Recommended Procedure

Clinical Application of Otoacoustic Emissions (OAEs) in Children and Adults

Date: February 2023
Review date: February 2027

BSA OD104-120 v2 (01/09/2022, review 13/02/2023)

General foreword

This document presents Practice Guidance by the British Society of Audiology (BSA). This Practice Guidance represents, to the best knowledge of the BSA, the evidence-base and consensus on good practice, given the stated methodology and scope of the document and at the time of publication.

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Published by the British Society of Audiology

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Declarations of interests

- Declarations of interests by the authors: ERA Training & Consultancy Ltd offer training courses in ERA testing, training and accreditation in ABR peer review and offer clinical support for centres performing ABR testing. Diagnostic Group, Demont design and sell OAE equipment through Interacoustics, Maico and GSI.

Shared Decision-Making

It is implied throughout this document that the service user should be involved in shared decision-making when undertaking audiological intervention, receiving subsequent information and understanding how it will impact on the personalisation of care. Individual preferences should be taken into account and the role of the clinician is to enable a person to make a meaningful and informed choice. Audiological interventions bring a variety of information for both the clinician and the patient which can be used for counselling and decision-making regarding technology and anticipated outcomes.

Contents

1. Abbreviations

AABR	Automated Auditory brainstem response (screening test)
ABR	Auditory brainstem response (full assessment/ diagnostic test)
ANSD	Auditory Neuropathy Spectrum Disorder
AN	Acoustic Neuroma
BM	Basilar Membrane
CR	Clear response
DPOAE	Distortion-product Otoacoustic Emissions
ME	Middle ear
MEE	Middle ear effusion
MRSA	Methicillin-resistant Staphylococcus aureus (bacteriological infection)
NCR	No clear response
NHSP	Newborn Hearing Screening Programme (England)
NICU/SCBU	Neonatal intensive care unit / Special care baby unit (terms used interchangeably). The NHSP NICU/SCBU screen protocol applies to those babies on the unit for ≥48 hours.
NIHL	Noise-induced hearing loss
NOHL	Non-organic hearing loss
OAE	Otoacoustic emissions
OHC	Outer hair cell
PCHI	Permanent Childhood Hearing Impairment - defined here as ≥40dBHL averaged over 0.5, 1, 2 & 4 kHz pure tone audiometry thresholds. It includes both sensorineural and permanent conductive impairments.
SFOAE	Stimulus-frequency Otoacoustic Emissions
SNHL	Sensorineural hearing loss
SNR	Signal-to-noise ratio
SOAE	Spontaneous Otoacoustic Emissions
TEOAE	Transient Evoked Otoacoustic Emissions
TW	Travelling wave
VRA	Visual Reinforcement Audiometry

2. Introduction

2.1. Development of the recommended procedure

The development of this recommended procedure was conducted by the members of the Electrophysiology Special Interest Group (EPSIG) and has been developed in accordance with BSA Procedure for Processing Documents (2003).

2.2. Background and aims

Prof. David Kemp first reported OAEs in 1978 (Kemp, 1978). They are sounds of cochlear origin that are recorded through a microphone placed in the external ear canal. The motion of the cochlea's sensory outer hair cells (OHCs) produces them as they dynamically respond to auditory stimulation (Kemp, 2002). This stimulation has to pass through the middle ear to reach the inner ear where the energy associated with activity of the outer hair cells travels in the reverse direction through the middle ear to be recorded as OAEs in the external ear canal. Therefore, successful stimulation and detection of OAEs signifies a high degree of functioning of both the middle and inner ear when recording from a patent ear canal.

OAEs are used throughout the world for newborn hearing screening, including in the UK (Davis et al, 1997; Norton et al., 2000; Chapchap & Serge, 2001; Uloziene & Grandori, 2003; Stevens et al., 2014; Rissmann et al., 2018). Research findings also support other clinical applications in children and adults, such as confirmation of hearing status as part of a test battery, diagnosis of spurious and false hearing loss (HL), identification and diagnosis of auditory neuropathy spectrum disorder (ANSD), evaluation of central control mechanisms, and also longitudinal monitoring and assessment of the effect of ototoxic drugs.

There are at least four misconceptions related to the clinical application of OAEs:

1. *OAEs are only useful for Newborn Hearing Screening:* Though this is the commonest clinical application, OAEs also have a significant role in the diagnosis and management of many pathologies, affecting all of the age groups seen in audiology.
2. *Diagnostic OAEs can be analysed only as 'CR' or 'NCR':* this is appropriate for the screening approach. However, detailed diagnostic analysis can provide much more information that can be clinically useful e.g. as part of a diagnostic test battery or when monitoring different changes in frequency responses to indicate progressive cochlear damage.
3. *TEOAEs and DPOAEs provide the same information:* This is broadly correct for screening applications but not correct for diagnostic applications. Each present a different aspect of OHC function as they are generated through different mechanisms. They can therefore sometimes complement each other.
4. *OAEs provide the same information provided by pure-tone audiometry (PTA):* OAEs and pure tone audiometry are very different measures of auditory function. Although normal OAEs are often associated with normal hearing sensitivity and abnormal OAEs with hearing loss, abnormal OAEs may be recorded in persons with normal pure tone thresholds and, in contrast, normal OAEs may be recorded in persons with hearing loss. OAEs and pure tone audiometry provide complimentary

information. It is also worth noting that OAEs are not a true measure of "hearing". OAEs along with other objective auditory measures offer a cross-check for diagnostic behavioural audiological testing.

This recommended procedure aims to clarify the measurement, analysis, and interpretation of OAE findings in different clinical settings and populations and to provide guidance for common clinical applications of OAEs, including:

1) Hearing screening of children or adults
2) Hearing monitoring to assess cochlear damage caused by ototoxic agents or noise (including hearing conservation programmes)
3) Diagnostic assessment or differential diagnosis of patient populations at risk for cochlear dysfunction, such as:

   a. Sensory versus neural auditory dysfunction in auditory neuropathy spectrum disorder (ANSD), auditory processing disorder (APD), acoustic neuroma (AN)
   b. Non-organic (false) hearing loss
   c. Non-cooperative and difficult-to-test patients

A standardised method should be used for each of these cases in order to allow for clear, comparable and accurate interpretation of outcomes across services and to establish the use of this tool within the audiological battery of tests.

2.3. Scope

This recommended procedure offers guidelines for selected screening and diagnostic applications of OAEs in paediatric and adult populations. The development and operation of newborn hearing screening programmes, including universal newborn hearing screening, is outside the scope of this document. However, test parameters for newborn hearing screening with OAEs is addressed briefly under Section 6 to 8 of this document. These guidelines do not cover all evidence-based clinical applications of OAEs or OAE applications in all disorders or pathologies. Readers interested in exploring this further are advised to visit text books such as *Otoacoustic Emissions: Principles, Procedures and Protocols* (Dhar & Hall, 2018) or *Otoacoustic Emissions: Clinical applications* (Robinette & Glattke, 2007).

These guidelines focus on the technical procedure of carrying out and reporting results of transient-evoked OAEs (TEOAEs) and distortion-product OAEs (DPOAEs) testing, as these are the most clinically applicable OAE test types at the present time.

The following measurements and interpretation are outside the scope of this document;

- spontaneous OAEs and stimulus-frequency OAEs
- contralateral suppression of OAEs to assess inhibitory efferent auditory pathways (see Chapter 9 of Dhar & Hall, 2018 for further information).

Please note also that the use of OAEs in newborn hearing screening programmes is not specifically addressed here however, some of this document will be valuable in gaining a better understanding of OAE use in screening.

3. Types and classifications of OAEs

3.1. Stimulus-based classification

The original and conventional classification of OAEs was based on whether they required a stimulus to evoke an OAE response or whether they were present spontaneously.

1. **Spontaneous OAEs (SOAEs):** OAEs recorded in the external ear canal without presentation of an external stimulus.
2. **Evoked OAE:**

    a. **Transient-evoked OAEs (TEOAEs):** OAEs evoked by the presentation of a broadband click/ Chirp or less commonly a tone burst stimulus,
    b. **Distortion-Product OAEs (DPOAEs)** : OAEs evoked by the presentation of two closely linked simultaneously presented pure-tones (f1 and f2),
    c. **Stimulus-frequency OAEs (SFOAEs):** OAEs evoked by a pure-tone stimulus and are detected by the vectorial difference between the stimulus waveform and the recorded waveform using methods such as the interleaved suppression technique.

This simple classification is widely used, however it implies that all OAEs provide the same information in relation to cochlear function and only differ by the type of evoking stimulus (Probst, Lonsbury-Martin & Martin, 1991), but this is not the case.

3.2. Source-based classification

Evoked otoacoustic emissions arise from a mix of two fundamentally different mechanisms/sources namely, linear coherent reflection and non-linear distortion mechanisms (Shera and Guinan, 1999):

Reflection source: This is the main generation model for TEOAEs and SFOAEs at low levels, where emissions are generated by the reflection of the travelling wave from the normal yet imperfectly alignment of OHCs.
Distortion source: This is the main generation model for DPOAEs. This is where the areas of the basilar membrane stimulated by two tones (the lower frequency 'f1' with stimulus level L1 and the higher frequency 'f2' with stimulus level L2) overlap, multiple 'intermodulation' distortions are generated. The largest and most commonly recorded being 2f1-f2 (figure 1). This figure illustrates the mix of linear coherent reflection and non-linear distortion mechanisms involved in generating a DPOAE.

