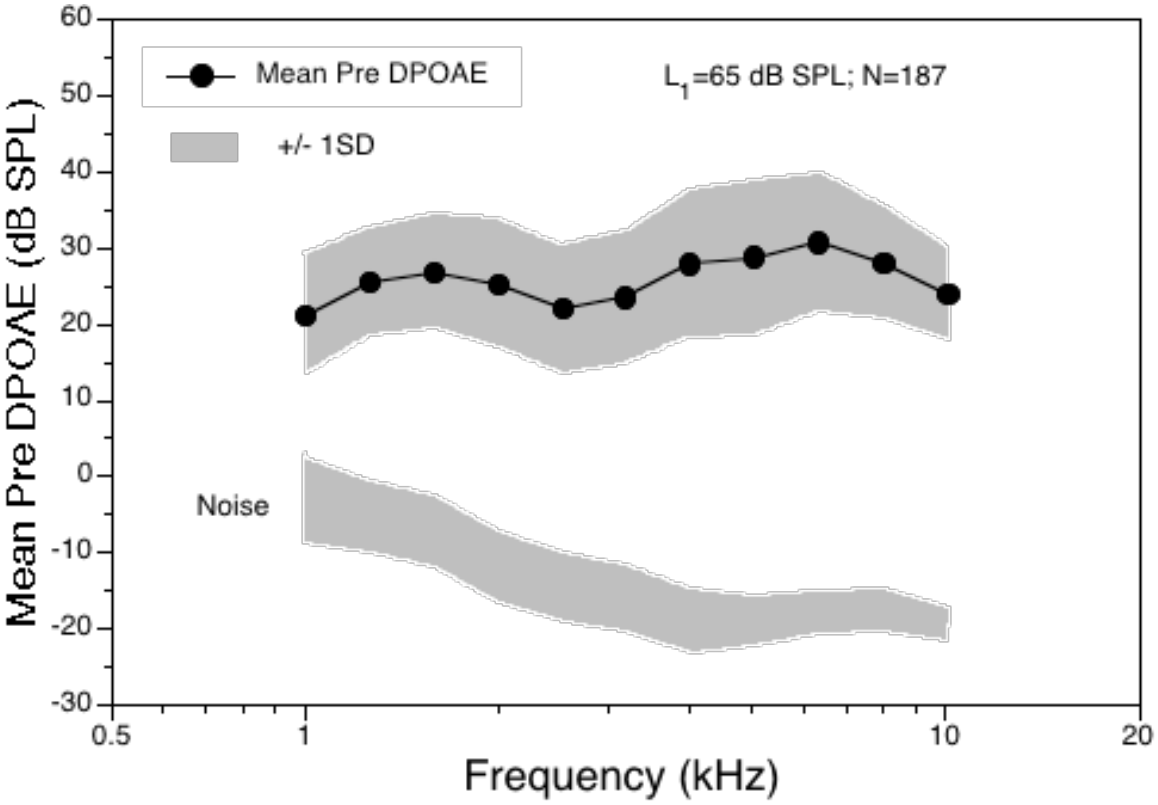

Fig. 1. Mean DPOAE of the subject population (n=187) as a function of frequency prior to any noise exposure. Each datum point represents the mean DPOAE level measured over each adjacent one-third octave band.

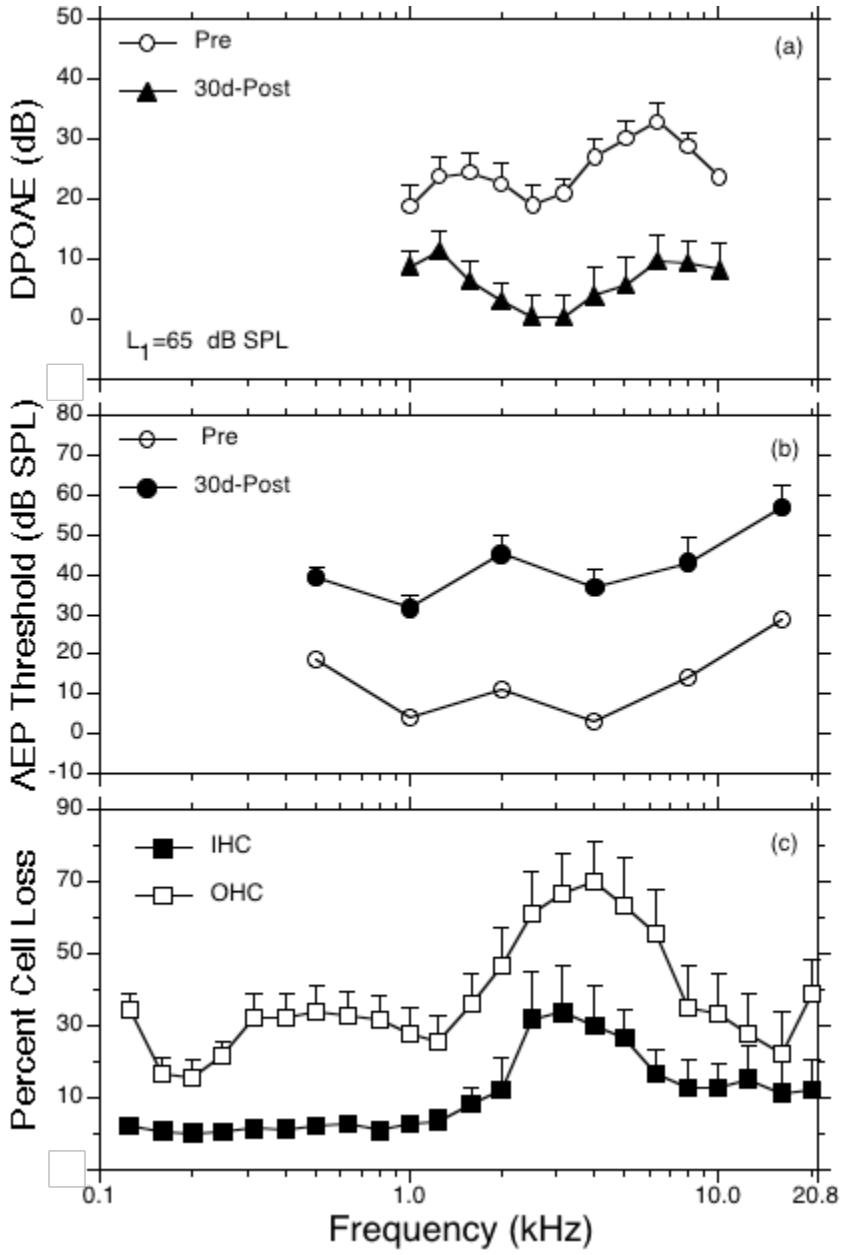

Fig. 2. Group mean (N = 11) (a) DPOAE level and (b) AEP audiograms measured at the indicated times for the animals exposed to a non-Gaussian noise presented at 100 dB (A) for 5 days. Each DPOAE datum point represents the mean DPOAE level measured over each adjacent one third octave band and is plotted as a function of f_2. (c) The group mean cochleogram. Each datum point represents the mean percent IHC or OHC loss measured over one-third octave band lengths of the cochlea. (Bar = standard error).