Ototoxicity in patients receiving concurrent cisplatin and cranial irradiation therapy for the treatment of head and neck cancers: an audiometric follow-up

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Abstract

Cisplatin is a potent chemotherapeutic agent that is commonly used to treat a wide variety of tumours. Although highly effective, its administration is complicated by its ototoxic effect, a well known side effect that occurs in a significant number of patients. The hearing loss observed is typically irreversible, progressive, bilateral, high-frequency sensorineural hearing loss associated with tinnitus. At present there is no approved method for protecting or remedying against deterioration of hearing status, therefore, the detection and appropriate management of cisplatin-induced ototoxicity is reliant on effective audiological monitoring. The present study aimed to investigate the prevalence of ototoxicity in head and neck oncology patients who received cisplatin in combination with cranial irradiation. In addition, the study also aimed to examine the current state of audiological monitoring for this population at Christchurch Hospital.

Post-treatment diagnostic audiological assessments were performed for 23 participants. The post-treatment assessment battery included case history, standard pure-tone audiometry (0.25 – 8 kHz), extended high-frequency audiometry (9 – 16 kHz), speech audiometry, tympanometry, acoustic reflexes and distortion product otoacoustic emissions. Prior to the assessments, a search of the Christchurch Audiology and Ear, Nose and Throat (ENT) Department oncology audiogram files was undertaken to match any previous audiograms to participating individuals.

The results showed that pre-treatment assessment had been performed for 16 of the 23 participants. Of those 16, 15 participants experienced a significant cochleotoxic change in their hearing thresholds according to the ASHA criteria. One participant only received one dose of cisplatin due to deteriorating hearing, while one other participant elected to stop cisplatin treatment after the first dose due to a significant increase in tinnitus severity.

Ototoxicity resulting from cisplatin chemotherapy constitutes a significant clinical problem that may have serious vocational, educational, and social consequences. Findings from this study highlight the importance of effective audiological monitoring for the timely detection and appropriate management of cisplatin-induced ototoxicity.

Abbreviations

AAA: American Academy of Audiology

ABR: Auditory brainstem response

ART: Acoustic reflex threshold

ASHA: American Speech-Language-Hearing Association

ATP: Adenosine triphosphate

Bcl-2: B-cell lymphoma 2

BM: Basilar membrane

BUN: Blood urea nitrogen

CVD: Cardiovascular disease

dB HL: Decibel hearing level

dB SPL: Decibel sound pressure level

DCN: Dorsal cochlear nucleus

DM: Diabetes mellitus

DNA: Deoxyribonucleic acid

DPOAE: Distortion product otoacoustic emissions

EAC: External auditory canal

EHF: Extended high frequency

IDDM: Insulin-dependent diabetes mellitus

IHC: Inner hair cell

IT: Intratympanic

IV: Intravenously

MET: Mechanoelectrical transduction

NIHL: Noise-induced hearing loss

NZAS: New Zealand Audiological Society

OAE: Otoacoustic emissions

OHC: Outer hair cell

Pt: Platinum

PTA: Pure-tone average

PTS: Permanent threshold shift

ROS: Reactive oxygen species

SCC: Squamous cell carcinoma

SNHL: Sensorineural hearing loss

SNR: Signal to noise ratio

STS: Sodium thiosulfate

TEOAE: Transient-evoked otoacoustic emissions

TM: Tympanic membrane

TNF-R: Tumour necrosis factor receptor

TNM: Tumour-node-metastasis

TOMI: Tinnitus ototoxicity monitoring interview

TTS: Temporary threshold shift

VOR: Vestibulo-ocular reflex

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1 Introduction

Cancer represents a spectrum of disorders resulting from the deregulation of cell growth and maturation that occurs normally in organ development during embryogenesis, growth, and tissue repair and remodelling after injury (Rybak, Huang, & Campbell, 2007). Cancers of the head and neck are mostly squamous cell carcinomas (SCC) that develop after exposure to carcinogens such as tobacco and alcohol (Argiris, Karamouzis, Raben, & Ferris, 2008), and are the sixth most common type of cancer worldwide (Parkin, Bray, Ferlay, & Pisani, 2005). Treatment for these epithelial malignancies typically involves surgical removal of the tumour and radiotherapy. The incorporation of chemotherapy into curative therapy, however, has improved clinical outcomes. The platinum compound cisplatin is considered the standard agent in use for the treatment of head and neck cancers (Argiris, et al., 2008). Advancements in medical knowledge have resulted in notable improvements in relative five-year survival rates not only for head and neck cancers, but for many cancer sites and for all cancers combined (Jemal et al., 2008). This has serious implications for quality of life post-cancer treatment. A well-recognised side effect of cisplatin chemotherapy is ototoxicity, resulting in bilateral high frequency sensorineural hearing loss (SNHL) that is typically permanent and associated with tinnitus (Daldal, Odabasi, & Serbetcioglu, 2007). Hearing loss can have significant social, emotional, educational and vocational implications. There is currently no approved method of preventing nor reducing cisplatin-induced ototoxicity.

Originally, the purpose of this thesis was to cover a Phase III clinical trial at Christchurch Hospital, which proposed the trial of intratympanic dexamethasone administration to investigate potential protective effects against ototoxicity while preserving cisplatin's chemotherapeutic actions. Due to significant administrative delays, however, the focus of the current study shifted to the prevalence of cisplatin-induced ototoxicity in a subset of cancer patients.

The present study aims to ascertain the current hearing status of individuals who have received combined chemotherapy and irradiation therapy for the treatment of head and neck cancer. Behavioural and objective measures of auditory function were used in the test battery. Data collected from post-treatment assessments were compared to baseline data obtained prior to commencing treatment. In addition, this study aims to examine the current state of audiological monitoring for this population at Christchurch Hospital. The remaining sections of this chapter will provide background to the biochemical basis of hearing and the concept of ototoxicity.

1.1 Physiological and biochemical basis of hearing

The auditory system consists of specialised cells and structures that function both independently and in combination with one another to result in normal hearing. Disruption to anatomical or physiological components within the auditory pathway may result in a loss of hearing sensitivity. This section aims to provide a broad overview of the physiological and biochemical basis of peripheral hearing in order to interpret the effect of toxicity on the auditory system.

1.1.1 The peripheral auditory system

The peripheral auditory system is divided anatomically into three sections: the outer ear, consisting of the pinna and external auditory canal (EAC); the middle ear, which is bordered by the tympanic membrane (TM) and contains the ossicular chain; and the inner ear, which consists of the cochlea, utricle, saccule, and semicircular canals (Figure 1.1).

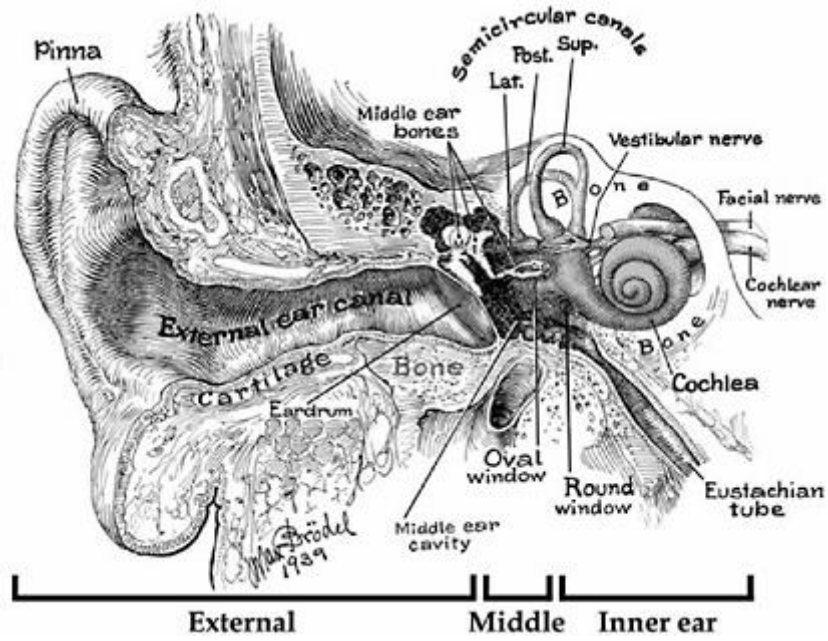

Figure 1.1: The peripheral auditory system (adapted from Brödel, 1946)

The peripheral auditory system is responsible for performing two tasks: converting mechanical energy into bioelectrical signals, and coding the frequency, intensity and timing information content of these signals (Fuchs, 2010). This is achieved by combining multiple elements within the auditory peripheral system. Firstly, airborne vibrations are collected by the pinna and directed into the EAC. Sound waves vibrate the tympanic membrane and ossicles—the malleus, incus and stapes—transforming acoustic energy to mechanical energy. The middle ear functions as an impedance-matching transformer, allowing energy to change from one medium (air) to another (fluid) with minimal loss.

The cochlea consists of a membranous labyrinth within a bony shell (the osseous labyrinth) that is coiled into approximately 2 ½ turns (Yost, 2007). Within the cochlea are three distinct ducts: scala vestibuli, which is superior; scala media (also referred to as the cochlear duct) which is the central duct; and scala tympani, the inferior duct. Scala vestibuli and scala media are separated by Reissner's membrane, while the basilar membrane (BM) forms the boundary between scala media and scala tympani[1]. Movement of the stapes footplate against the oval window membrane elicits longitudinal waves within the cochlear fluids. This stimulates displacement of the BM, which is narrow and stiff near the basal end and becomes progressively wider and more flexible toward the apex. The stiffness and mass gradients of the BM cause it to vibrate in frequency-specific patterns, with maximal vibration for higher frequency tones occurring at the basal end of the cochlea, and maximal vibration for lower frequency tones occurring nearer the apex of the cochlea. Consequently, frequency is arranged tonotopically along the BM.

The organ of Corti is situated on top of the BM in scala media and contains a single row of inner hair cells (IHCs) and multiple rows of outer hair cells (OHCs). The OHCs are positioned closer to the stria vascularis, while the IHCs reside closest to the modiolus—a central bony core that encompasses nerve fibres from the hair cells, and blood vessels (Figure 1.2) (Yost, 2007). The OHCs and IHCs are divided by the pillars of Corti. Alongside the inner and outer hair cells are supporting cells including Deiters' cells, pillar cells, Hensen cells, Claudius cells, and Boettcher's (Figure 1.2) (Musiek & Baran, 2007). Of particular importance to the OHCs are Dieters' cells and Hensen cells.

[1] However, in terms of fluid spaces, the boundary between the endolymph of scala media and the perilymph of scala tympani is the reticular lamina.