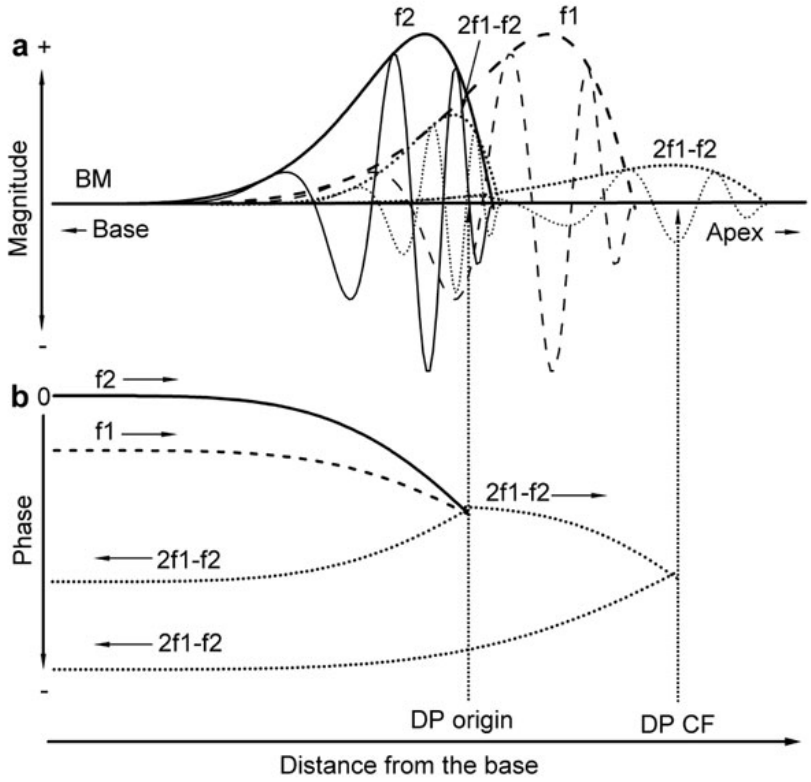

Figure 1: Showing the theory of the propagation of the DPOAE in the cochlea. (a) Waveforms and envelopes of basilar membrane (BM) vibration at f1, f2, and 2f1 - f2; (b) equivalent phase curves. The acoustic energy at the DPOAE frequency of 2f1-f1 is generated near the "DP origin", where f1 & f2 overlap, and spreads in both directions along the BM. The backward traveling wave (TW) vibrates the stapes and appears as the OAEs in the ear canal. The forward-TW is partially reflected near DP characteristic frequency place (DP CF – 2f1-f2) and forms a second backward TW. The phase of the backward traveling waves shows a positive relationship with the distance from the base (Ren, 2004).

TEOAEs are related to the strength of the travelling wave which depends on electromotility (expansion or contraction of the OHCs). DPOAEs demonstrate the equally important non-linear aspect of OHC physiology (e.g. transduction) (Dhar & Hall, 2018). Clinically, this means that each of these types of OAEs provide slightly different information and so when tested together may give more detailed information regarding the integrity of the cochlear function.

4. Equipment selection

4.1. Standards

The relevant British Standards relating to the technical construction and characteristics of OAE equipment are published in the BS EN 60645-6:2010 document (http://shop.bsigroup.com). This is identical to the International Electro technical Commission (IEC) 60645-6:2009 document. Instruments are divided into two categories, for screening and diagnostic purposes in these standards. As some national screening programmes pre-date these standards, users should refer to the technical requirements for screening equipment as specified by their own programme. Currently, there are no American National Standards Institute (ANSI) standards for OAE equipment.

4.2. Types of available equipment

Commercially available equipment for both TEOAEs and DPOAEs can be classified as either 'screening' or 'diagnostic' and often one instrument can perform all functions (both screening and diagnostic TEOAEs and DPOAEs).

With screening OAE equipment, minimal control is required from the operator with 'automatic decision making' regarding the stimulus waveform and the response waveform. The operator often cannot view the stimulus or the response waveform. The equipment reports either a 'Pass' or 'Refer' when minimal pre-set stop criteria are reached. Screening OAE equipment is designed so recording is fast (e.g. DPOAE screening equipment may only collect OAE data for 2 frequencies per octave).

With diagnostic OAE equipment, the operator has more control over the settings of the equipment. Also, the operator can view the stimulus and response waveform, and other parameters such as noise levels, the number of artefacts, and the artefact rejection limit. The operator can then decide when to start and finish recording or to extend test time to reach the desired recording quality encapsulated in the signal-to-noise level ratio (SNR) parameter. Testing for diagnostic purposes typically takes longer than screening tests as 5 or 6 half octave bands maybe assessed in TEOAE diagnostic testing and in DPOAE diagnostic testing > 16 points per octave may be analysed. Higher SNRs are also desirable for the most accurate recording of an OAE level.

5. Preparation

5.1. Equipment preparation

5.1.1. Stage B calibration

Equipment should have a documented (Stage B) calibration record on a timely basis as per manufacturer recommendation (e.g. annually). Regular safety and electrical testing is also required in accordance with local protocols.

5.1.2. New Probe calibration

New probes should be set up and checked as per the manufacturer instructions. Before using an OAE probe for the first time it is recommended to perform a probe calibration check to keep as a reference of the probe's original performance for comparison over time. From then on, it is recommended that regular probe calibration checks are performed frequently. Refer to manufacturers guidelines to identify the tolerances for accepting a correctly functioning probe.

5.1.3. Stage A checks

Probes are vulnerable to blockage by wax and debris as well as mechanical damage to the speaker and microphone. Frequent Stage A checks, defined below are required, preferably prior to each clinical test session, after cleaning or servicing of the probe and whenever a fault is suspected or unexpected results are obtained, to ensure that the equipment is producing consistent outcomes. Ideally the stage A checks should be carried out in a acoustically quiet surroundings.

The Stage A check should include;

- a visual inspection for any obvious signs of damage of the device or probe or probe blockage.
- a probe test to check probe performance (i.e. a measure of the loudspeaker outputs and microphone sensitivity within its usual test cavity and comparison against the initial measures made at delivery with accepted tolerances as per manufacturer's recommendation).
- an occlusion test, where possible, to ensure no artefactual 'false OAE' is being generated in the recording system and low levels of probe "noise" floor.
- a test recording in a test cavity to ensure there is no 'false OAE' present in either the recording or stimulating systems
- a real ear biological check with a known response to confirm adequate function.

5.1.4. Coupler tubes

Probe performance can normally be confirmed using the manufacturers probe test facility e.g., probe cavity test. Performance can degrade if the coupler tubes are blocked with debris or wax.

5.1.5. OAE probe tips and precautions against cross infection

The probe tips provided by the manufacturer must be used with the appropriate instrument. Use of alternative tips affects the acoustics, stimulus settings, recording output, and increases chances of ear discomfort, dislodging or impaction of that tip in the ear canal. Disposable probe tips should be discarded after a patient has been tested, in order to avoid cross infection and maintain hygiene requirements for health and safety. However, if the manufacturer states that repeated use is acceptable, appropriate cleaning procedures between patients must be applied to meet local infection control guidelines.

If a patient with a Patient Safety Alert for an infection with a biological hazard such as MRSA needs to be tested, OAE recording can be performed, but the equipment needs to be appropriately covered according to the local health and safety protocols and after recording is complete the equipment needs to be cleaned

according to local health and safety protocols and replacement of the coupler tubes is recommended where possible.

5.2. Test environment and recording conditions

5.2.1. Noise

Sources of noise can be generated acoustically in the environment or produced physiologically by patients. Although OAEs probes are not sensitive to electrical noise, high electrical and radio fields could induce noise into the sensitive OAE detection circuits. Proximity to powerful electric installations should be avoided.

Ambient noise

OAEs can be recorded effectively in a quiet room and do not necessarily need to be performed in a sound-treated room (Gorga et al., 2000, Cone-Wesson et al., 2000). However, efforts must consistently be made to minimise sources of ambient acoustic noise, e.g. closing the door to the test room, requesting that persons in the test room refrain from talking, turning off the power for any unnecessary noisy equipment/ lights/fans, and locating the patient away from any noise sources. Continuous noise, such as air conditioning, ventilation, and road traffic noise may be more problematic than occasional short-lived noise that is more likely to be rejected by the artefact reject system and reduced through additional signal averaging (Kemp, 2002). Noise usually impacts more on measurement of OAEs for lower frequency stimuli (< 1500 Hz). A deep well-fitted probe is important to achieve the target stimulus level within the ear canal and to minimize adverse effects of external noise whilst enhancing the OAE signal. The noise rejection level should be set appropriately. Setting high rejection levels in the presence of background noise can be counter-productive and should be avoided.

Patient generated noise

It is important to take steps to minimize patient generated noise. Adult and older paediatric patients should be asked to remain still and quiet and to avoid talking or chewing. Movement of the probe wire over clothing can also cause noise. Optimal OAE recordings are made from infants and young children who are not chewing, sucking, or crying. However, it is often possible to record clinically useful OAEs under less-than-ideal test conditions.

5.3. Patient / Carer instructions

OAE recording does not require the patient to be awake, conscious, or provide behavioural responses to the stimuli. All that is required is to be able to fit the probe in the patient's ear canal securely and for the patient to remain still and quiet for the duration of testing. Babies are best tested while sleeping or, if awake, in a very settled state.

Prior to initiating OAE recording, the operator should provide the patient with a brief explanation of the procedure and what is expected of the patient:

1. A small probe with a soft tip will be placed into the external ear canal.
2. There is no need for the patient to listen to the sounds or to tell the operator if the patient hears the sounds. The machine will automatically record sounds produced by the ears.

3. The patient only needs to sit quietly and to relax while the test is underway.
4. The patient is reminded to as much as possible refrain from moving, speaking or chewing during the procedure.

5.4. Probe fitting

A good probe fit is an essential requirement for obtaining accurate recordings of OAEs. A good probe fit with deep probe insertion reduces the ambient noise, seals the stimulus in the ear canal, minimizes stimulus ringing, avoids the need to hold the probe and increases the probability of measuring an OAE with low background noise.

The main factors that can affect probe fitting include:

- Choosing the correct size for the probe tip by closely inspecting the size of the ear canal opening. Manufacturers of OAE equipment provide a range of probe tip sizes suitable for neonatal, paediatric and adult ear canals.
- Accurate consideration of the shape and angle of the ear canal either by visual inspection and/or otoscopy.
- Noting and removing as indicated debris, foreign objects, and excessive cerumen in the ear canal.
- Adequate technical skill and clinical experience of the person performing the OAE test.