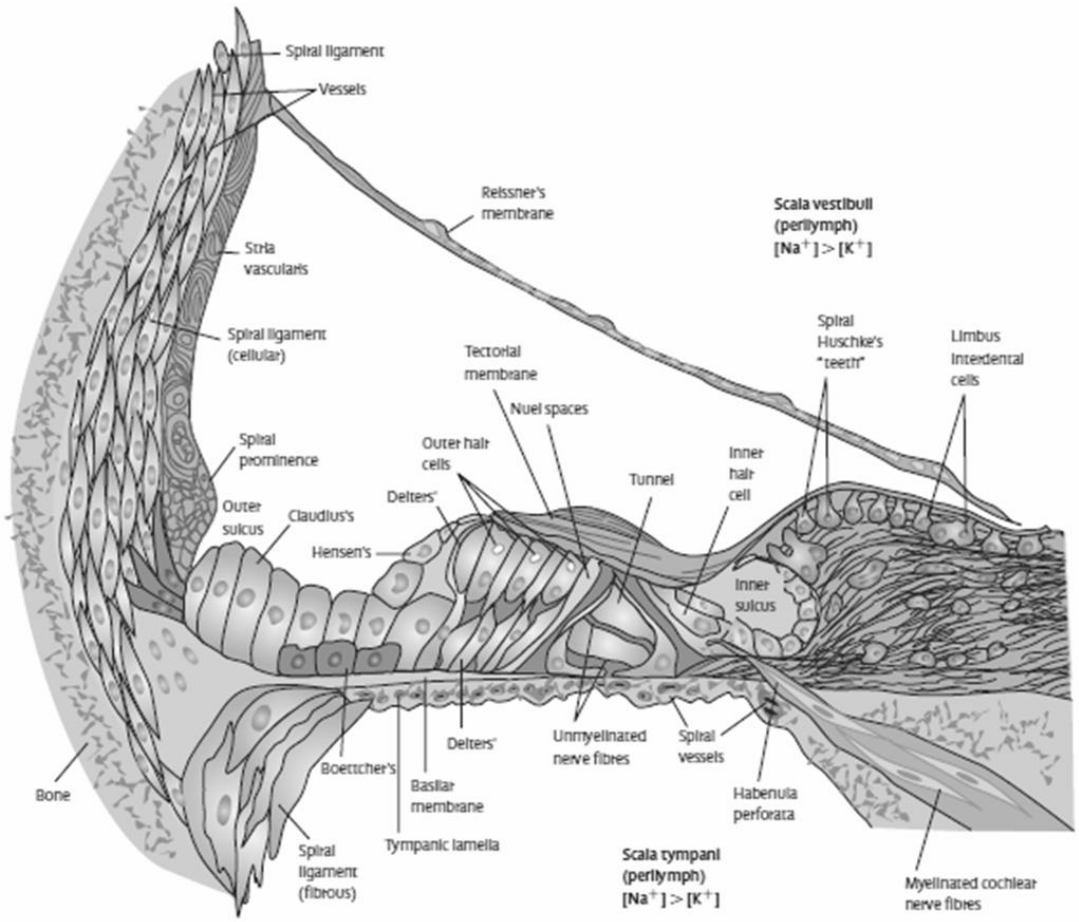

Figure 1.2: Cross section of the cochlea (Gates & Mills, 2005)

Protruding from the apical surface of each hair cell are stereocilia—axially-directed actin-filled microvilli with a myosin cap (McFadden, 2007). The stereocilia of the OHC only are embedded in the tectorial membrane. The stereocilia are arranged in rows based on height so that the shortest row is located on the modiolar side of the hair cell. They are connected via tip links which connect the tips of the shorter stereocilia to the next taller stereocilia, and lateral links, believed to tie adjacent stereocilia together enabling them to move as a unit (Pickles, Comis, & Osborne, 1984). These tip links are responsible for opening and closing mechanoelectrial transduction (MET) channels located near the tip of each stereocilia, which occurs with deflection of the hair cell bundle towards or away from the tallest stereocilia respectively. The deflection of the stereocilia happens in response to radial shearing between the reticular lamina and the tectorial membrane with displacement of the BM. Each time the BM moves towards scala vestibuli, the MET channels open and there is an influx of potassium (K^+) ions from the endolymph in scala media into the hair cells. Movement of the BM towards scala tympani results in closure of the MET channels. This cyclical flow of K+ into the hair cell produces a fluctuating receptor current and causes cyclic changes in membrane potential. The influx of K^+ into the inner hair cell causes the cell to depolarise and release neurotransmitter, which initiates an action potential in the primary afferent neurons. In addition, changes in

membrane potential of OHCs produces cyclical changes in cell length (Brownell, Bader, Bertrand, & de Ribaupierre, 1985) via the protein prestin (Liberman et al., 2002). This acts to cancel friction and increase the amplitude of the BM vibration by approximately 1000-fold (or 60 dB), particularly in the higher-frequency regions of the cochlea (Patuzzi, 2009). This mechanism is referred to as the active process and is a form of electromechanical (EMT) transduction (Dallos, 1992). As will be discussed below, the active process of the OHCs is highly vulnerable to mechanical or chemical insults, giving rise to primarily a high-frequency hearing loss.

1.2 Ototoxicity

Ototoxicity is a term used to describe the tendency of certain chemical or pharmaceutical agents to cause functional impairment and cellular degeneration of the inner ear and the eighth cranial nerve. Over 130 chemicals and drugs are reported to be potentially ototoxic and can result in impaired auditory and/or vestibular function (Seligmann, Podoshin, Ben-David, Fradis, & Goldsher, 1996). These agents are referred to as cochleotoxic and vestibulotoxic, respectively. Different ototoxic agents may cause damage of varying degrees that is either temporary or permanent (Brummett, 1980). The major groups of ototoxic agents described in the literature include aminoglycoside antibiotics and other antimicrobials, salicylates, loop diuretics, antimalarial drugs, and antineoplastic agents.

1.2.1 Mechanisms of ototoxicity

Cell death in the cochlea can result from both natural causes, such as the ageing process, and event-related trauma including exposure to intense and/or prolonged noise and ototoxic agents. The mechanisms behind cell death can be grouped into two general types: necrosis and programmed cell death (PCD), including apoptosis.

1.2.1.1 Necrosis

Necrotic cell death is a passive event that occurs when cells are exposed to extreme stress conditions which result in deregulation of normal cellular activities. This is characterised morphologically by extensive vacuolation of the cytoplasm, swelling of the mitochondria, dilation of the endoplasmic reticulum, and rupture of the plasma membrane (Artal-Sanz & Tavernarakis, 2005). Spillage of the cell's content may precipitate damage to neighbouring cells and initiate an inflammatory response, typically resulting in the death of groups of cells (Henderson, Bielefeld, Harris, & Hu, 2006). One example of necrosis in the cochlea is that which occurs as a result of traumatic noise exposure.

1.2.1.2 Apoptosis

In contrast to necrosis, apoptosis is an active process that is genetically regulated. The morphologic features of apoptosis include nuclear and cytoplasmic condensation, internucleosomal deoxyribonucleic acid (DNA) cleavage and packaging of the cell into apoptotic bodies that are engulfed by phagocytes, preventing release of intracellular components (Hengartner, 2001). Four major functional molecular groups are involved in

triggering and effecting the apoptosis process. These include the caspases, the adapter proteins, members of the tumour necrosis factor receptor (TNF-R) super family, and members of the B-cell lymphoma 2 (Bcl-2) family of proteins (Strasser, O'Connor, & Dixit, 2000). Caspases constitute a family of at least 14 cysteine proteases which specifically cleave after an aspartic residue in target proteins (Artal-Sanz & Tavernarakis, 2005). Pro-apoptotic caspases contain both initiator caspases (caspase-2, caspase-8, caspase-9, and caspase-10) and effector or executioner caspases (caspase-3, caspase-6, and caspase-7) (Leist & Jäättelä, 2001). Caspases are synthesized as zymogens—an inactive form of an enzyme that requires a portion of its protein structure to be removed in order for it to be activated (Wang & Bobbin, 2007).

There are two main pathways that can initiate the apoptotic programme — the extrinsic (extracellular) and the intrinsic (intracellular) route (Figure 1.3). The main extrinsic pathway involves the activation of receptors on the cell membrane that belong to the TNF-R family. These death receptors are activated by ligands and are then linked to the pro-caspase proteins via adapter proteins, forming the death-inducing signalling complex (DISC). The DISC is then able to recruit and activate the zymogens to generate the active initiator caspase protein, such as caspase-8, which can subsequently activate downstream executioner caspases, thus leading to proteolytic degradation of cellular proteins and apoptosis (Strasser, et al., 2000).

The intrinsic pathway, also known as the mitochondrial pathway, accounts for the initiation of apoptosis in response to stimuli such as ionizing radiation, chemotherapeutic drugs, and certain developmental cues (Stennicke & Salvesen, 2000). It is signified by the release of cytochrome *c*, as well as changes in the transmembrane potential and mitochondrial permeability (T. H. Kim, Zhao, Barber, Kuharsky, & Yin, 2000).The mitochondrial pathway involves the Bcl-2 family of proteins. The Bcl-2 family can be divided into three groups, encompassing those that are pro-apoptotic (Group I) and those that are anti-apoptotic (Groups II and III). The pro-apoptotic groups contain Bax, Bok and Bak in Group II, and Bad, Bik, Bid and Bim in Group III, while the anti-apoptotic Group I consists of Bcl-2 and Bcl-XL (Strasser, et al., 2000). The pro-apoptotic Bcl-2 family members such as Bax, Bak and Bid, and Bcl-2 anti-apoptotic family members interact at the outer membrane of the mitochondria. It is the balance of pro-apoptotic and anti-apoptotic components in the particular cell that determines whether or not apoptosis occurs. If the pro-apoptosis molecules predominate, a variety of molecules are released from the intermembrane mitochondrial compartment, including the primary molecule cytochrome *c*—a caspase activator. This particular protein links with the apoptotic protease-activating factor (Apaf-1), procaspase-9, and deoxyadenosine triphosphate (dATP), to form the apoptosome complex. As a result, procaspase-9 is activated (forming caspase-9), which in turn activates downstream effector caspases, such as caspase-3, and caspase-7 (Wang & Bobbin, 2007). This ultimately leads to apoptosis.

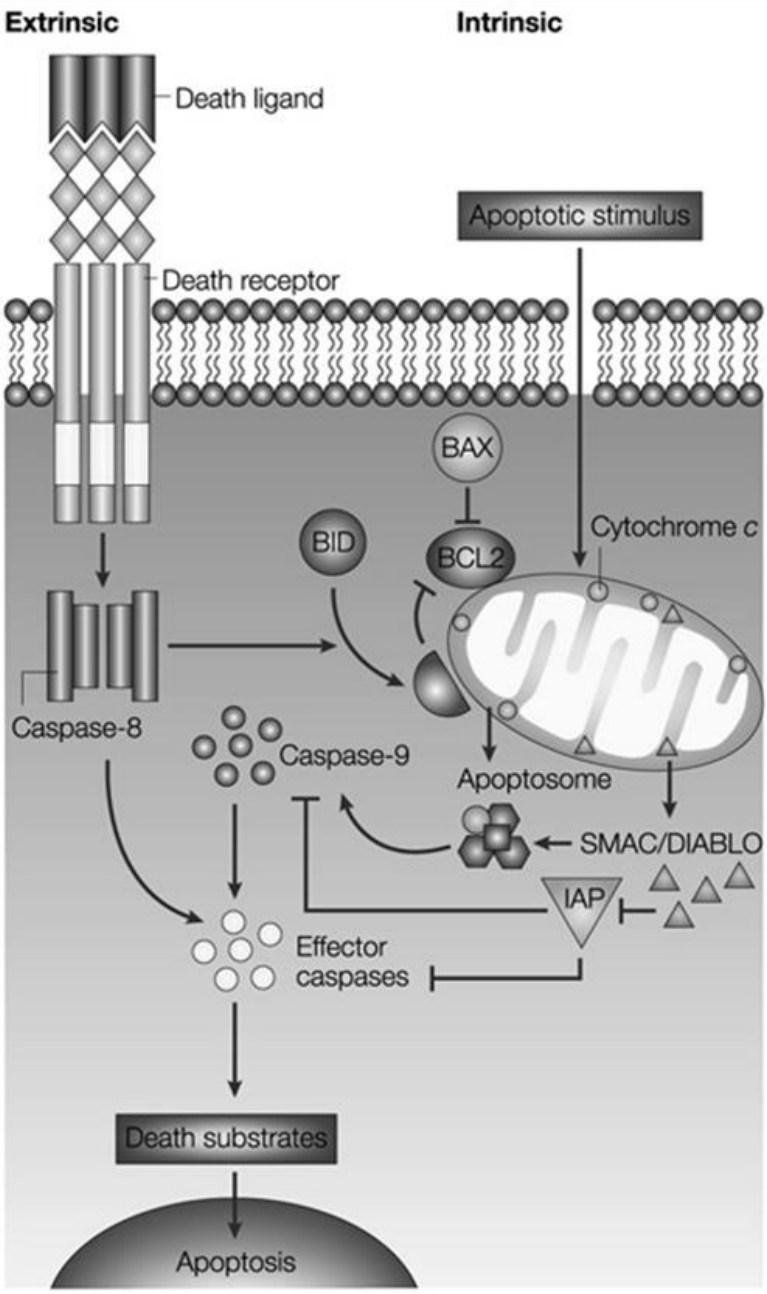

Figure 1.3: Illustration of the extrinsic and intrinsic apoptotic pathways (Altieri, 2003).

1.2.1.3 Reactive oxygen species

Reactive oxygen species (ROS) are also thought to play a role in PCD. Mitochondria serve as the major energy-producing powerhouses within cells, generating adenosine triphosphate (ATP) which is associated with the utilisation of molecular oxygen. It is estimated that 2 – 3% of this molecular oxygen is reduced in a one-electron fashion yielding a series of reactive oxygen species (Heck, Kagan, Shvedova, & Laskin, 2005).

Free radicals are molecules with an unpaired electron in their outer orbit (Halliwell & Gutteridge, 1999), making them highly reactive with the potential to destabilise other molecules and break down molecular bonds, leading to tissue and cell damage

(Henderson, et al., 2006). ROS are oxygen-based molecules that either act as free radicals themselves or have the ability to generate free radicals. They may be produced in the cochlea due to high-level noise, enzymatic reactions, ischemia and reperfusion, and excitotoxicity (Schmidt, Knief, Lagosch, Deuster, & Zehnhoff-Dinnesen, 2008). Three important ROS that are generated in the reduction of O_2 to H_2O are the superoxide anion ($O_2^{\bullet}$), hydrogen peroxide (H_2O_2) and the hydroxyl radical ($OH^{\bullet}$). The generation of these ROS can lead to the formation of other more damaging species, such as peroxiradicals (Clerici, DiMartino, & Prasad, 1995). Reactive species have been shown to be damaging to biologic tissues, causing lipid peroxidation, carbohydrate and protein damage, DNA strand breaks, and altered membrane-bound enzymes and receptors (Ghersi-Egea, Livertoux, Minn, Perrin, & Siest, 1991). Mitochondria respond to oxidative damage by neutralising free radicals via water-soluble and lipid-soluble antioxidants such as glutathione, ascorbate, vitamin E, and coenzyme Q, and antioxidant enzymes such as glutathione peroxidise, catalase, thioredoxins and peroxiredoxin (Heck, et al., 2005). Eventually, however, damage accumulates due to these processes being overwhelmed. This process is in illustrated in Figure 1.4.

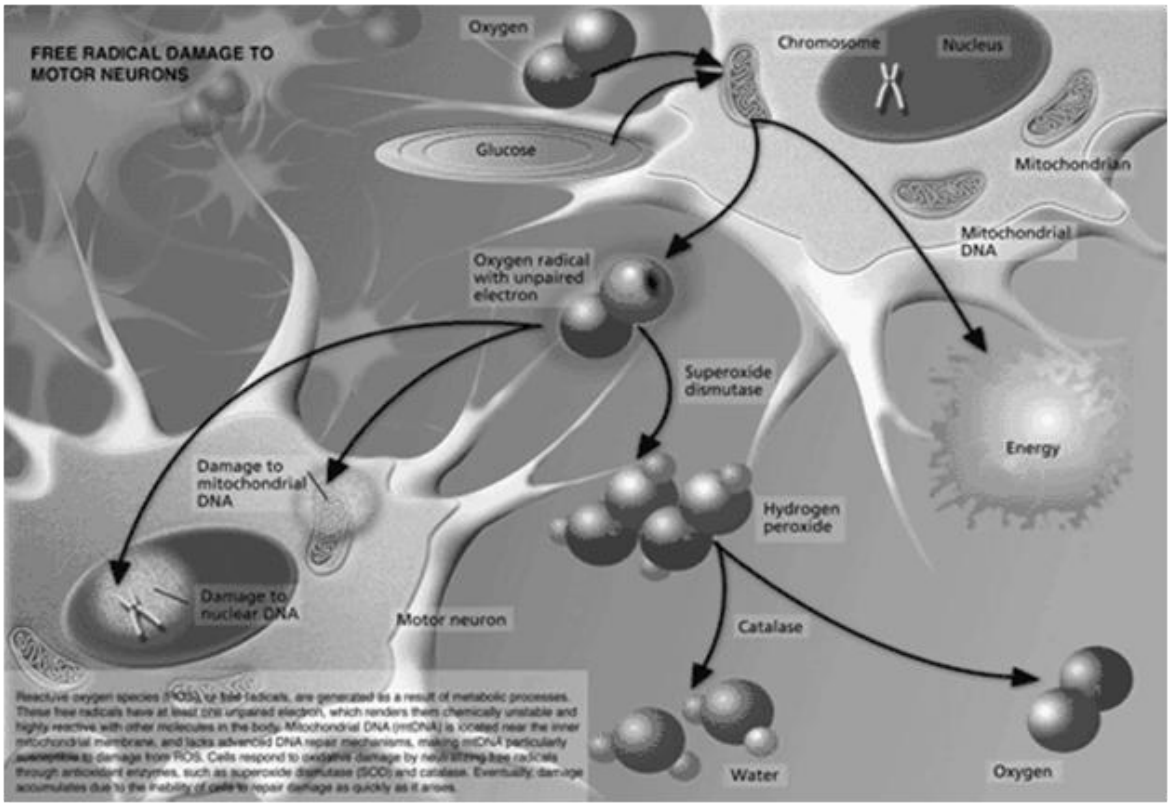

Figure 1.4: Illustration of the process in which free radicals are made and also managed by the body's cells (Eisen, 2000).

The cochlear pathology observed with exposure to ototoxic agents is typically classed as a motor loss, where problems are limited to the OHCs only, or a mixed loss, which involves disruptions to both the OHCs and IHCs, and is dependent on the particular agent (Patuzzi, 2009). The following section will discuss the ototoxic antineoplastic agent cisplatin and its effect on the cochlea.

1.3 Cisplatin

1.3.1 Structure

Cis-diamminedichloroplatinum II (cisplatin; CDDP; [$N_2Cl_2PtH_6$]) is a chemotherapeutic agent derived from the heavy metal platinum (Pt). Cisplatin originated from a discovery in 1965 where inhibition of the cell division process was noted in a study examining cultured bacteria and electrical fields using platinum electrodes (Rosenberg, Van Camp, & Krigas, 1965). Subsequent investigation involving mice showed platinum compounds to have anti-tumour activity (Rosenberg, Van Camp, Trosko, & Mansour, 1969). Cisplatin is a square-planar neutral platinum (II) complex consisting of a divalent Pt(II) central atom and four ligands of *cis*-positioned pairs of chlorine atoms or amine groups (Figure 1.5) (Rybak, Huang, et al., 2007). This unique structure of cisplatin is critical for its cytotoxic activity, which occurs as a result of coordinative bonds between the platinum atom and genomic DNA, and the formation of inter- and intra-strand crosslinks (McKeage, 1995).

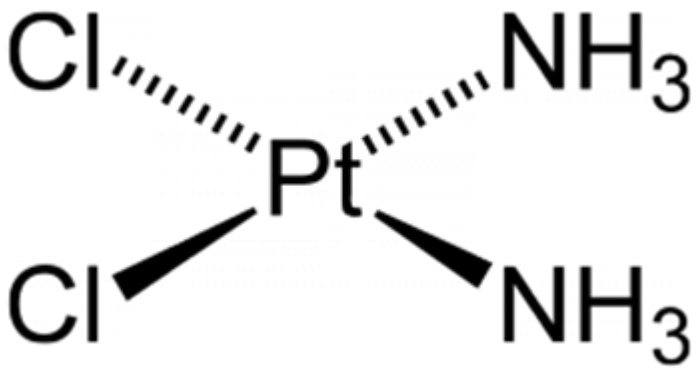

Figure 1.5: Structural formula for cisplatin molecule (Weiss, 2009)

1.3.2 Clinical application

Cisplatin is used extensively as a potent anti-neoplastic drug in the management of a wide variety of soft-tissue neoplasms including testicular, prostate, ovarian, endometrial, cervical, bladder and lung carcinoma, and SCC of the head and neck. It is also used in the treatment of paediatric malignancies, such as neuroblastomas, hepatoblastomas, brain cancer and osteosarcoma (Schmidt, et al., 2008). The toxicity profile of cisplatin is significant, however, and includes nephrotoxicity, gastrointestinal toxicity, peripheral neurotoxicity, haematological toxicity and ototoxicity. Successful modifications of

cisplatin administration involving saline hydration and mannitol diuresis have ameliorated nephrotoxicity, which was originally the most significant dose-limiting side effect (McKeage, 1995). In spite of this, ototoxicity remains a significant dose-limiting factor in cisplatin-based chemotherapy. Cisplatin has the highest ototoxic potential of all platinum compounds and is regarded as the most ototoxic agent in clinical use (Anniko & Sobin, 1986; Barr-Hamilton, Matheson, & Keay, 1991).There is large inter-patient variability in the ototoxic side effect of cisplatin. Whether this variability is a result of differences in drug concentrations within the inner ear or due to physiological factors is yet to be established.

1.3.3 Pharmacokinetics

Due to the significant toxicity profile of cisplatin, determining the pharmacokinetic parameters is very important. Consideration is given to its properties of absorption, distribution, metabolism, excretion and elimination (Figure 1.6).

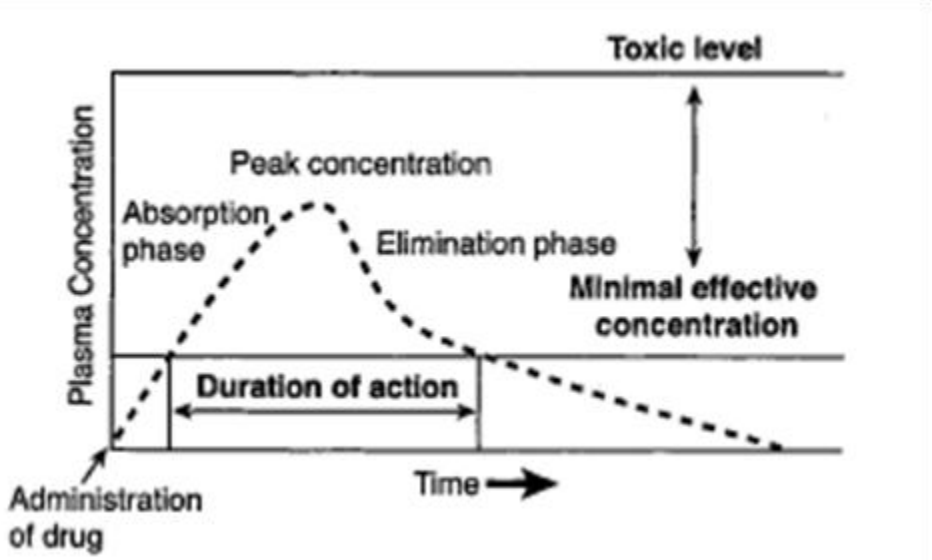

Figure 1.6: Pharmacokinetics of any given drug (Rey, 2007)

In the body cisplatin takes two forms, one which undergoes irreversible protein binding in plasma, rendering it biologically inactive, and the free (unbound) potentially active form (Urien & Lokiec, 2004). It is this unbound form that is capable of diffusing across membranes and interacting with target receptors. When measuring the distribution of a particular drug, however, the plasma concentration is often used because accurate evaluation of drug concentration in tissue or organs is difficult. Investigations have shown that following intravenous (IV) administration of cisplatin, initial peak plasma concentration is 3 to >5 µg/ml (Matsumoto, 2008). The levels of cisplatin decline in a triphasic fashion, with an initial plasma half-life ($t_{1/2}$) of 20 - 30 minutes, a second phase $t_{1/2}$ of 60 minutes, and a terminal $t_{1/2}$ of more than 24 hours (Himmelstein et al., 1981). Guinea pig models suggest that distribution of cisplatin to the perilymph occurs at a

slower rate, with the highest concentration measured at 4µg/ml 20 minutes post-administration and a perilymph:plasma ratio at 0.40 (Laurell, Anderson, & Engström, 1995). There was no observed accumulation in the perilymph compartment.