6. TEOAE measurement

6.1. Stimulus parameters

Table 1 shows typical stimulus and recording parameters for measurement of TEOAEs. Selected parameters may vary with devices from different manufacturers.

Stimulus parameters	Recommended Setting
Type	Click
Duration	80- µs pulse
Level	81 – 87 dB peSPL (e.g. 0.3Pa)
Rate	50 - 80/s
Polarity	Alternating polarity and amplitude for non-linear detection
Recording parameters	Recommended Setting
Analysis time	12 - 20 ms
Frequency scale	0 Hz- 6000 Hz
Frequency resolution	50-80 Hz depending on stimulus rate
Noise rejection threshold	~ 47 dB SPL

Sets of averaging buffers	Verification method: Alternate collection of two averages (A and B). Response = mean of A+B and noise equal A-B (actually (A-B/(√ 2)
Measurement bandwidth	Measurement band width: Half octaves
Amplitude of response	≥ 0 dB SPL (A + B) with a minimum signal level of -5dB SPL per half octave band
Amplitude of noise	≤ -5 to -20 dB SPL (A – B) (ideally)
Acceptable SNR	≥ 6 dB (response signal – noise) for each half octave band
Number of accepted sweeps/buffer	Minimum of 40 (260 are commonly used in diagnostic TEOAE)
Test time	Can be preset e.g. 90 sec or 5 min
Frequency range	1000 - 4000 Hz (commonly used) 500 – 5500 Hz (currently available in most commercial devices)

Table 1: Typical stimulus and recording parameters for TEOAE testing *(table adapted and modified from Dhar and Hall, 2018) – see Appendix D for UK Screening Protocols*

6.1.1. Stimulation level

The recommended stimulation level for click-evoked TEOAE measurement is between 81 and 87 dB peak equivalent sound pressure level (dB peSPL) with an average target level of 84 dB peSPL. These levels typically evoke a robust TEOAE if hearing thresholds are 20 dB HL or better (Kemp, 1978; Norton et al., 2000; Glattke & Robinette, 2002).

Infants have significantly smaller ear canals compared to older children and adults. As a result, sound pressure level of the stimulus will be higher if the instrument calibration does not adjust the stimulus levels according to the ear canal size of the ear being tested. The optimal selection of the 'neonate setting' and use of the 'auto-adjust' feature will allow for the ear canal size to be accounted for. However, caution needs to be taken in trying to use the 'auto-adjust' feature to readjust the stimulus level automatically rather than securing a deep probe fit. This feature aims to compensate for the difference in ear canal size but does not compensate for inappropriate probe fitting and will not ensure achievement of a true repeatable stimulus level.

6.1.2. Click stimulus waveform

Ideally, a clear positive and negative deflection over a maximum period of 1ms, followed by a straight line to indicate the absence of oscillations (or ringing) of the waveform, is required (
Figure 2). Figure 3 highlights the relationship between the stimulus and response waveforms showing that the stimulus lasts 2.5 ms and the response recording window starts at 2.5 ms (or in some cases 4 ms, depending on the clinical application). The stimulus amplitude is about 1000 times larger than the response, as evidenced by the scale units used (Pa vs. mPa). The high frequency response occurs first since the base of the cochlea is

closer to the recording probe.

Excessive 'ringing' of the stimulus beyond 2.5 ms may lead to artefacts that may be incorrectly interpreted as a high frequency TEOAE response (as seen in Appendix C). An optimal probe fit (correct probe tip size, angle and depth of insertion) can minimise ringing and be confirmed by examining the stimulus (click) waveform and the ear canal response/probe check. The probe fitting should be adjusted so that 'probe check' is as flat as possible to 6000 Hz. This response is affected by ear canal shape and size. Some deviation from flat is normal e.g., neonates can show a peak at 2000 - 3000 Hz due to their ear canal resonance (Figure 4). Strong resonances (sharp peaks) increase the risk of artefactual responses and should be avoided.

'**Stimulus Stability'** demonstrates any change in probe fit from the start of the test. The closer this stimulus stability is to 100% the more confident the tester is that the stimulus remained stable over the duration of the recording. Users should obtain guidance from device manufacturers regarding the acceptable ranges of stimulus stability for their specific TEOAE device (usually ≥ 85% is acceptable).

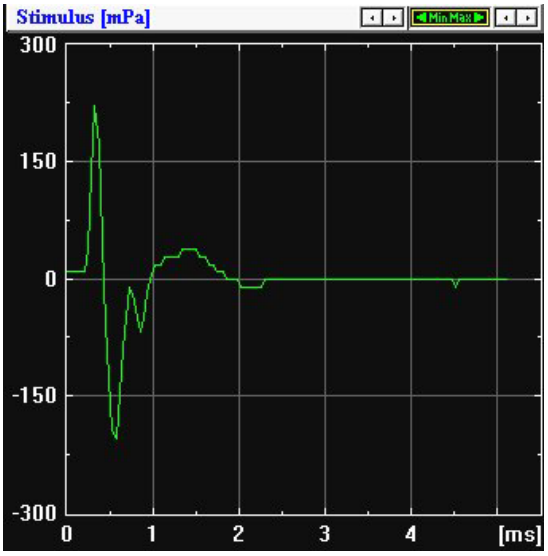

Figure 2: Ideal shape of a click TEOAE stimulus
(http://www.otoemissions.org/index.php/en/basics-of-oaes/teoaes/3-teoaes-test-procedures)

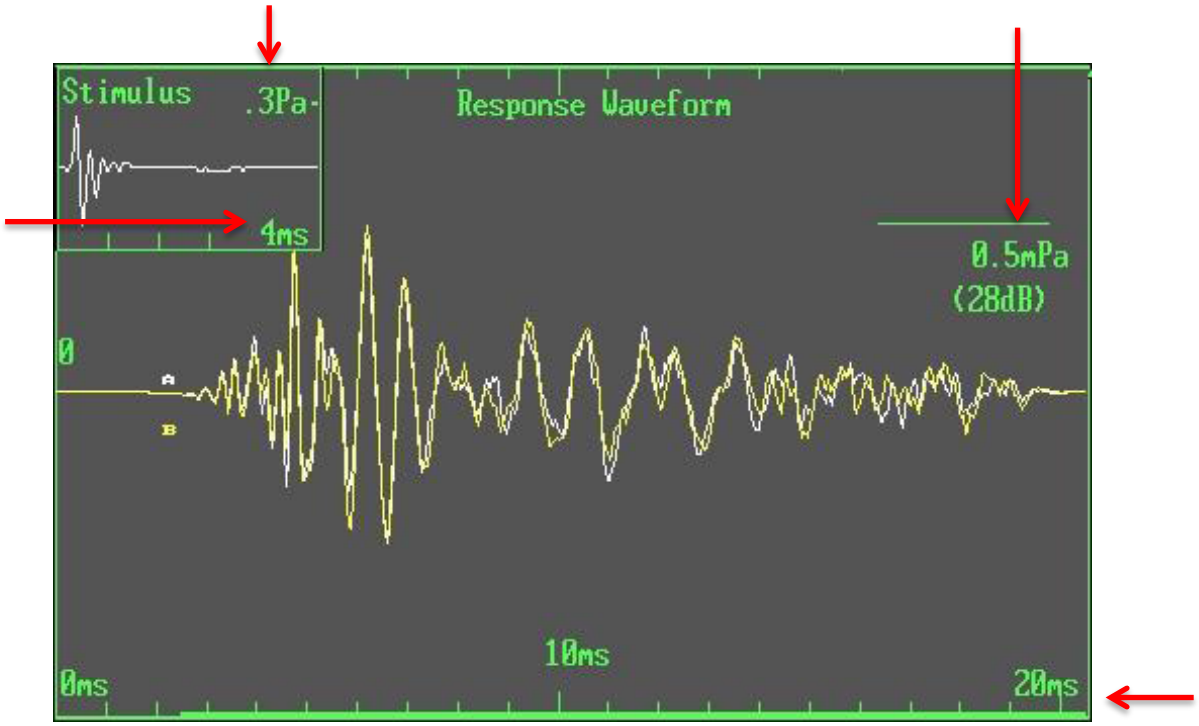

Figure 3: Stimulus and response waveform windows highlighting that the response is 1000 times smaller than the stimulus (Pa *vs.* mPa) and that the stimulus and response are separated by time (stimulus window 0- 4ms and response window recordings start at 4ms to 20ms) *(Picture courtesy of Otodynamics Ltd.)*

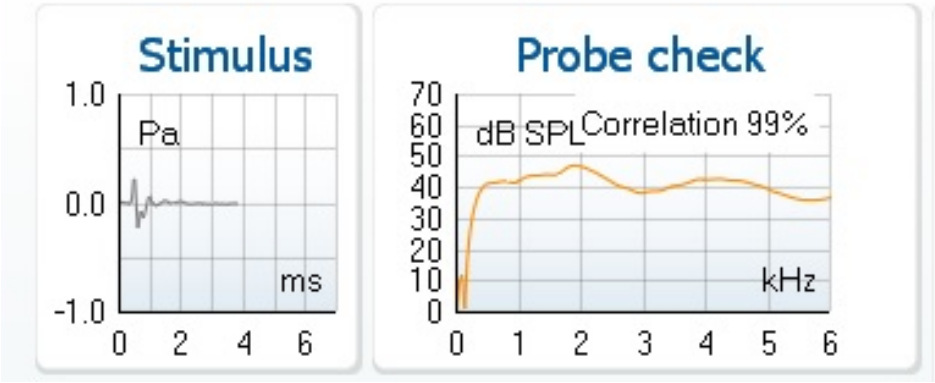

Figure 4: Display windows of the click stimulus (left panel) and the stimulus waveform in a subject's ear canal (right panel labelled 'Probe check'). These panels are used to confirm that a satisfactory stimulus is delivered as a consequence of appropriate probe fitting. *(Picture courtesy of Interacoustics Ltd.)*

6.1.3. Recording window

To prevent stimulus artefacts in the analysis TEOAE window, the start of data collection with clinical devices is delayed for 2.5 - 4 ms following the click stimulus. This will inevitably lead to the limitation in ability to record the higher frequency components of the response. The length of the data collection time will vary depending on the stimulus rate used. The end of data collection and analysis window is typically 12 ms to 20 ms. The longer window length allows more low frequency (<=1kHz) OAEs to be collected due to their longer latency, but the test time is longer. The shorter window can be used to minimise testing time especially where there is low frequency noise (e.g., infant screening) or where only higher frequencies are of clinical interest (e.g., ototoxic monitoring).