1.4 Cisplatin ototoxicity

1.4.1 Clinical features

Cisplatin-induced ototoxicity typically manifests as irreversible, progressive, bilateral, high frequency SNHL associated with tinnitus (Daldal, et al., 2007). Some audiometric studies have reported elevated pure-tone thresholds in 75-100% of patients treated with cisplatin (McKeage, 1995). There is, however, significant variation in the severity of the loss, ranging from a loss detectable only by extended audiometric evaluation to a severe loss affecting communication. Cisplatin ototoxicity mainly affects the cochlea, although limited vestibular dysfunction has also been documented (Cass, 1991).

The hearing loss after cisplatin exposure is most often described as symmetrical. Unilateral hearing loss resulting from cisplatin administration is rarely reported and is usually accounted for by unilateral cranial irradiation and/or surgical intervention. The idea that symmetrical damage to the inner ear occurs from the systemic administration of cisplatin is based on the assumption that the physiology of the structures is symmetrical. Interestingly, a recently study investigating hearing thresholds in 55 children (aged between 4.0 and 16.5 years) who were receiving cisplatin chemotherapy showed a small but significant asymmetry in behavioural thresholds at 4000, 6000 and 8000 Hz, with ototoxicity more pronounced in the left ear than the right (Schmidt, et al., 2008). A gender effect was also noted, with girls appearing less affected by the asymmetry than boys. The mechanisms behind this initial observation are currently unknown, however the author hypothesised that the asymmetry in hearing thresholds may be due to (1) different peripheral cisplatin effect between the ears, possibly resulting from a difference in cochlear blood flow; (2) supracochlear influences, such as the role of the medial olivocochlear system (MOCS) in the protection of the cochlea; and/or (3) the presence of cortical alterations due to cisplatin administration. Whether this effect also occurs in adults is unknown, and further research is warranted in this area.

1.4.2 Targets of cisplatin-induced ototoxicity

Investigations into the mechanisms and targets of cisplatin ototoxicity in the inner ear rely on electrophysiologic and histopathologic analysis. These methods are typically invasive and therefore ethically untenable in humans. As a result, what is currently known about the effects of cisplatin on the cochlea has been ascertained from animal models, in particular, guinea pigs, rats and mice. Experimental studies performed on animals have ascertained at least three major targets of cisplatin ototoxicity in the cochlea: the organ of Corti, spiral ganglion cells, and the lateral wall including the stria vascularis and spiral ligament.

Within the guinea pig organ of Corti, a wide range of cellular changes have been observed as early as one day after IV administration of high dose cisplatin (Laurell & Bagger-Sjöbäck, 1991). This study documented morphological changes in the cochlea of guinea pigs injected with a single high dose (12.5 mg/kg) of cisplatin that occurred after one, two, three and four days post-cisplatin injection. Three major stages of damage to the organ of Corti were identified. The first stage included disturbance of the supporting cells, namely swelling of the Hensen's cells and of Dieters' cells with protrusion into the space of Nuel (Figure 1.2). The supporting cells of the IHCs appeared less vulnerable. The second stage was characterised by the degeneration of the OHCs, including loss of stereocilia and intracellular vascuolisation. In addition, vacuoles appeared below the base of the IHCs. This typically occurred after all the OHCs had degenerated. In the final stage, degeneration of the entire organ of Corti and collapse of Reissner's membrane was noted. In this final stage, damage to the IHCs ranged from changes in hair cell shape to complete degeneration. This overall progression of events is corroborated by other studies (Ramírez-Camacho, García-Berrocal, Buján, Martín-Marero, & Trinidad, 2004). However, results are variable with reports of Dieters and Hensen cells remaining unaffected by cisplatin (Dehne, Lautermann, Petrat, Rauen, & de Groot, 2001).

In addition to the damage exerted on the organ of Corti, there is evidence that the stria vascularis is affected with reduction of the endocochlear potential, and elevation of the compound action potential and cochlear microphonic thresholds (Tsukasaki, Whitworth, & Rybak, 2000). Morphologically, strial damage has been noted to include oedema, bulging, rupture and/or compression of the marginal cells, and depletion of the cytoplasmic organelles (Meech, Campbell, Hughes, & Rybak, 1998). Evidence for cisplatin-induced degeneration of the spiral ganglion cells is limited, although detachment of the myelin sheaths of the type I spiral ganglion cells has been observed (van Ruijven, de Groot, & Smoorenburg, 2004). Further investigation (van Ruijven, de Groot, Klis, & Smoorenburg, 2005) attempted to time sequence these events, however, their examination failed to reveal any evidence of any one ototoxic process triggering another and thus concluded that both processes occur simultaneously and in parallel rather than sequentially.

1.4.3 Mechanisms of cisplatin-induced ototoxicity

The cellular and molecular mechanisms of cisplatin-induced ototoxicity are currently not well understood. A recent study by García-Berrocal et al., (2007) collected data supporting the involvement of the intrinsic apoptotic pathway in rat cochleae. Thirty female Sprague-Dawley rats were injected intraperitoneally with 5 mg kg^{-1} of cisplatin in 1.0 ml of normal solution (0.9% NaCl). A further six rats were injected with only 10 ml kg^{-1} 0.9% NaCl to serve as a control. The thirty rats were subsequently divided into three groups each containing ten rats: (1) rats that were decapitated 2 days post cisplatin administration; (2) animals that were decapitated seven days post cisplatin

administration; and (3) animals that were killed thirty days after cisplatin administration. The remaining six rats in the control group were also divided into three groups that were decapitated at two days (n = 2), at seven days (n = 2) and at thirty days (n = 2). Auditory brainstem response (ABR) traces were recorded before cisplatin administration and again directly before the animals were decapitated. Immunohistochemical techniques, including luciferase assays and Western blotting, examined the different caspase activities and ATP levels in protein extracts. ABR traces showed elevated thresholds in all thirty rats exposed to cisplatin, although this threshold shift was only found to be significant in group 1 ($p < 0.05$). The authors reported a significant decrease in ATP levels with cisplatin administration, consistent with increased energy requirements of cells undergoing cell death by apoptosis (Eguchi, Shimizu, & Tsujimoto, 1997). In addition, they found evidence to support the involvement of the intrinsic apoptotic pathway, with cochlear extracts exhibiting progressively higher expressions of caspase-9. (Devarajan et al., 2002) reported cisplatin-induced apoptosis in an *in vitro* model system using cochlear half-turns from Immortomouse. Increases in both caspase-8 and caspase-9 activity were noted, indicating the involvement of both the death receptor mechanism (extrinsic pathway) as well as mitochondrial (intrinsic) pathways. In contrast, Wang et al., (2004) did not observe a significant increase in caspase-8 activation in cisplatin treated guinea pig cochleae. Furthermore, local scala tympani perfusion of a caspase-8 inhibitor (z-IETD-fmk) was ineffective in ameliorating cisplatin-induced hair cell death and hearing loss. These results suggest that *in vivo* cisplatin-induced apoptosis of cochlear cells is caspase-8 independent. The authors postulated this difference may result from *in vitro* versus *in vivo* conditions; however, activation of caspase-3 and caspase-9 was detected. Perfusion of their respective inhibitors, z-DEVD-fmk and z-LEHD-fmk, significantly reduced DNA fragmentation, hair cell death and hearing loss. Overall, the literature indicates the cisplatin-induced ototoxicity is mediated through the intrinsic apoptotic pathway (Wang & Bobbin, 2007).

In conjunction, evidence has arisen accumulated from numerous studies implicating ROS in the destruction of sensory cells in the cochlea (Mukherjea et al., 2006). Cisplatin administration has been shown to result in depletion of glutathione and antioxidant enzymes (superoxide dismutase, catalase, glutathione peroxidise and glutathione reductase) in cochlear tissues, with an equivalent increase in malondialdehyde levels (Rybak, Husain, Morris, Whitworth, & Somani, 2000). This decrease in glutathione levels is thought to indicate the formation of ROS in cisplatin oto- and nephrotoxicity (Husain et al., 1998). Exposure to cisplatin generates the superoxide anion which, although not highly toxic itself, can transform into hydrogen peroxide and subsequently into the highly reactive hydroxyl radical as a result of catalysis by iron (the Fenton reaction). The hydroxyl radical is then free to react with all biological macromolecules and polyunsaturated fatty acids, generating the toxic aldehyde 4-hydroxynonenal (4-HNE) through lipid peroxidation (Figure 1.7). Findings by Lee et al., (2004) suggest hair cell

degeneration is in part due to the hydroxyl radical, indicating that iron plays an important role in cisplatin ototoxicity (Dehne, et al., 2001). Exposure to ROS can induce apoptosis (Wang & Bobbin, 2007).

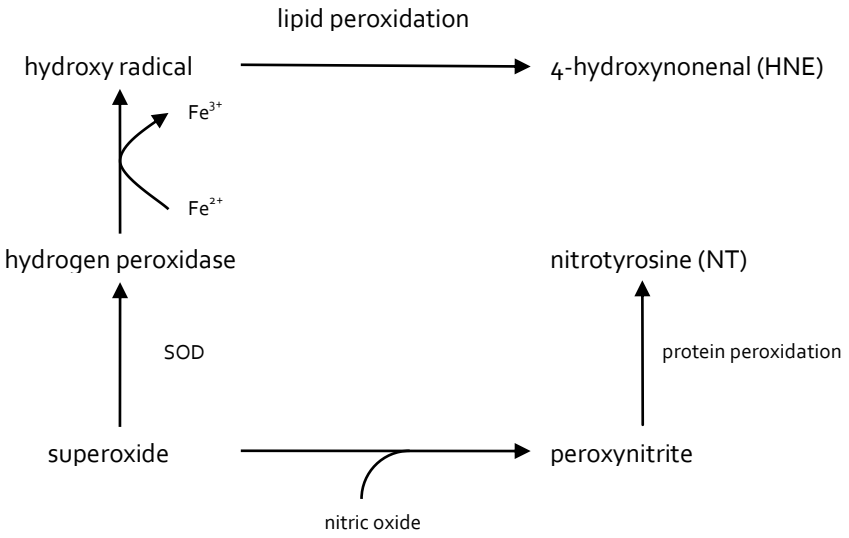

Figure 1.7: Diagram of the generation of highly reactive radical species. SOD – superoxide dismutase (J. E. Lee, et al., 2004)

1.4.4 Risk factors

There appears to be substantial variation in human susceptibility to cisplatin-induced ototoxicity possibly as a result of treatment and patient-related factors, such as cumulative dose, age, renal dysfunction, cranial irradiation and diet. Each of these factors is discussed below.

1.4.4.1 Cumulative dose

A number of studies have investigated the effect of cumulative cisplatin dose on observed ototoxicity, particularly cumulative doses greater than 400 mg/m^2. Li, Womer & Silber (2004) examined pure-tone audiograms from 153 children, ranging in age from 6 months to 18 years, who had received cisplatin therapy at doses of 40 to 200 mg/m^2/cycle. The risk of developing bilateral moderate to severe high-frequency hearing loss was significantly related to individual and cumulative cisplatin dosage (both $p < 0.005$). This is supported by Brock, Bellman, Yeomans, Pinkerton and Pritchard(1991) who retrospectively assessed 29 children who had been treated with 60 - 100 mg/m^2/cycle cisplatin. The risk of developing ototoxicity increased significantly with the cumulative dose ($p = 0.027$). No evidence of hearing loss was found in children who received a cumulative dose less than 400 mg/m^2.

1.4.4.2 Age

Research suggests that cisplatin-induced ototoxicity is age-dependent, with increased susceptibility of young children and older adults. Li, et al., (2004) demonstrated that

children younger than five years of age at the time of treatment are more likely to experience cisplatin-induced ototoxicity than their older peers. A logistic regression model predicts that approximately 40% of the children younger than 5 years would develop moderate to severe losses when they receive a cumulative dose of 400 mg/m^2, compared with the 5% risk among children between 15 and 20 years of age. This translates into an average of an eight-fold increase in relative risk. Helson, Okonkwo, Anton and Cvitkovic (1978) observed that hearing loss was more severe in patients aged 8 to 20 years, or older than 46 years of age, who received a cumulative dose greater than 400 mg/m^2 than in patients aged 21 to 45 years receiving the same dosage.

1.4.4.3 Renal dysfunction

Given the role of the kidneys in the clearance of cisplatin, renal function measured by serum creatinine levels is of significance. A study by Bokemeyer et al., (1998) examined various aspects of ototoxicity in 86 patients who had been in complete remission for at least 12 months. Information regarding previous auditory symptoms, potential risk factors and treatment variables was collected. Serum creatinine levels were measured prior to cisplatin administration and showed that patients with higher levels (92 μmol 1-1) were significantly more likely to report persisting ototoxic symptoms that patients with lower levels (83 μmol 1-1) (P = 0.04). This observation is in accordance with reports from (Schaefer, Post, Close, & Wright, 1985). Patients with renal insufficiency (poor renal creatinine clearance) are at greater risk of ototoxicity due to increased serum active cisplatin levels (Rybak, 2007).

1.4.4.4 Noise

Bokemeyer et al., (1998) also examined noise exposure as a risk factor. A history of noise exposure was independently correlated to both persisting ototoxic symptoms (P = 0.006) and to audiometrically verified hearing loss (P = 0.04). Seven of 15 (47%) patients with previous noise exposure, compared with 10 of 66 (15%) patients without a history of noise exposure, complained about ototoxic symptoms. This showed a 3.1-fold increased relative risk for ototoxicity in patients with a history of noise exposure.

1.4.4.5 Cranial irradiation

Cranial irradiation is a risk factor that is particularly pertinent to this study. Hearing loss is a relatively common complication of irradiation to the head and neck area (Honoré, Bentzen, Møller, & Grau, 2002; Raaijmakers & Engelen, 2002; Talmi, Finkelstein, & Zohar, 1989). Irradiation can cause two kinds of hearing impairment; conductive hearing loss (such as otitis media) and SNHL (Honoré, et al., 2002). A systematic review of the literature yielded substantial variability in the reported incidence of SNHL resulting from irradiation alone, ranging from 0% to 50% (Raaijmakers & Engelen, 2002). The authors concluded that at least one out of three patients receiving a standard dose of 70 Gy in 2 Gy per fraction near the inner ear can be expected to develop hearing loss of 10 dB or more at 4 kHz. When in combination with cisplatin treatment, an increase in risk was

noted (Low, Toh, Wee, Fook-Chong, & Wang, 2006). Hearing thresholds in patients receiving 25 mg/m2/day cisplatin for four days and 70 Gy in 2 Gy per fraction irradiation (n = 58) were significantly poorer (p = 0.001) when compared with those receiving irradiation alone (n = 57) (Low, et al., 2006).

1.4.4.6 Diet

A study investigating the effect of dietary factors on cisplatin ototoxicity in guinea pigs found a correlation between low-protein diets and severity of hearing loss (Lautermann, Song, McLaren, & Schacht, 1995). Four experimental groups of pigmented, adult male guinea pigs were maintained either on a regular guinea pig diet (18.5% protein) or a low protein diet (7% protein) for two weeks before the start of drug treatment. The groups consisted of: (1) a control group with 9 guinea pigs on the full protein diet; (2) 9 guinea pigs on the low protein diet; (3) 18 animals in the cisplatin-treated group on the full protein diet; and (4) 22 animals in the cisplatin-treated group on the low protein diet. Cisplatin (1 mg/kg) was injected subcutaneously into animals in groups 3 and 4 for 12 consecutive days. Every other day the animals were weighed and the dose of cisplatin adjusted accordingly. ABR recordings were obtained from all groups at the beginning of the study and on experimental days 13 and 15. Serum platinum, serum albumin, blood urea nitrogen (BUN) and creatine levels were ascertained in addition to glutathione levels in the tissue. Results showed that the control animals on either diet did not develop any hearing loss. The guinea pigs fed on the full protein diet (group 3) displayed minimal hearing loss (9 ± 6 dB at 8 kHz, and 10 ± 9 dB at 18 kHz), while guinea pigs on the low protein diet (group 4) displayed significantly greater hearing loss (23 ± 17 dB at 8 kHz, and 32 ± 23 dB at 18 kHz) ($p < 0.005$). Glutathione levels in the control animals on a low protein diet were half that of those on a full protein diet. The addition of cisplatin, however, did not seem to decrease these levels any further. The mean values of serum albumin and serum platinum levels were not statistically significant between the four groups. BUN levels were significantly reduced by the low protein diet (group 2), while treatment with cisplatin elevated BUN in both group 3 and 4. In contrast, creatine levels remained unaffected by diet but increased in response to cisplatin treatment. The authors concluded that the severity of ototoxicity is influenced by dietary factors. This finding is in agreement with clinical studies that have associated cisplatin ototoxicity with patient's general health (Blakley, Gupta, Myers, & Schwan, 1994).

1.4.5 Protection against cisplatin-induced ototoxicity

The cochlea is thought to have endogenous cytoprotective responses to injury that may arise from, for example, oxidative stress resulting from cisplatin exposure. The cytoprotective responses involve many molecules, including glutathione and the antioxidant enzymes, heat shock proteins, adenosine A1 receptors, NRF2 and heme-oxygenase-1, and the kidney injury molecule (KIM-1) (Mukherjea, et al., 2006). High

concentrations of ROS, however, may overwhelm this regenerative process and lead to cell death.

In current clinical practice, cisplatin-induced ototoxicity is tolerated as a side-effect of cancer treatment. Numerous agents have been investigated for their protective properties against cisplatin-mediated damage in the cochlea and include both upstream and downstream protection (Table 1.1). Due to concerns regarding potential interference with the anti-tumour effect of cisplatin, there are currently no otoprotective agents approved for use in humans by the Food and Drug Administration (FDA) or Medsafe. The following section will discuss the various agents that have been investigated for protecting the cochlea against cisplatin-induced ototoxicity.

Table 1.1. Effects of protective agents against cisplatin ototoxicity (adapted from Rybak & Whitworth, 2005)

Agent	Mechanism	In vivo[a]	In vitro[b]	Species	Degree of protection[c]
Thiosulfate	Upstream chelator	Cochlear perfusion		Guinea pig	+++
Thiosulfate	Upstream chelator	Chronic round window		Guinea pig	0
Amifostine	Upstream chelator	i.p		Hamster	+++
Glutathione ester	Antioxidant	i.p		Rat	+
Diethyldithiocarbamate	Upstream chelator	i.p		Rat	++
Methylthiobenzoic acid	Upstream chelator	i.p		Rat	++
Ebselen		i.p		Rat	+++
Ebselen & Allopurinol		p.o		Rat	++
Salicylate	Antioxidant	s.c		Rat	++
Salicylate	Antioxidant	s.c		Rat	+++
α - Tocopherol	Antioxidant	i.p		Rat	++
α - Tocopherol	Antioxidant	i.p		Guinea pig	++
Trolox	Antioxidant	Round window		Guinea pig	++
α - Tocopherol + tiopronin	Upstream chelator and antioxidant	i.p		Guinea pig	++
Tiopronin	Upstream chelator	i.p		Rat	++
Aminoguanidine	Inhibits iNOS	i.p		Rat	++
R-PIA	Increases antioxidant concentrations	Round window		Chinchilla	++
CCPA	Adenosine receptor modifier	Round window		Chinchilla	++
Z-DEVD-fluoromethyl ketone (caspase-3 inhibitor)	Downstream apoptosis prevention	Cochlear perfusion		Guinea pig	+++
Z-LEKD-fluoromethyl ketone (caspase-9 inhibitor)	Downstream apoptosis prevention	Cochlear perfusion		Guinea pig	+++
Pifithrin			X		++
D-JNKI 1	Downstream apoptosis prevention	Cochlear perfusion		Guinea pig	0
M40403			X		0
D-methionine	Prevents antioxidant enzyme depletion	i.p		Rat	+++

[a] Abbreviations: i.p., intraperitoneal; p.o., *per os*; s.c., subcutaneous.
[b] Key: X denotes that *in vitro* studies have been carried out.
[c] Key: +, low efficacy; ++, moderate efficacy; +++, high efficacy

Otoprotective agents can be classed as either upstream protectors or downstream protectors.

1.4.5.1 Upstream protection

One strategy to protect the cochlea from cisplatin-induced ototoxicity is the administration of antioxidant drugs. Antioxidants are chemicals that protect cellular components from the oxidative damage caused by free radicals and other reactive oxygen species. Antioxidants are thought to provide upstream protection by preventing the initiation of cell death in the cochlea (Rybak, Whitworth, Mukherjea, & Ramkumar, 2007). A variety of antioxidant compounds have been tested against cisplatin-induced ototoxicity, several of which contain thiol groups. The effectiveness of this group is based on the high affinity of sulphur for platinum (Campbell & Rybak, 2007). Sodium thiosulfate (STS) is thought to neutralise cisplatin by forming an inactive platinum-thiosulfate complex that is excreted by the kidney, reducing its ototoxic and chemotherapeutic properties (Wimmer et al., 2004). Wang, et al., (2003) investigated direct application of STS to the cochlea through perilymphatic perfusion. Twelve guinea pigs were divided into two groups and fitted with an osmotic minipump to their right cochlea containing either (1) artificial perilymph (n = 6), or (2) 10 mM STS (n = 6). After two days, all 12 guinea pigs received intraperitoneal injections of 2 mg/kg/day cisplatin for 5 consecutive days. Audiograms were derived from the compound action potential (CAP) for both ears daily and distortion product otoacoustic emissions (DPOAEs) were measured at the end of the treatment period. Guinea pigs that received a perfusion of artificial perilymph experienced hearing loss in both the left and right ear, consistent with cisplatin-induced ototoxicity. In contrast, guinea pigs that received a perfusion of STS showed a statistically significant difference between the left ear and the right ear ($P < 0.01$). DPOAE results remained unchanged in the right ear. Histological analysis revealed minimal loss of OHC in the organ of Corti and no damage to the marginal cells of the stria vascularis. Furthermore, it prevented cisplatin-induced mitochondrial damage by suppressing apoptotic and necrotic hair cell degeneration. Although effective, it is unlikely that this highly invasive route would be considered for routine use in humans. Similar research by Wimmer, et al.,(2004) found no protection against cisplatin-induced ototoxicity when STS was applied to the round window membrane. Potential reasons for this include insufficient dose of STS relative to the higher dose of cisplatin used in the latter study, or problems with the placement of the round window catheter (Rybak, Whitworth, et al., 2007). Another member of the thiol group, D-Methionine (D-Met), has also been investigated for protection against cisplatin-induced hearing loss, OHC loss and damage to the stria vascularis in rat cochleae, with promising results (Campbell, Meech, Rybak, & Hughes, 1999; Campbell, Rybak, Meech, & Hughes, 1996; Meech, et al., 1998). D-Met is advantageous in that it does not interfere with the tumouricidal action of cisplatin (Rybak, Whitworth, et al., 2007). α-tocopherol (vitamin E), a slow-acting free radical scavenger is another antioxidant that appears to have a protective effect against

cisplatin ototoxicity in both rats (Kalkanis, Whitworth, & Rybak, 2004) and guinea pigs (Teranishi, Nakashima, & Wakabayashi, 2001). α-tocopherol can scavenge the highly reactive hydroxyl radical preventing lipid peroxidation (Figure 1.8).