6.2 TEOAE analysis and interpretation

Responses to sets of clicks are sub-averaged and alternately sent to two different buffers (A & B). After the required sub-averages have been collected in each buffer, the test is complete and two TEOAE waveforms are overlapped and displayed on the screen (Response waveform window). The extent to which the two waveforms are correlated is often expressed as a "Reproducibility" percentage (provided by correlation of A & B). The term repeatability could also be used to describe the correlation or agreement between TEOAE waveforms. The TEOAE level is displayed as well as the level of corresponding noise (Gorga et al., 1993). Good reproducibility of the entire TEOAE waveform (e.g., >70%) is desirable but not generally used any more as a response criterion. It has given way to frequency band analysis because an apparently poorly reproduced TEOAE can still contain highly reproducible signals within specific half octave frequency bands.

In healthy ears a TEOAE is generally considered to be "Clear Response" (CR) when it has:

- An amplitude that may vary from ~ -10 dB SPL to ~ +30 dB SPL and
- A signal-to-noise ratio (SNR) of ≥ 6 dB SPL

This conclusion is made for each frequency band tested. It is most common to interpret TEOAEs from their frequency analysis. Typically, a 1/2 octave analysis is provided. Adequate reproducibility is assessed by the signal to noise ratio in each band. The strength of OAE in each band is measured in dBSPL and will be lower than the dBSPL of the entire waveform. Depending on whether this is considered an overall acceptable response is based on the clinical application of TEOAEs. For example, in newborn hearing screening, achieving these outcomes in two or more half octave bands may be considered a 'pass'. However, for an application such as monitoring for noise-induced hearing loss, changes in absolute level in one or more of ½ octave bands relative to a baseline reference measurement could indicate OHC noise damage.

It is appropriate to conclude:

- "No Clear Response (NCR)" outcome when adequately low noise levels (≤ -5 dB SPL) are achieved and the required TEOAE amplitude and SNR scores are not achieved.
- "Inconclusive" outcome when recording conditions are not adequate to allow for low noise levels to be reached e.g. due to noisy or incomplete recordings or a poor probe fit. In such conditions it cannot be determined whether OAEs are NCR or CR but obscured by noise.

Amplitudes for TEOAEs, as well as DPOAEs, are larger in infants than adults contributing to the application of OAEs in hearing screening (Kramer, 2013).

In general, TEOAEs will not be detected for patients with a cochlear hearing loss involving outer hair cell dysfunction greater than 35 dB HL, although this is dependent upon the hearing loss configuration (e.g. an OAE can be obtained with good low frequency hearing in the presence of a high frequency hearing loss). TEOAEs are present in 99% of cases when all audiometric hearing thresholds are better than 20 dB HL (Robinette, Cevette, & Probst (2007). However, TEOAEs may be NCR for persons with subtle cochlear dysfunction who have hearing thresholds within normal limits. Similarly, TEOAEs are NCR for cochlear hearing loss involving outer hair cells when hearing thresholds are greater than 40 dB HL. TEOAEs are typically abnormal (abnormally reduced in amplitude or NCR) in patients with a cochlear hearing loss involving outer hair cells and pure tone thresholds between 25 and 35 dB HL. Also, it's important to note here that normal TEOAEs may be recorded in persons with varying degrees of hearing loss associated with inner hair cell dysfunction, neural auditory dysfunction, or false (non-organic) hearing loss.

7. DPOAE measurement

7.1. Stimulus and recording parameters

DPOAE stimulation requires the simultaneous presentation of two pure-tone frequencies (f1 is the lower frequency primary tone at level L1 and f2 is the higher frequency primary tone at level L2). These are closely spaced and typically set at a frequency ratio of 1.22. This maximises the amplitude of the DPOAE response. The non-linear OHC response which generates DPOAE is initiated in the region of the basilar membrane where f1 and f2 overlap and is maximum near to the f2 tonotopic place. Most distortion travels directly back to the ear canal to create DPOAE but some reflects back from the basilar membrane place that codes the distortion-product frequency, and this constitutes a second 'interfering' source of DPOAE. The '$2f_1 - f_2$' DP component is the most prominent DP recorded in humans (Kim 1980; Shera & Guinan 1999).

The following example clarifies how that cubic difference DP frequency tone is calculated: if f1 = 1000 Hz and f2 = 1200 Hz, then 2f1-f2 = 2(1000) – 1200 = 2000 – 1200 = 800 Hz Figure 5). This DP is usually at 50 dB lower level than f1 with amplitudes normally ranging between -10 and 35 dB SPL.

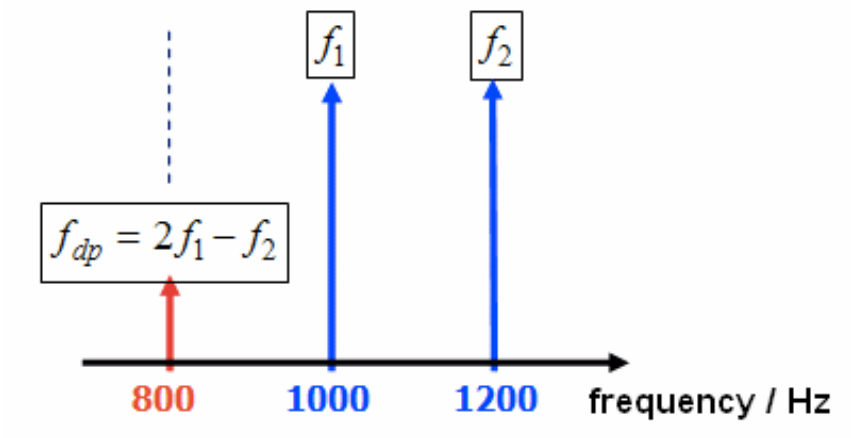

Figure 5: Example of a DPOAE at 2f1-f2 evoked by two pure tones separated by a ratio of 1.2 with f1 = 1000 Hz and f2 = 1200 Hz. The DPOAE occurs at a frequency fdp of 800 Hz (source: www.ptb.de)

Stimulus levels of L1 = 65 and L2= 55 or 50 dB are typically used in clinical DPOAE recordings (Petersen et al., 2017). DPOAE amplitudes elicited with these levels are usually robust in persons with normal outer hair cell function yet abnormally reduced in persons with outer hair cell dysfunction. Lower stimulus levels may enhance sensitivity of DPOAEs to cochlear dysfunction for selected clinical applications, e.g., monitoring ototoxicity. The use of levels > 65 dB SPL and symmetrical protocols (e.g. L1 = L2 = 70 dB SPL) reduce sensitivity of DPOAEs to cochlear dysfunction and may be associated with artefact components in recordings.

DPOAEs can be recorded for f2 stimulus frequencies within the range of 500 Hz to over 10,000 Hz. The frequency of the DP recorded clinically (2f1-f2) is lower than the f2 or f1 frequency. The range of test frequencies in clinical DPOAE recording varies depending on the clinical application and equipment manufacturer. The DPOAE level is plotted against the f2 frequency in the 'DPgram' as this frequency best represents the originating place in the cochlea (Figure 6).

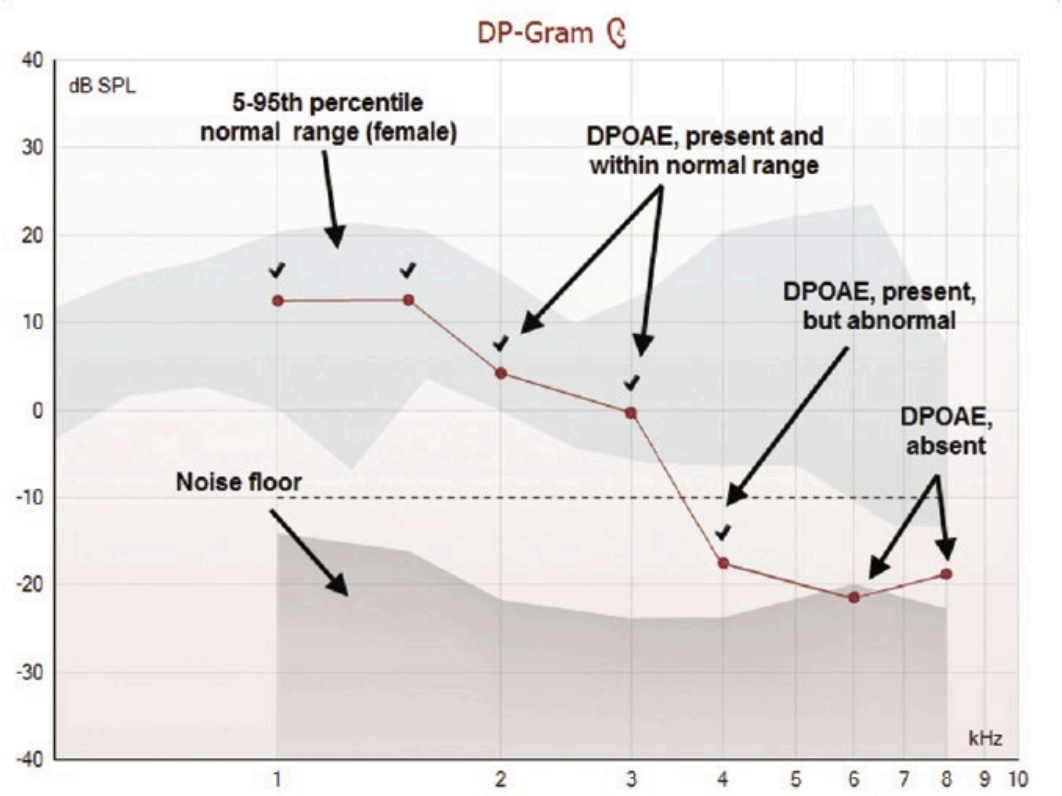

Figure 6: A DP-Gram illustrating basic steps in the analysis of DPOAEs (Ramos et al., 2013)

The number of recordings per octave can be changed according to the aim of testing e.g. 2 points/octave in screening DPOAEs or 4 to ≥16 points/octave for detailed diagnostic DPOAE recordings. At ≥ 16 points per octave, a detailed study of the fine structure of a DPOAE over a small region of the cochlea is possible. At 2 points per octave the DPOAE will be less representative of the fine detail of the cochlear function within the octave band.