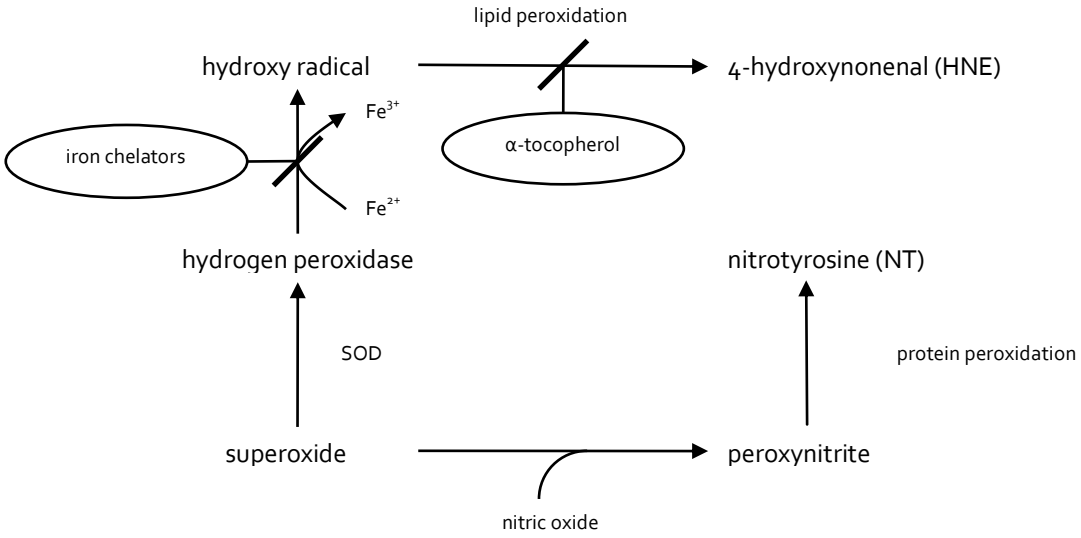

Figure 1.8: Illustration of defence mechanisms against damage by ROS. Iron chelators bind to iron ions and minimise the formation of the hydroxyl radical. A-tocopherol acts as a radical scavenger of the hydroxyl radical. SOD – superoxide dismutase (J. E. Lee, et al., 2004).

Another agent that provides upstream protection is tiopronin. Intraperitoneal injections of tiopronin have been shown to exert a protective effect on the rat cochlea (Fetoni et al., 2004). Twenty-four adult Wistar rats were divided into three equal groups: (1) those who received saline only; (2) those who received 2 mg/kg cisplatin injections; and (3) those who received 2 mg/kg cisplatin and 300 mg/kg tiopronin. Dosage was repeated for eight consecutive days. Cochlear function was measured by DPOAEs before treatment and on the fourth and ninth day post-injection. DPOAE responses were significantly reduced in group 2 compared to the controls (group 1) ($p < 0.05$) while DPOAE responses from group 3 were significantly increased compared to those obtained with cisplatin administration alone ($p < 0.05$). Electron microscopy of the cochlea showed that tiopronin had a significant protective effect on the basal half and in the middle of the lower turn of the cochlear.

Glucocorticoids are a class of drugs that have shown promising results as an otoprotectant, also functioning as an upstream protector. Nagura et al., (1999) examined the effect of one glucocorticoid, hydrocortisone, on impaired cochlear blood flow induced by ROS in guinea pigs. Cochlear microcirculatory disorders were induced by photochemical reactions. Hartley guinea pigs were divided into the following five groups:

(1) those who received 0.8 ml/kg of saline (n = 6), (2) those who received 600 mg/kg of amidotriziate (n = 6), (3) those who received 4 mg/kg of ATP (n = 6), (4) those who received 50 mg/kg of hydrocortisone (n = 5), and (5) those who received 100 mg/kg of hydrocortisone (n = 5). The drugs were administered by IV infusion 10 minutes prior to the start of the photochemical reaction. Cochlear blood flow was continuously measured with a non-contact laser flowmeter for 30 minutes. Of the three drugs tested, hydrocortisone was found to be the most effective in attenuating the impairment of cochlear blood flow and cochlear vascular conductance. It was found to have significantly prevented a decrease in the cochlear blood flow ($p < 0.05$) in a dose dependent manner, and reduced the size of the degenerated portion of the stria vascularis ($p < 0.01$). These observations support the hypothesis that hydrocortisone has therapeutic potential for improving tissue inflammation of the cochlea induced by ROS. This is in agreement with previous research that reported hydrocortisone as a non-enzymatic antioxidant that can prevent lipid perioxidation (Otamiri, 1989). Subsequent research has shown another glucocorticoid, dexamethasone, to significantly reduce aminoglycoside ototoxicity in guinea pigs (Himeno et al., 2002) and chinchillas (Park, Choi, Russell, John, & Jung, 2004), presumably by inhibiting the synthesis of nitric oxide and free radical formation. This may be significant, as aminoglycoside ototoxicity is thought to have a similar pathogenesis to cisplatin ototoxicity. However, corticosteroids, such as dexamethasone, have also been shown to down-regulate apoptosis genes in tumour cells (Herr et al., 2003). This raises concern that systemic administration may decrease the efficacy of cisplatin's anti-tumour properties. In addition, prolonged administration of high-dose oral corticosteroids have been associated with serious adverse side-effects including bone fractures, osteoporosis, susceptibility to infections, hyperglycaemia and weight gain (Manson, Brown, Cerulli, & Vidaurre, 2009).

The systemic administration of corticosteroids, such as dexamethasone, is currently used extensively in the management of a number of inner ear disorders including autoimmune disease, idiopathic sudden SNHL, acute postmeningitic labyrinthitis and Cogan's syndrome. Intratympanic (IT) administration of drugs is a contemporary method used in the treatment of the disorders listed above and allows a much higher concentration of drug within the inner ear when compared to oral or parenteral routes (Bird, Begg, Zhang, Keast, & Murray, 2007). Other advantages may include avoidance of common side-effects associated with systemic steroids. Potential disadvantages, however, may include pain, chronic tympanic membrane perforation, acute otitis media, otorrhea, vertigo, and the possibility of further deterioration in hearing (Haynes, O'Malley, Cohen, Watford, & Labadie, 2007). Pharmacokinetic profiles of dexamethasone in guinea pig models showed elevated perilymph concentrations at > 5 mg/L for six hours following round window membrane administration and placement of a saturated gel foam pad within the middle ear for 45 minutes (Yang et al., 2008). The human model showed peak concentration of 20 mg/L with variability in half-life ($t_{1/2}$) between 13.5 and 27 minutes (Bird, et al., 2007).

Daldal et al., (2007) investigated the protective effect of IT dexamethasone on cisplatin-induced ototoxicity in 24 adult female guinea pigs. The animals were divided into four groups: those exposed to (1) cisplatin only, (2) IT dexamethasone only, (3) cisplatin and IT dexamethasone, and (4) cisplatin and IT saline. Cochlear function was assessed using DPOAEs. Group 1 experienced statistically significant decreases of both DPOAE amplitude and signal to noise ratio (SNR) ($p = 0.002$). Groups 2 and 4 showed no significant difference ($p > 0.05$), indicating that intratympanic dexamethasone and saline had no toxic effect on cochlear emissions in this study. Of particular importance are the results from group 3 that showed no significant differences between DPOAE amplitudes and SNR values before and after cisplatin treatment for those who also had dexamethasone injections ($p > 0.05$). This was further investigated by Hill, Morest and Parham (2008) who conducted a three phase trial using female CBA/J mice. Pre-treatment ABRs were obtained in ten mice. On day one each mouse received IT dexamethasone (24 mg/ml) in one ear and IT 0.9% saline in the contralateral ear, serving as a control. The mice were divided so that five of the mice received dexamethasone injections in the left ear and saline in the right, whereas the other five received the dexamethasone to the right ear and saline in the left. Following the initial IT injections, all mice were administered 14 mg/kg intraperitoneal cisplatin. IT dexamethasone and saline injections were repeated on days two to five. Post-treatment ABR was performed on day eight. There was a 20% mortality rate observed and one case of otitis media in a dexamethasone-treated ear which was excluded from the analysis. ABR traces from the remaining seven dexamethasone-treated ears and the eight saline-treated ears were compared. Average click-evoked ABR thresholds were elevated by 14 ± 6 dB for ears treated with IT saline, whereas ears treated with IT dexamethasone had a minimal average click-evoked ABR threshold shift of 2 ± 2 dB ($p = 0.0005$). A similar result was obtained with pure-tone evoked ABR at 8 kHz ($p = 0.03$) and 16 kHz ($p = 0.002$). There was, however, no significant difference observed between dexamethasone and saline-treated ears at 32 kHz ($p = 0.8$). The authors speculate this may be due to decreased efficacy at the basal turn of the cochlea where there is increased susceptibility to cisplatin ototoxicity. Overall, these results support those found by Daldal et al., (2007) that IT dexamethasone appears to play a protective role against cisplatin-induced ototoxicity. To the best of our knowledge, these findings have not yet been replicated in humans.

1.4.5.2 Downstream protection

Downstream protection has been investigated less frequently than upstream protection. Downstream protection against cisplatin-induced ototoxicity in guinea pigs has been achieved with intracochlear perfusion of caspase-3 inhibitor (z-DEVD-fmk) and caspase-9 inhibitor (z-LEHD-fmk) (Wang, et al., 2004). Both agents have dramatically reduced the incidence of hearing loss, apoptosis and hair cell loss, although, the method of administration is invasive and therefore may not be appropriate for use in patients.

1.5 Audiologic assessment & monitoring

Hearing loss can result in significant vocational, educational and social consequences. Risk factors for developing hearing loss from ototoxic agents have been identified, although these are highly variable. Hearing loss from ototoxicity can be minimised or prevented if detection is timely and intervention appropriate, such as modifying the dose of the ototoxic drug or changing to an alternative, less ototoxic therapy. For this to occur, a stringent protocol is required, involving the coordination and education of a number of health professionals. One aim of the present study was to determine the extent to which this has been happening at Christchurch Public Hospital, in New Zealand.

One of the largest governing bodies for audiologists, the American Speech-Language-Hearing Association (ASHA), formed an Ad Hoc Committee on Audiologic Management of Individuals Receiving Ototoxic and/or Vestibulotoxic Drug Therapy and subsequently developed "Guidelines for the audiologic management of individuals receiving cochleotoxic drug therapy" (American Speech-Language-Hearing Association, 1994). In it, they outlined six fundamental elements of a cochleotoxicity monitoring programme: (1) specific criteria for identification of toxicity; (2) timely identification of at-risk patients; (3) pre-treatment counselling regarding potential cochleotoxic effects; (4) valid baseline measures (pre-treatment or early in treatment); (5) monitoring evaluations at sufficient intervals to document progression of hearing loss or fluctuation in sensitivity; and (6) follow-up evaluations to determine post treatment effects. Each of these fundamental elements is outlined below.

1.5.1 Basic principles of cochleotoxicity monitoring

1.5.1.1 ASHA criteria for cochleotoxicity

Determining whether ototoxicity has occurred clinically is achieved by comparing results of audiometric tests to baseline data obtained prior to the beginning of treatment. This method takes into account the patient's previous hearing status, thus serving as their own control. ASHA (American Speech-Language-Hearing Association, 1994) defines clinically significant changes in pure-tone thresholds as: (1) ≥ 20 dB decrease at any one test frequency; (2) ≥ 10 dB decrease at any two adjacent test frequencies; or (3) loss of response at three consecutive test frequencies where responses were previously obtained. These thresholds must be confirmed by a repeat assessment. The third criterion refers specifically to the highest frequencies tested, where previous responses were obtained close to the limits of the audiometer. Criteria for clinically significant changes in threshold must be sensitive and specific to minimise rates of false positives and false negatives. Test-retest reliability for behavioural pure-tone thresholds is reported to be ± 10 dB for the frequency range 0.5 – 16 kHz (Frank, 2001; Schmuziger, Probst, & Smurzynski, 2004), while threshold shifts at two adjacent frequencies are thought to

better represent an actual change in hearing sensitivity rather than normal variation (Pasic & Dobie, 1991).

1.5.1.2 Patient identification

ASHA (American Speech-Language-Hearing Association, 1994) recommends all patients receiving treatment with drugs known or suspected to have cochleotoxic properties should undergo monitoring as part of a protocol that is implemented in a timely manner. For this to occur, it requires access to a registry of patients (both inpatients and outpatients) who are being treated with potentially cochleotoxic medication, and effective communication and cooperation between audiology, oncology, nursing and hospital pharmacy personnel. Patients who are likely to be particularly susceptible to ototoxicity should also be identified. These include very young patients (Li, et al., 2004), those with poor renal function (Rybak, Huang, et al., 2007) and those prescribed prior or concurrent cranial irradiation (Honoré, et al., 2002; Raaijmakers & Engelen, 2002).