Table 2 shows examples of stimulus and recording parameters that would be appropriate for DPOAE measurement in hearing screening, monitoring and diagnosis of cochlear dysfunction. It is important to note that default DPOAE stimulus and recording parameters and measurement protocols differ among equipment manufacturers. In addition, DPOAE recording parameters reported in peer-reviewed publications vary considerably. For example, the f2/f1 ratio of 1.22 is not consistently used in DPOAE measurement, although the ratio is usually within the range of 1.20 to 1.25. The optimal ratio depends on different factors, including stimulus frequency and level. And the optimal ratio for producing the largest DPOAE varies from one person to the next.

Parameters	Recommended Setting for Clinical Applications				
	Infant and Pediatric Screening	General Diagnostic	Ototoxicity Monitoring	NIHL Monitoring	Meniere's Disease
F2/F1 ratio	1.22	1.22	1.22	1.22	1.22
L1 level (dB SPL)	65	65	65/55 *	65	65
L2 level (dB SPL)	55	55	55/45 *	55	55
F2 range (Hz)	2000–50000	500 – 8000	2000 - ≥10,000	1000-8000	500-20000

Points/octave	4 or 5	5-8	8-16	8	4
Noise reduction algorithm	High noise	Conventional	Low noise	Low noise	High noise

Table 2: Recommended stimulus and recording parameters for DPOAEs used for selected clinical applications. **Decrease stimulus level to increase test sensitivity to cochlear damage. (Table adapted from Dhar & Hall, 2018)*

7.2. DPOAE analysis and interpretation

The most common presentation of the DPOAE is through a 'DP-Gram' (Figure 6). The DP-Gram displays the level of the DPOAE and a representation of the noise at each of the test frequencies, which typically range from 1 kHz to 8 kHz or 10 kHz. The DP amplitudes, the corresponding noise levels around the same frequencies and the signal-to-noise (SNR) ratio, calculated by subtracting the noise from the DPOAE, are used to determine the confidence of the result. The derivation of the noise level present can differ between manufactures and configurations. The noise level can be taken as the average noise present near to the DPOAE frequency. More conservatively and because widely differing noise levels can appear at adjacent frequencies, noise may be assessed as one or two standard deviations above the average noise. The latter gives increased confidence in a valid response and greater accuracy of DPOAE measurement.

DPOAE analysis for all test frequencies is performed for amplitudes, noise floors, and DP-noise floor differences relative to normative data. Manufacturer values for normative data are dependent on algorithms used for signal processing and DP detection. The following criteria and categories are offered as a guide for initial analysis of DPOAEs recorded with clinical devices. Figure 6 also illustrates steps and categories for the analysis of DPOAEs.

DPOAE Clear Response Present and Normal

- DPOAE amplitude within an appropriate normal region (usually > 0 dB SPL)
- SNR (i.e. DP – noise floor) ≥ 6 dB
- Low noise levels (ideally < -10 dB SPL)

DPOAE Clear Response Present but Abnormal

- DPOAE amplitude below normal limits (e.g., < 5%ile of normal and usually < 0 dB SPL)
- SNR (DP – noise floor) ≥ 6dB
- Low noise levels (ideally < -10 dB SPL)

DPOAE No Clear Response

- SNR (DP – noise floor) ≤ 6 dB SPL
- Low noise levels (ideally < -10 dB SPL)

Manufacturers of OAE equipment usually provide normative data for default test protocols (Dhar & Hall, 2018). Most manufacturers also offer the option to include user defined custom normative databases. Individual clinicians and clinical departments may wish to compile normative data for the OAE devices used in the clinic and groups of normative subjects that represent clinic patient populations, e.g., newborn infants, children undergoing chemotherapy monitored for ototoxicity, adults with bothersome tinnitus or at risk for sound induced hearing loss. If so, then appropriate sampling and careful consideration of characteristics of the local population should be considered.

In general, DPOAEs at test frequencies are expected to be CR present and normal (amplitudes within an appropriate normal region) if pure tone hearing thresholds are better than 15 dB HL, CR present but abnormal for cochlear (outer hair cell) hearing loss (pure tone hearing thresholds) within the range of 15 to 40 or 50 dB HL, and NCR for cochlear (outer hair cell) hearing loss greater than 40 or 50 dB HL. However, as stated already, the relation between the presence of DPOAEs and pure tone hearing sensitivity in individual patients is not always predictable as it is influenced by factors such as middle ear function, the specific site of auditory dysfunction (e.g., outer hair cell, inner hair cell, or neural), and for cochlear hearing loss the extent of outer hair cell dysfunction (Kramer, 2013; Dhar & Hall, 2018).

8. Clinical applications

There are three general clinical applications of OAEs: The first application is screening to detect cochlear dysfunction in apparently normal populations (e.g. newborn infants, preschool children, young school age children) or adult populations at risk for hearing loss (e.g. industrial workers, musicians, military personnel, persons with recreational noise exposure, or adults with learning disabilities). Persons with a 'Refer' (did not pass) outcome are typically referred for diagnostic audiological assessment. The second application is to monitor OAE levels for changes with time, also in patients at risk for developing cochlear dysfunction (e.g., ototoxicity monitoring or industrial monitoring). The third application is to include OAEs in a test battery for diagnosis of auditory dysfunction and hearing loss, specifically to provide information about the type, degree, configuration or site of auditory dysfunction

8.1. Hearing screening

Automated OAEs (TEOAEs and DPOAEs) are used throughout the world for hearing screening. TEOAEs are the technique of choice within the UK Newborn Hearing Screening programmes. Additional information can be found with the following links: https://www.gov.uk/topic/population and http://www.thebsa.org.uk/resources/.

The Pass/Refer criteria used in the UK newborn hearing screening program are intended to identify those persons with bilateral moderate or worse permanent childhood hearing impairment (PCHI). Moderate or worse is defined as an average hearing threshold (over the frequencies 0.5, 1.0, 2.0 and 4.0 kHz) of 40 dB or

more. Typical pass criteria for an automated OAE is a SNR of 6dB with a minimum signal level of -5dB SPL per half octave band in at least 2 frequency bands and a minimum overall signal of > 0dBSPL . However, it is the responsibility of the tester to ensure that the pass criteria set on their screening equipment meets the requirements of their screening programme (for UK settings, see Appendix D). OAE hearing screening may also be combined with automated auditory brainstem response (ABR) hearing screening to minimize false-negative and false-positive screening errors (Hall, Smith & Popelka, 2004; Joint Committee on Infant Hearing, 2019). Peer reviewed literature and textbooks (e.g., Dhar & Hall, 2018) provide additional information about the application of DPOAEs and TEOAEs in hearing screening of newborn (e.g.,Kanji, Khoza-Shangase & Moroe, 2019; preschool (e.g., Hall, 2016), and school hearing screening programmes.

8.2. Monitoring cochlear function

8.2.1. Monitoring for ototoxicity

DPOAEs are included in clinical practice guidelines for ototoxicity monitoring (American Academy of Audiology, 2009). Cochlear damage caused by ototoxic drugs, such as aminoglycoside antibiotics, and antineoplastic drugs such as cisplatin, initially affect the OHCs at the high frequency basal turn of the cochlea before extending towards the apical end. This selective damage potentially makes DPOAE testing a very effective monitoring tool, as it is capable of assessing the early high frequency OHC damage, before speech frequencies are affected and preferably before the appearance of audiometric hearing loss (American Academy of Audiology, 2009). The specific rationale for use of DPOAEs rather than TEOAEs is the ability to monitor outer hair cell function for frequencies above about 4000 Hz where ototoxic effects first occur. DPOAEs are quick, safe, objective and suitable for monitoring children and adults who are unwell due to severe infections or cancer and therefore unable to provide valid findings on serial subjective conventional and high frequency pure tone audiometry (see Table 3 for advantages/disadvantages of using OAEs for cochlear monitoring).

Pros	Cons
Both TEOAEs and DPOAEs are highly sensitive to OHC cochlear dysfunction	OAEs can be affected by middle ear changes e.g. otitis media / Eustachian tube dysfunction
Most ototoxic drugs affect the OHCs first	Changes in middle ear pressure can affect repeatability of recordings. Cochlear dysfunction unrelated to ototoxicity (e.g., noise or aging) may limit the clinical value of OAEs in monitoring for ototoxicity.
DPOAEs allow for earlier identification of cochlear damage (at the high frequency basal end of the basilar membrane) before it is evident through routine audiometry	Repeatability can be affected by probe fitting, time difference from baseline, and changes in middle ear condition

As objective measures, OAEs can be performed in young and very ill patients	
Test time is brief (usually < 5 minutes)	
Only a quiet (not sound-treated) testing environment is needed	
High degree of detailed (8-16 points/octave) frequency selective information can be provided.	

Table 3: Pros and cons of using OAEs (especially DPOAEs) as monitoring tools for early detection of inner ear dysfunction due to ototoxicity or noise-induced hearing loss.

Whenever possible, comprehensive audiological assessment including DPOAE measurement should be performed before exposure to the ototoxic drug or within the first 48 hrs of the first dose of cisplatin or 72 hrs of the first dose of aminoglycosides (ASHA, 1994; and American Academy of Audiology Clinical Practices Guideline on Ototoxicity Monitoring., 2009).

This baseline pre-exposure assessment should include otoscopy, tympanometry, conventional and high frequency audiometry (500 to-16000 Hz) and high frequency DPOAE testing (2000 to 10000 Hz). The serial monitoring during/ following each cycle or course of treatment should be performed using DPOAEs. DPOAE monitoring can be conducted in a setting that is best for the patient, i.e., within a ward, an outpatient clinic, or an audiology unit. In recording DPOAEs for ototoxicity monitoring, it is important to achieve a secure deep probe insertion to reduce ambient noise and test-retest variability between measurements. The signal to noise ratio achieved during the recording also affects the repeatability of DPOAE level measurements. With a 6 dB SNR (DP to noise floor difference) statistical variations of around 1 dB can be expected with the same probe placement. This variation increases with lower SNRs. DPOAE recordings plotted in the form of a DP-Gram should routinely be replicated during ototoxicity monitoring to verify repeatability.

Changes in DPOAE amplitude (not SNR) that exceed the acceptable test-retest range of variability from baseline, particularly for the highest test frequencies, are considered evidence of ototoxicity-induced cochlear damage. Evidence-based criteria for analysis of DPOAE changes are displayed in Appendix B. It is not necessary for DPOAE amplitudes to decrease below normal limits before ototoxicity is suspected. Whenever clinically feasible, the patient should be referred for further detailed audiological assessment to include high frequency audiometry in order to allow for communication with managing physicians regarding modification of the treatment regimen and/or to begin rehabilitative solutions as required.

8.2.2 Monitoring for noise- or music-induced hearing loss

Persons exposed to high sound levels (noise or music) are at risk for cochlear hearing loss. Chronic exposure to high levels of sound or even short duration exposure to transient high impact sound initially produces outer hair cell dysfunction that is detected with OAE monitoring. Decreases in OAE amplitude with sound exposure

are typically detected before hearing loss is documented with pure tone audiometry. Because of their sensitivity to sound induced cochlear dysfunction, OAEs are well suited for monitoring persons at risk of noise or music induced hearing loss (see Dhar & Hall, 2018 for review). Also, refer to information in Appendix B.

Noise-induced hearing loss commonly affects the 3000 to 6000 Hz frequency region of the cochlea as evidence by the classical 'audiometric noise notch'. DPOAEs are a more suitable tool for monitoring for sound-induced hearing loss as they yield information on outer hair cell function throughout the frequency range of interest. However, TEOAEs may provide some evidence of sound-induced cochlear dysfunction.

The test parameters for TEOAEs and DPOAEs displayed in Table 1 and
Table 2 can be used depending on whether the test will be used for screening or for regular health surveillance monitoring. In some health surveillance programmes higher stimulus levels are used for L1 and L2 of 75 dB SPL and 70 dB SPL respectively to allow for noisier work place test environments and to allow for some degree of sensorineural hearing loss within the workforce being tested (Helleman, 2010*).* However, if these higher levels are used the test will not be as sensitive to early or minor changes in function or be able to provide frequency specific information as the louder stimuli will stimulate a larger proportion of the cochlea at the same time. Therefore, it is important to verify the aims of the surveillance programme from the start in order to choose the appropriate protocol parameters.

Monitoring of noise-exposed workers should include baseline OAE measurement, ideally before a subject is initially exposed to loud sounds and then annual monitoring with OAEs for the first two years of employment and then at three-yearly intervals, to compare shifts in OAE amplitude thresholds at the different test frequencies and assess if they have changed significantly beyond the accepted test-retest variability limit. More frequent monitoring may be indicated if OAE changes are documented or hearing loss is detected and also in worker whose risk of hearing loss is high.
(http://www.hse.gov.uk/noise/healthsurveillance.htm).

As previously discussed under section 8.2.1 for ototoxicity monitoring, in general, a reliable decrease in DPOAE amplitude (not SNR), of 6dB from baseline at frequencies ranging between 1000 to 6000 Hz should be considered as evidence of cochlear dysfunction and would warrant follow-up and management. Evidence-based criteria for analysis of DPOAE changes are displayed in Appendix B. Frequencies above and below this range need to demonstrate a larger amplitude shift in order to include the larger normal test-retest standard error of measurement (SEM) recorded at these frequencies (Reavis et al., 2015). Decreased OAE amplitude is the common finding demonstrating inner ear damage. However, Helleman and Dreshler (2012) reported evidence of DPOAE enhancement within the around 3000 Hz region in serial monitoring among adults occupationally exposed to noise. Enhancement below the "audiometric edge" of the assumed impairment is consistent with animal models of noise (Harding and Bohne, 2004) and ototoxic exposures (Kakigi et al., 1998; Mei et al., 2009; Reavis et al., 2015).

8.3 Diagnostic assessment of cochlear function

Both TEOAEs and DPOAEs can play a role in diagnostic assessment of auditory function in patients with a wide variety of disorders and diseases. Examples of test parameters for diagnostic OAE measurements were shown earlier in Table 1 and Table 2. Clinical practise guidelines for auditory assessment of infants and young children

include OAEs within the recommended diagnostic test battery (e.g., Joint Committee on Infant Hearing, 2019). OAEs can also contribute importantly to the diagnosis of hearing loss and related disorders (e.g., bothersome tinnitus) in adult patient populations (Dhar & Hall, 2018).

8.3.1 Auditory neuropathy spectrum disorder (ANSD)

The use of OAEs in the assessment and diagnosis of ANSD is described in the BSA recommended procedure ' Assessment and Management of Auditory Neuropathy Spectrum Disorder in Young Infants' (http://www.thebsa.org.uk/wp-content/uploads/2019/01/FINAL-JAN2019_Recommended-Procedure-Assessment-and-Management-of-ANSD-in-Young-Infants-GL22-01-19.pdf).

8.3.2 Non-organic hearing loss (NOHL / pseudohypacusis)

OAE measurement contributes importantly to timely and confident diagnosis of NOHL, especially if performed in combination with tympanometry and stapedial acoustic reflexes to exclude conductive hearing loss and to confirm or rule out sensory hearing loss (Peck, 2011; Dhar & Hall, 2018). In contrast to behavioural auditory tests, OAE measurement as an objective procedure is not dependent on factors such as motivation or attention. NOHL must be considered as a possible diagnosis for patients with apparent pure tone hearing loss yet normal findings for diagnostic OAE assessment, i.e. OAE amplitudes within a normal region for all test frequencies. For patients who are exaggerating a genuine SNHL loss, OAEs may be reduced in amplitude or be NCR depending on the extent of cochlear dysfunction. Confirmation of NOHL often includes assessment with other objective measures including ABR, auditory steady-state response, or cortical auditory evoked potential responses.

8.3.3 Non-cooperative (non-compliant) subjects

OAE measurement in combination with other objective auditory procedures (e.g., aural immittance measures and ABR) can provide valuable clinical information on cochlear function in subjects who are non-cooperative or difficult-to-test with behavioural audiometry, including younger patients with developmental delay and patients of all ages with cognitive impairment.

8.4 Relationship between pure tone audiometry and OAE findings

OAEs complement pure tone audiometry findings. Results of OAEs and pure tone audiometry are in general agreement in many cases. That is, OAEs are normal in patients with normal pure tone audiometry and abnormal in patients with hearing loss by pure tone audiometry. However, in some cases OAEs may provide valuable clinical information that complements or adds to information from pure tone audiometry. Combinations of selected findings for pure tone audiometry and OAEs are summarized in Table 4. For example, cochlear dysfunction is likely in a patient with abnormal or NCR OAEs yet normal pure tone hearing sensitivity pure tone audiometry, perhaps warranting more detailed history and further audiological or medical assessment. Further, normal outer hair cell function and perhaps cochlear (outer and inner hair cell function) is likely in a patient with normal OAEs yet abnormal pure tone hearing sensitivity pure tone audiometry. This combination of findings also warrants more detailed history and further audiological or medical assessme

	PTA results	OAE results	Interpretation
Scenario 1	Normal	Normal	OAEs confirm normal cochlear(outer hair cell) function in patients with normal hearing sensitivity
Scenario 2	Normal	Abnormal	With confirmation of normal middle ear function, abnormal OAEs offer evidence of early and/or subtle OHC dysfunction. OAEs may be abnormally reduced in amplitude or NCR for some or all test frequencies. Middle ear dysfunction not affecting the pure tone thresholds may result in abnormal or NCR OAEs. Middle ear measurement (tympanometry and acoustic reflexes) is useful to confirm middle ear involvement or to confirm OHC dysfunction.
Scenario 3	Abnormal	Normal	Technical problem with pure tone audiometry **OR** Cognitive impairment or patient does not understand or cannot perform the task **OR** False hearing loss **OR** Cochlear dysfunction involving only inner hair cells **OR** Neural auditory dysfunction and/or ANSD

Table 4: Possible reasons for the combinations of outcomes that may be obtained for pure tone audiometry (PTA) and OAE testing.

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Appendix A. Examples of DPOAE and TEOAE displays for the Biologic, Interacoustics Titan and Otodynamics instruments.