1.5.1.3 Pre-treatment counselling

Prior to patients undergoing medical treatment with cochleotoxic drugs, appropriate counselling should be utilised. Fausti et al., (2007) suggests three different phases of patient counselling by the audiologist: (1) initiating contact with and educating the patient about potentially ototoxic medications; (2) counselling the patient about possible hearing changes and post-treatment rehabilitation; and (3) emphasising the importance of hearing protection during and following therapeutic treatment. Patients should be encouraged to report symptoms such as tinnitus, aural fullness, loss of balance, and changes in hearing sensitivity to their physician if they occur.

1.5.1.4 Baseline testing

Obtaining accurate baseline data is crucial for the successful monitoring of patients receiving ototoxic medication. As cisplatin can cause measureable hearing loss following administration of a single dose, ASHA (American Speech-Language-Hearing Association, 1994) recommends that a baseline evaluation should preferably be carried out prior to the first dose of cisplatin, and no later than 24 hours after. Testing should begin with a comprehensive case history, ascertaining the presence of any current auditory and vestibular symptoms, details of previous noise exposure and prior exposure to ototoxic medication. In addition, Fausti et al., (2007) recommend that a form of tinnitus evaluation is administered such as the Tinnitus Ototoxicity Monitoring Interview (TOMI) (Table 1.2). This was designed to document tinnitus onset and any perceptual changes that occur during the monitoring phase. The rest of the baseline evaluation should include otoscopy, tympanometry, acoustic reflexes to assess the status of the middle ear, and pure-tone audiometry to obtain air conduction thresholds at 0.5, 1, 2, 3, 4, 6, 8, 9, 10, 11.2, 12.5, 14, 16, 18, and 20 kHz bilaterally. Bone conduction thresholds should also be obtained at 0.5, 1, 2 and 4 kHz in order to identify any conductive pathology. A test of

speech discrimination should also be included. Lastly, an objective measure should be employed, such as DPOAEs.

Table 1.2 The Tinnitus Ototoxicity Monitoring Interview (TOMI) (Fausti, et al., 2007)

You are being treated with a medication that has the potential to affect the auditory system. One possible effect is tinnitus, which is ringing, humming, buzzing, or other noises in your ears or head.			
1. [Clinician: ask only at the first visit] Did you have persistent tinnitus before the start of treatment?	☐ No	☐ Yes	
1a. If yes, how long have you had tinnitus?	☐ Less than 1 year	☐ 1-2 years	☐ 3-5 years
	☐ 6-10 years	☐ 11-20 years	☐ More than 20 years
	☐ Not sure		
2. Have you noticed any persistent tinnitus since you started the treatment?	☐ No	☐ Yes	
	If no, the interview is complete. No further questions are required. If Yes, continue to question 3.		
3. What does your tinnitus sound like? (Mark all that apply)	☐ Ringing	☐ Hissing	☐ Buzzing ☐ Sizzling
	☐ Crickets	☐ Whistle	☐ Hum
	☐ Other:		
4. Does your tinnitus have a pulsing quality to it?	☐ No	☐ Yes	
5. Where is your tinnitus located?	☐ Left ear only	☐ Right ear only	
	☐ Both ears	☐ Inside head	
	☐ Other:		
6. Is your tinnitus louder on one side of your head than the other?	☐ Right is louder than left		
	☐ Left is louder than right	☐ Equal	
7. How loud is your tinnitus on average?	☐ Not loud at all	☐ Slightly loud	☐ Moderately loud
	☐ Very loud	☐ Extremely loud	
8. How much of the time do you think your tinnitus is present?	☐ Occasionally	☐ Some of the time	
	☐ Most of the time	☐ Always	
9. On average, how much of a problem is your tinnitus?	☐ Not a problem	☐ Slight problem	☐ Moderate problem
	☐ Big problem	☐ Very big problem	
[Clinician: Ask the following questions only if the patient (1) had tinnitus before the start of treatment, or (2) reported tinnitus previously with this TOMI. The objective is to determine if the patient's tinnitus is being affected by the drug treatment. If the patient has previously responded to this interview, each response should reflect the period of time since the last interview. Otherwise, each response reflects the period of time since before the start of treatment.			
10. Has the sound of your tinnitus changed?	☐ No	☐ Yes	☐ Not sure
	If yes, how is it different?		
11. Has the location of your tinnitus changed?	☐ No	☐ Yes	☐ Not sure
	If yes, how is it different?		
12. Has the loudness of your tinnitus changed?	☐ No	☐ Yes, louder now	
	☐ Yes, quieter now	☐ Not sure	
13. Has the amount of time your tinnitus is present changed?	☐ No	☐ Yes, more often	
	☐ Yes, less often	☐ Not sure	

1.5.1.5 *Monitoring schedule*

Monitoring assessments should be scheduled at intervals that will allow the earliest possible detection of cochlear damage, ideally before conventional frequencies are affected so as to preserve speech perception (Jacob, Aguiar, Tomiasi, Tschoeke, & de Bitencourt, 2006). Appropriate time intervals may vary depending on the type of cancer and frequency and dose of cochleotoxic medication.

1.5.1.6 *Follow-up evaluations*

The purpose of follow up evaluation is to detect post-treatment cochleotoxicity and/or to document any recovery in hearing sensitivity. Fausti et al., (2007) recommends that testing be conducted at one month and three months after the cessation of treatment with the potentially ototoxic agent. At six months post-treatment a repeat assessment should be carried out to assess the patient's overall hearing health. Rehabilitative counselling may also be appropriate depending on test outcomes.

1.5.2 Measures of ototoxicity

1.5.2.1 *Pure-tone audiometry*

Cisplatin ototoxicity is well documented to cause initial damage in the basal turn of the cochlea, thus affecting high frequencies before progressing to affect lower frequencies. Consequently, a number of studies have demonstrated extended high-frequency (EHF) audiometry (> 8 kHz) to have increased sensitivity over conventional audiometry (≤ 8 kHz) in the early detection of ototoxicity (Dreschler, Hulst, Tange, & Urbanus, 1989; Fausti, Frey, Henry, Olson, & Schaffer, 1993; Knight, Kraemer, Winter, & Neuwelt, 2007; Ress et al., 1999). Identifying hearing loss before damage occurs at conventional frequencies may allow the preservation of hearing at frequencies most important for speech understanding and communication, thus reducing the impact on individuals' quality of life.

The use of continuous versus pulsed tones in EHF audiometry has been investigated. It has been noted that relative to continuous tones, pulsed tones decrease the number of false positives in both normal hearing listeners and listeners with SNHL with tinnitus (Mineau & Schlauch, 1997). There appears to be no significant difference in thresholds obtained using the two stimuli in normal listeners from 10 to 16 kHz (Hamill & Haas, 1986). More recently, Burk and Wiley (2004) found a preference for pulsed tones, particularly under more difficult listening situations such as low intensity and high frequency tones. This preference did not adversely affect the test's outcome and, in combination with the previous observations, supports the use of pulsed tones in EHF audiometry (Figure 1.9).

Figure 1.9: Illustration of a continuous pure-tone stimulus versus a pulsed tone stimulus

1.5.2.2 Otoacoustic emissions

OAEs provide a non-invasive objective measure of cochlear function. OAEs consist of acoustic energy produced by the cochlea that is recorded in the EAC, and are thought to result from electromechanical transduction by the OHCs of the cochlea (Kemp, 1978). OAEs can be observed via a number of different modes, commonly referred to as 'types' of OAEs (Kemp, 2008). These types include spontaneous otoacoustic emissions (SOAEs), stimulus frequency otoacoustic emissions (SFOAEs), transient-evoked otoacoustic emissions (TEOAEs), and DPOAEs. For the purpose of ototoxicity monitoring, DPOAEs have been found to be more effective than TEOAEs which elicit a broad band cochlear response (Schmidt, et al., 2008). DPOAEs are particularly valuable for monitoring ototoxicity in patients who are unable to provide reliable behavioural thresholds due to age (Knight, et al., 2007) or illness (Reavis et al., 2008).

The non-linearity of the cochlea is an essential component of cochlear function. One aspect of this non-linear phenomenon is distortion, the output of energy that is not present in the eliciting input frequencies (Prieve & Fitzgerald, 2002). DPOAEs are one result of this non-linear behaviour. The frequency of the distortion product is mathematically related to the frequencies of the two primary stimuli, f_1 and f_2. Although DPOAEs are produced at various frequencies, the largest amplitude response in humans is described by $2f_1 - f_2$ (Probst, Lonsbury-Martin, & Martin, 1991).

In the measurement of DPOAEs, two stimulus tones are applied which are normally less than half an octave apart. The presence or absence of DPOAEs is determined statistically by identifying the level of the response above the level of background noise at neighbouring frequencies (Kemp, 2008), commonly referred to as the signal-to-noise ratio (SNR). For behavioural thresholds up to 20 dB HL, DPOAEs typically have a SNR of greater than 5 dB (Hall, 2000), although OAEs are usually absent or significantly reduced when hearing thresholds are greater than 40 to 50 dB HL in cases of SNHL (Gorga, Neely, Dorn, & Hoover, 1997; Harris, 1990). The reliability, specificity and sensitivity of DPOAEs are generally high, with studies reporting sensitivity from 94% (Harris, 1990) to 100% (Gorga, Neely, & Dorn, 1999). OAEs were not in widespread clinical use when the specific ototoxicity guidelines were stipulated by ASHA, and therefore do not form a part of the test battery.

1.5.2.3 Tinnitus

Tinnitus is defined as the sensation of sound in the absence of exogenous stimuli (Lustig, 2010). Tinnitus can be divided into two general categories: objective and subjective tinnitus. Objective tinnitus is thought to originate from internally generated sounds that reach the ear via conduction in body tissues, and can be recorded objectively with a microphone or heard by another listener. Subjective tinnitus is thought of as a symptom with multiple aetiologies (McCombe et al., 2001). It has been associated with various forms of hearing loss including noise-induced hearing loss, presbycusis, and drug-induced ototoxicity. Many of the major groups of medication contain one or more compounds with ototoxic properties (Table 1.3). Although there is no tool available to objectively measure the intensity or severity, questionnaires are available to help substantiate the effect of tinnitus on individuals' physical, emotional, social and occupational functioning (Newman, Jacobson, & Spitzer, 1996).

Table 1.3: Medications and substances that can cause tinnitus (Crummer & Hassan, 2004)

Analgesics
Aspirin
Nonsteroidal anti-inflammatory drugs
Antibiotics
Aminoglycosides
Chloramphenicol (Chloromycetin)
Erythomycin
Tetracycline
Vancomycin (Vancocin)
Chemotherapeutics
Bleomycin (Blenoxane)
Cisplatin (Platinol)
Mechlorethamine (Mustargen)
Methotrexate (Rheumatrex)
Vincristine (Oncovin)
Loop diuretics
Bumetanide (Bumex)
Ethacrynic (Edecrin)
Furosemide (Lasix)
Other
Chloroquine (Aralen)
Heavy metals: mercury, lead
Heterocyclic antidepressants
Quinine

1.6 Presbycusis

In cases where a number of years have elapsed between the initial baseline assessment and any follow-up assessments, consideration should be given to the effect of age on hearing thresholds. Presbycusis is a general term that refers to hearing loss commonly associated with advancing age (Baloh, 1998) and is the result of a culmination of a lifetime of insults to the auditory system (Gates & Mills, 2005). Age-related hearing impairment is the most common sensory impairment in the elderly (Van Eyken, Van Camp, & Van Laer, 2007). Although the entire auditory system experiences changes with age, it appears that age-related structural changes to the external and middle ear do not typically have an adverse effect on audiometric function or speech understanding ability. In contrast, the cochlea undergoes significant changes as a result of the ageing process (Liu & Yan, 2007). Based on histological temporal bone examinations, presbycusis has been classified into six different types dependent on the main structures affected: sensory (loss of hair cells and supporting cells), neural (loss of ganglion cells), metabolic (atrophy of the stria vascularis), cochlear presbycusis (thickening of the basilar membrane), mixed, and indeterminate (Gates & Mills, 2005; Jordan & Roland, 2000). Mixed presbycusis is characterised by the presence of two or more of the classic types; while indeterminate, a relatively new classification, is characterised by submicroscopic alterations in the cochlea (Weinstein, 2002), and is reported to account for 25% of cases (Schuknecht & Gacek, 1993). Despite these histological-based classifications, it is important to recognise that causation is complex and most likely multifactorial. For example, it is likely that genetic variance as well as a history of significant noise exposure contribute to the pathogenesis of presbycusis (Fuchs, 2010).