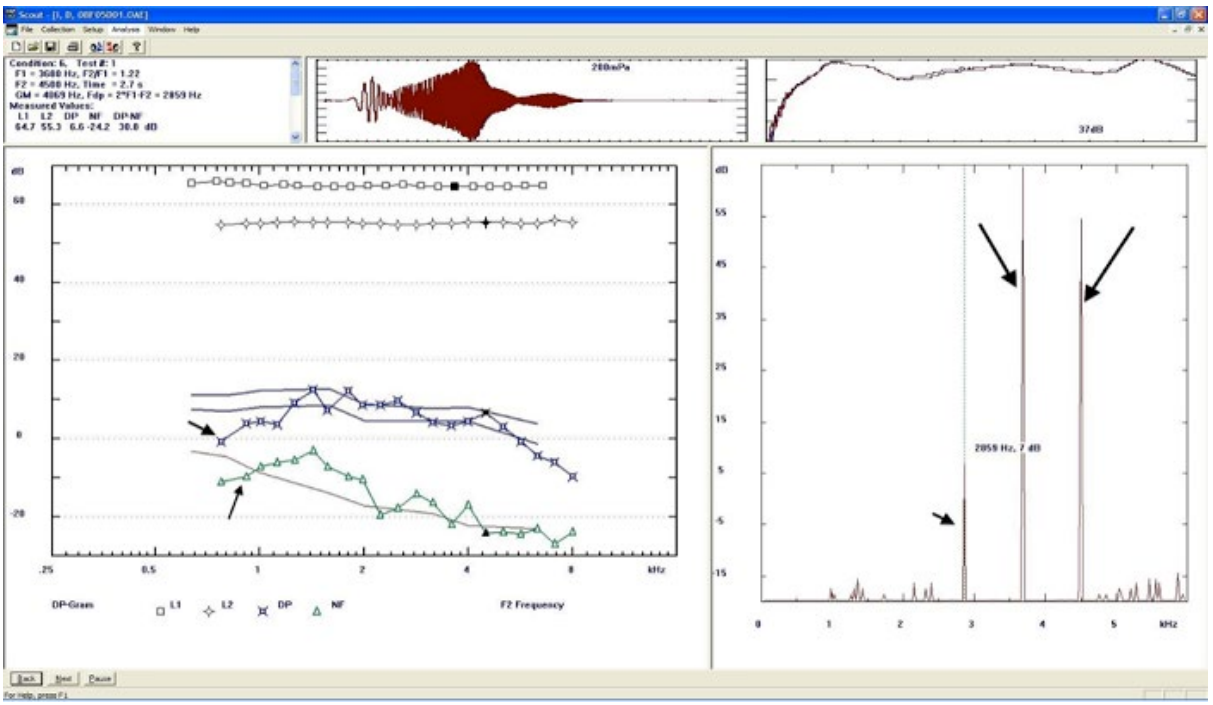

Figure 7: A DPOAE recording obtained using the BioLogic instrument. The lower right panel shows a representation of the two stimulus primary tones (large arrows pointing to f1 & f2) and the distortion 2f1-f2 (small arrow) in the frequency domain. The lower left panel shows the consistent level produced for the stimulus primary tones (L1 & L2) at 65/55 dB SPL and the recorded DPOAE and the averaged noise levels (green triangles). (Picture taken from online article by James Hall, 2015)

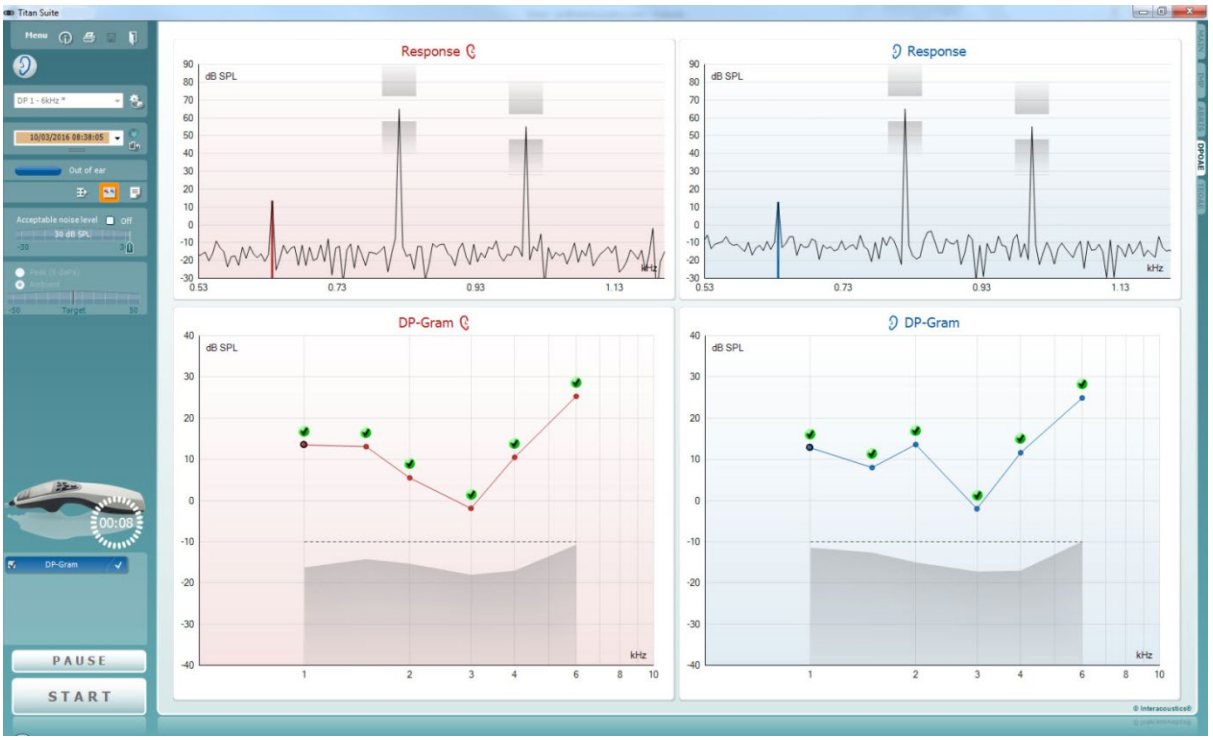

Figure 8: A DPOAE recording for right and left ears using the Interacoustics Titan instrument. The upper panels display the f1, f2 and DPOAE 2f1-f2 frequencies and their corresponding intensities. The lower panels display the amplitude of the DPOAE response and the corresponding noise floor. All frequency test points have passed the specified stop criteria and therefore have a small tick above each of the data points. It is also worth noting that test time was only 8 sec. (Picture courtesy of Interacoustics Ltd.)

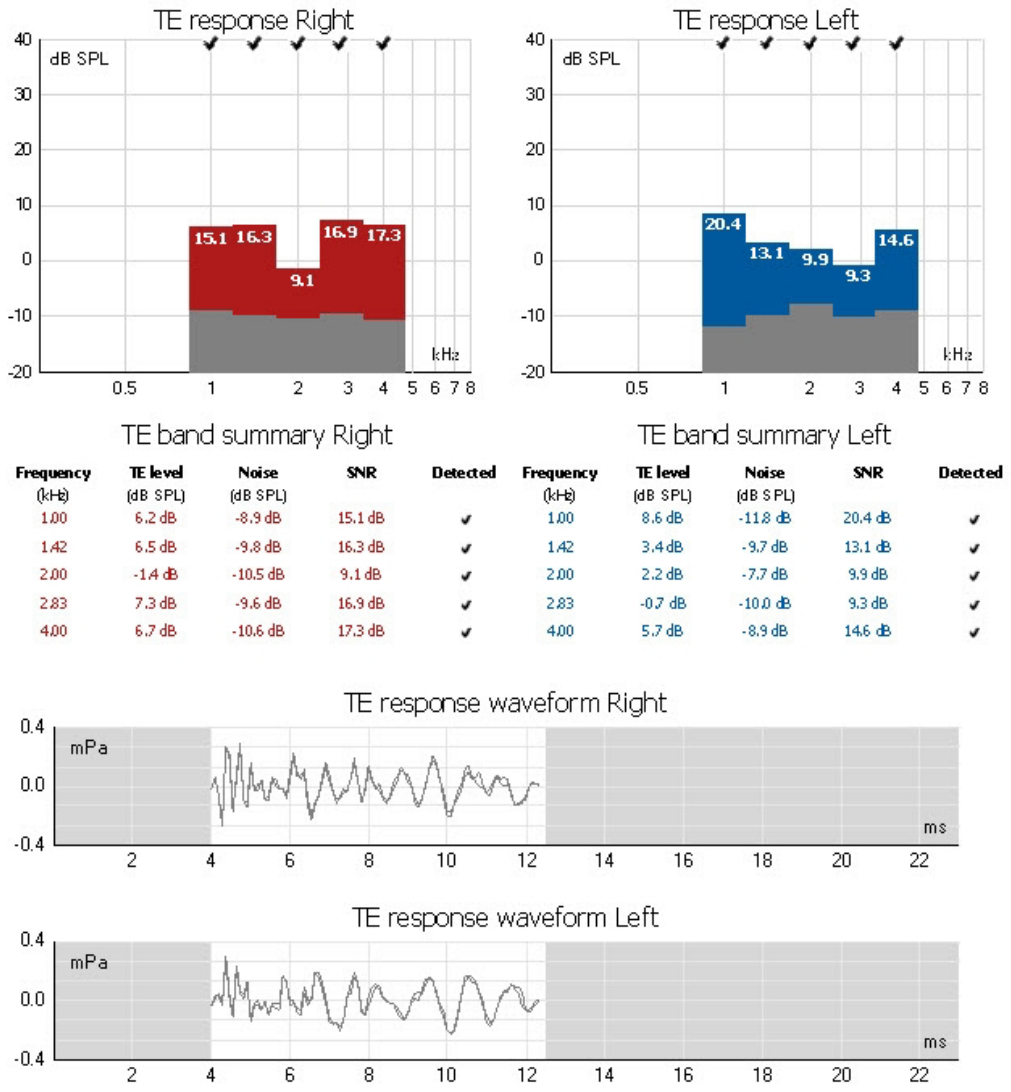

Figure 9: An example of a diagnostic TEOAE report that could be generated from testing a patient with suspected ANSD or NOHL. (Picture courtesy of Interacoustics Ltd.)

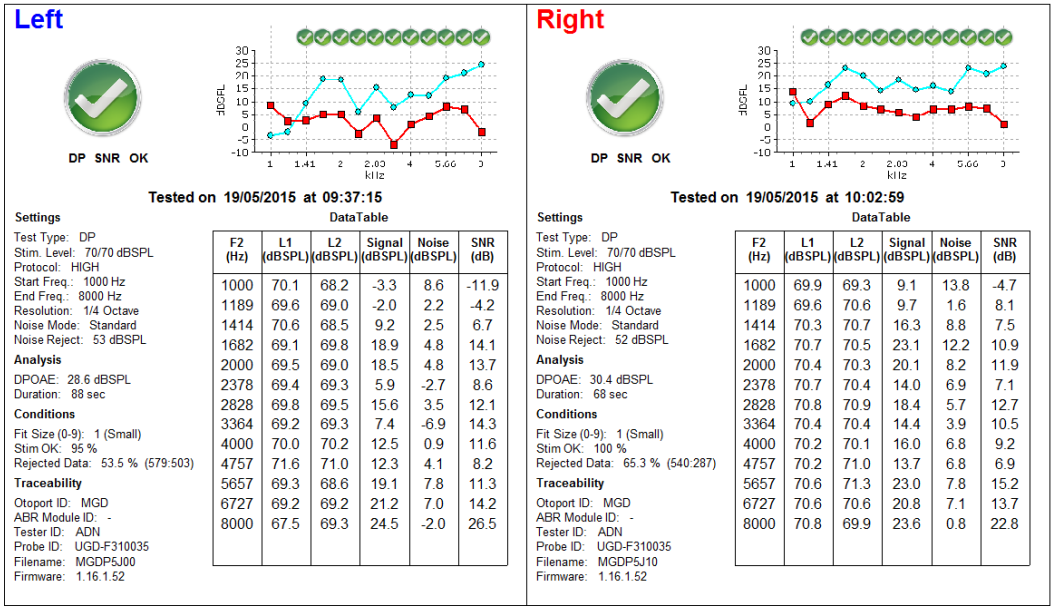

Figure 10: An example of a diagnostic DPOAE report that could be generated from testing a patient with suspected NOHL. *(Picture courtesy of Otodynamics Ltd.)*

Appendix B. Defining what constitutes a significant change in DPOAEs

Criteria to determine a significant change in DPOAE amplitude in ototoxoicity monitoring are displayed in Table 6. These data are derived from work performed by Reavis et al. (2015) who performed a meta-analysis of the DPOAE level test–retest literature performed in adult subjects. These reference limits are calculated using the mean Standard Error of Measurement (SEM) values, which are then used to calculate 90% reference limits. A 90% reference limit should yield a 10% total false referral rate, with 5% falling below the lower bound and 5% falling above the upper bound of the reference interval.

Table 6 shows the 90% reference limits specific to the f2 frequencies at four elapsed time points between baseline and follow-up measurements. Changes larger than these defined reference limits are considered significant and warrant follow-up testing. **In general, a shift of ±6 dB in DPOAE amplitude from baseline would warrant follow-up** (for more clarification and for identifying possible caveats for use please read Reavis et al., 2015).

Days From Baseline	**DPOAE f2 Frequency**							
	1000 Hz		2000 Hz		4000 Hz		6000 Hz	
	SEM	**90% Reference Limits**	**SEM**	**90% Reference Limits**	**SEM**	**90% Reference Limits**	**SEM**	**90% Reference Limits**
1	1.7	±3.95	1.7	±3.98	1.8	±4.16	1.6	±3.76
10	1.8	±4.24	1.9	±4.35	2.1	±4.85	2.0	±4.55
15	1.9	±4.41	2.0	±4.56	2.3	±5.24	2.1	±4.99
20	2.0	±4.57	2.0	±4.76	2.4	±5.63	2.3	±5.43

Table 6: Meta-analysis results of the accepted upper and lower 90% reference limits within which changes in DPOAE amplitude changes are considered within normal test-retest ranges of variability with a 10% possible false positive (referral) rate. These changes are calculated for four DPOAE f2 frequencies and presented for four different time points (in days) from baseline testing. *(Data accessed and adapted from Reavis et al., 2015)*

In an ototoxicity serial monitoring model by Dille et al., (2010) they describe a rapid **ototoxicity risk assessment (ORA)** model which incorporates *a priori* DPOAE change criteria, such as a minimum DPOAE level ***shift of 6 dB from pre-exposure baseline recordings***, and weighted combinations of pre-treatment hearing assessment and cumulative ototoxic drug dose (e.g. for cisplatin, as in this article, or others). The multivariate

DPOAE metrics assessing the DPOAE fine structure through serial monitoring of only the upper quarter/third octave range specific to each patient's high frequency limit is used to indicate early subtle changes in cochlear function. The same concept is also used for behavioural monitoring where the **significant range of ototoxicity (SRO)** corresponding to recording thresholds at one octave range (tested at $1/6^{th}$ points/octave) from the highest frequency a patient can hear are tested during the serial audiometric monitoring assessments from baseline.

Appendix C. Troubleshooting when interpreting the results

In order to confirm the presence of a middle ear and/or cochlear auditory pathology, other non-pathological factors that may affect OAE recordings must be excluded. Adequate OAE analysis is dependent on the selection of the appropriate test protocol, performance within adequate test conditions and exclusion of technical causes of interference with testing. A logical, methodical and systematic approach to troubleshooting will increase clinical skills in performing the test effectively and assist audiologists/screeners in addressing challenges encountered during testing.
Table 7 presents examples of the most common problems that may be encountered and suggests possible solutions. Figure 11 illustrates excessive stimulus ringing in TEOAE measurement.

Common problem	**Possible reason (s)**	**Suggested solution (s)**
High noise levels	Excessive environmental/ambient noise	Reduce noise level or move away from the noise source Improve probe fit within the EAC e.g. by changing probe tip size/ deeper insertion Limit stimulus frequency recordings to >1-2 kHz Increase signal averaging Increase noise rejection levels slightly as a last resort
	Excessive internal/physiological noise	Re-instruct patient to minimize movement/talking/chewing For infants: test them while they are sleeping, after feeding or during sedation after ABR testing Re-test on a separate occasion for verification.
NCR OAE responses	Inadequate stimulus levels	Improve probe fit Verify probe calibration Confirm stimulus matches target level
	Blocked external auditory canal	Perform Otoscopy if not performed before and exclude excessive ear wax, foreign body or presence of vernix in newborns
	Middle Ear problems	Should be excluded through: history taking, otoscopic examination and tympanometry and/or acoustic reflex testing
Variation in response greater than 3dB when	Significant Probe fault	Check the sound tubes, Change the couplers and repeat the test. If the change in response is still significant then

performing the regular probe calibration checks		contact your equipment dealer or manufacturer.

Table 7: Examples of common problems that may be encountered and suggest possible solutions to correct them

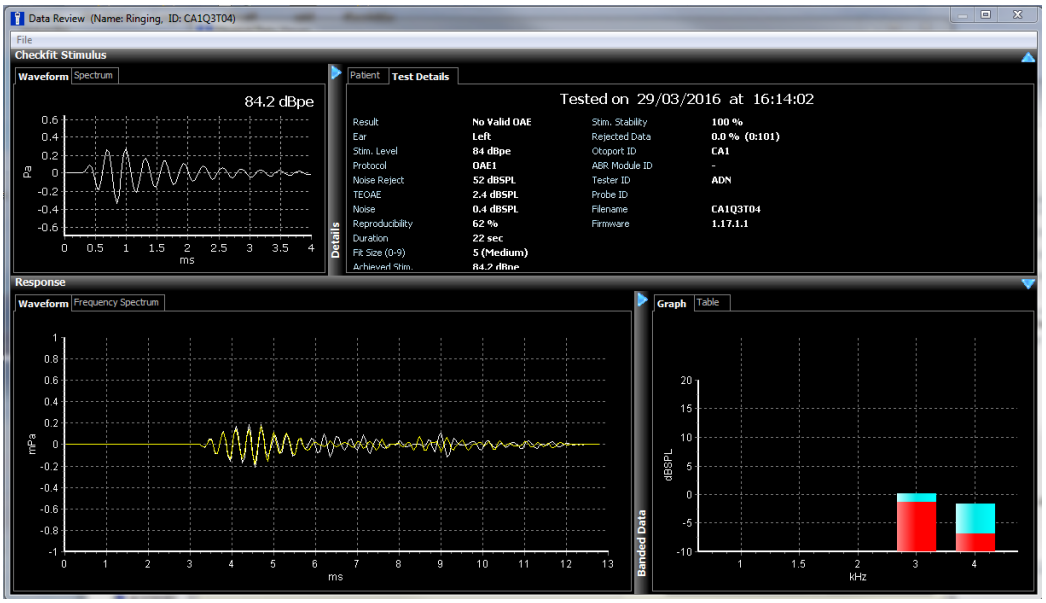

Figure 11: An abnormal oscillating (ringing) stimulus (upper left panel) which is falsely interpreted as a high frequency response (lower left panel - waveform response in the 4-6 ms region) and as a TEOAE response at the 3&4 kHz frequency regions (lower right panel) (*picture courtesy of Otodynamics ltd.)*

Appendix D

Table 8: SUMMARY: UK Pilot - Newborn Hearing Screening - Criteria from NHSP TOAE protocol 2002

Probe fitting	Well fitted probe with no significant change in fit over recording interval.
Stimulus:	Click between 75 and 100 p.p.s
Stimulus level (ppe) :	80 to 88dBpeSPL into neonatal ear canal or equivalent volume cavity
Variation of stimulus level between probes	+/- 2 dB.
Data reject level:	At or below 55 dB peak SPL
High pass filter to remove low frequency noise:	Around 1.2 kHz
Bandwidth	Able to record between 1000 and 5000Hz
Data collection / analysis window :	Start 4 ms. End 10 to 12.5 ms
Minimum number of responses averaged	240 sweeps at low stimulus level equivalent. E.g. 40 stimulus packets if 8 stimuli for each packet (6 low, 2 high).
Maximum recording time	6 minutes
Response present criteria	>= 6dB for 2 out of 4 half octave bands centred at 1.5,2,3,4 KHz or >=6dB for a single band.
Minimum level to accept as a response	0dB rms SPL