The characteristic loss of high-frequency threshold sensitivity is generally thought of as the first sign of presbycusis, however, each classification has been associated with individual audiometric patterns. Sensory presbycusis is characterised by normal low-frequency hearing with a steeply sloping high-frequency loss, often with a dip in the 4 kHz region resembling noise-induced hearing loss (Demeester et al., 2009; Liu & Yan, 2007). As hair cell loss occurs at the extreme basal end of the cochlea, the patient is likely to have good speech discrimination until the lower speech frequencies are affected (Weinstein, 2002). Metabolic presbycusis has an audiogram characterised by a flat or slightly sloping configuration of mild to moderate severity (Demeester, et al., 2009) with good preservation of speech discrimination (Jordan & Roland, 2000). Cochlear presbycusis is assumed when other types of presbycusis are histologically excluded, and typically results in small decrements of high-frequency hearing (Weinstein, 2002), while neural presbycusis is not associated with any particular audiometric pattern (Demeester, et al., 2009).

The process of presbycusis can begin as early as young adulthood, but usually does not become evident until the fifth decade of life (Veras & Mattos, 2007).The prevalence of

presbycusis is generally thought to increase with advancing age and it is rare to find a person over the age of 70 who has not experienced a decline in hearing. A longitudinal study by Lee, Matthews, Dubno and Mills (2005) showed that on average hearing thresholds deteriorate approximately 1 dB per year for persons aged 60 years and over, depending on age, gender and initial thresholds. Variations are most evident in older adults at higher frequencies (Figure 1.10).

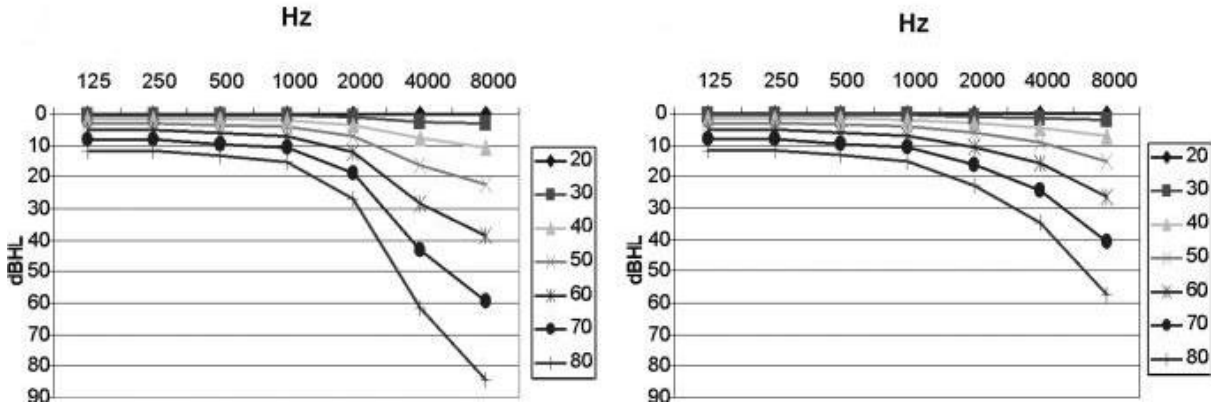

Figure 1.10: Median hearing thresholds in decibel hearing level (dB HL) across frequencies 125 to 8000 Hertz (Hz) according to the ISO 7029 standards for males (left) and for females (right) aged 20 to 80 years in 10 year increments (Van Eyken et al., 2006).

1.7 Rationale for the current study

Ototoxicity resulting from cisplatin chemotherapy constitutes a significant clinical problem that is currently tolerated as a side-effect of cancer treatment. At present there is no approved method for protecting or remedying against deterioration of hearing status. Therefore, the detection and appropriate management of cisplatin-induced ototoxicity is reliant on effective audiological monitoring. Guidelines for ototoxicity monitoring are not included in the Standards of Practice outlined by the governing body for audiologists in New Zealand, the New Zealand Audiological Society (NZAS). As a result, there is no cohesion, with protocols falling under the responsibility of individual audiology departments and clinics.

1.8 Aims of the current study

The present study has two main aims:

1. The first aim is to investigate the prevalence of ototoxicity in head and neck oncology patients who received cisplatin in combination with cranial irradiation.
2. The second aim of this study is to examine the current state of audiological monitoring for this population at Christchurch Hospital.

Guidelines established by ASHA emphasise the importance of pre-treatment assessment to provide a baseline measure for each individual patient. This is to be followed up with serial audiological assessments to monitor any deterioration in hearing status so that intervention and management can be timely and effective. This study will assess audiological monitoring via analysis of past audiometric data for the participants recruited into this study. Findings from this study will be useful in representing the current standard of audiological monitoring at Christchurch Hospital for patients receiving cochleotoxic therapy and how this may be improved. This is of particular relevance as this study precedes a Phase III clinical trial due to begin shortly at Christchurch Hospital, which proposes the trial of intratympanic dexamethasone administration to investigate potential protective effects against ototoxicity while preserving cisplatin's chemotherapeutic actions.

This study aims to increase audiologist's awareness of ototoxicity and the importance of comprehensive audiological monitoring. This research has the potential to improve patient hearing care and consequently improve their quality of life.

2 Method

2.1 Participants

In the three-month period from January to March 2010, a total of 23 participants underwent diagnostic audiological assessment at Christchurch Public Hospital for the purpose of the present study.

Individuals were eligible to be recruited into the present study based on the following criteria:

- Aged 18 years or older
- Previously received a diagnosis of carcinoma of the head and neck region
- Received treatment with cranial irradiation and concurrent cisplatin chemotherapy for the treatment or management of their cancer. This subset of patients is considered to be at high risk of ototoxicity due to concurrent cisplatin therapy and cranial irradiation (Low, et al., 2006)
- Canterbury District Health Board as their health provider

Accordingly, 39 eligible individuals were identified via the Christchurch Hospital Oncology Pharmacy database and sent a letter in December 2009 outlining the study and inviting them to take part (Appendix B). No monetary incentive was offered. Initially, 24 individuals accepted the invitation, giving a response rate of 61.5%. Unfortunately three individuals were not able to participate in the research; one individual was unable to be contacted via the contact details provided on the response form, one individual lived out of Christchurch and would not be available for testing until late 2010, and the last individual required an interpreter and was unable to be contacted to organise this. A follow-up letter was sent in February 2010 to the remaining 13 individuals who had not replied (Appendix C) in an attempt to increase participant numbers. Following this, an additional two individuals agreed to take part in this research giving an overall response rate of 66.7%. This is above the average response rate of 61% for postal correspondence and surveys (de Vaus, 2002). In total, 23 individuals were recruited for the present research.

The demographic characteristics of the participants are shown in Table 2.1. The age of the patients ranged from 51 to 81 years with a mean age of 60.2 years, and included 21 males and two females. Of the 23 patients, 13 had been diagnosed with SCC of the oropharynx, three of the oral cavity, two of the hypopharynx, two of the larynx, one of the nasopharynx, one of the neck, and the diagnosis of one individual was unknown. A schematic diagram of the head and neck region is shown in Figure 2.1.

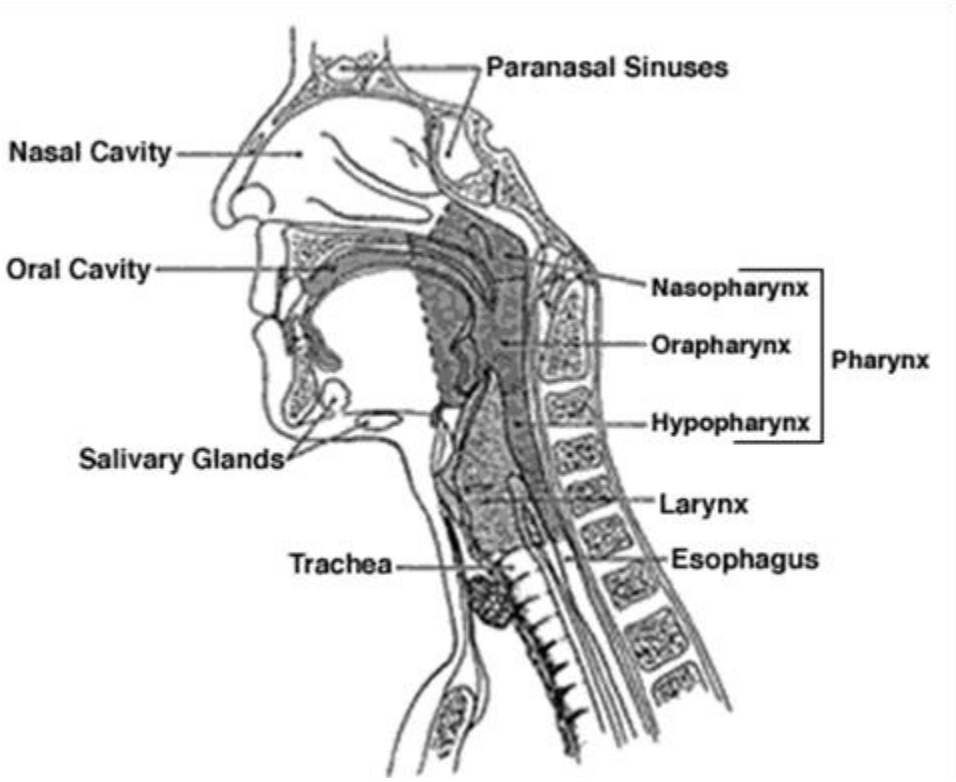

Figure 2.1: Diagram illustrating the different regions of the head and neck, including the oral cavity, nasopharynx, oropharynx, hypopharynx and larynx (American Cancer Society Inc, 2009).

The malignancies were staged according to the tumour-node-metastasis (TNM) staging system of the American Joint Committee on Cancer (AJCC) and International Union Against Cancer (UICC) (Patel & Shah, 2005). The TNM system describes three key pieces of information: the size of the primary tumour (T), the extent of spread to nearby lymph nodes (N), and whether the cancer has metastasized to other organs of the body (M). Categories marked with an 'X' indicate the primary tumour cannot be assessed, while '0' indicates no evidence of primary tumour. Grading 1 – 4, 'a' and 'b' indicate increasing severity and spread, respectively.

Table 2.1: Participant demographic characteristics, diagnosis, treatment dose, concurrent medications and comorbidities.

Case	Age (years)	Sex	Diagnosis	TNM Staging criteria*	Cisplatin dose (mg)			Total cisplatin dose (mg)	Total irradiation dose (Gy/Fractions)	Concurrent medications	Comorbidity
					Dose 1	Dose 2	Dose 3				
1	63	M	Oral cavity	T4N2bM0	190	190	190	570	70/35		
2**	59	M	Oropharynx	T2N2bMx	200	200		400	70/35	80 mg F	NH Lymphoma
3	57	M	Unknown	T0N2a	180	144	144	468	70/35		
4	56	M	Nasopharynx	T2N2c	200	200	200	600	70/35		
5	61	M	Hypopharynx	T2N2bMx	180	130		310	70/35		Renal dysfunction
6	53	M	Neck	T0N2b	200	200	200	600	70/35		
7	55	M	Larynx	cT3N0	192	192	192	576	70/35		Atrial fibrillation
8	52	M	Oral cavity	T4N2cM0	190	190	190	570	60/30		
9	69	M	Larynx	T4N1	200	200	200	600	70/35		
10***	67	M	Oropharynx	T3N2bMx	200	200		400	70/35	20 mg F	Hypertension, IDDM, Gout
11	51	M	Oral cavity	T3N2cM0	190	190		380	60/30		
12	56	M	Oropharynx	pT3N1M0	190	190		380	60/30	40 mg F	
13	67	M	Oropharynx	cT3N2bM0	188	188	150	526	70/35		
14	55	M	Oropharynx	T3N2cM0	197	197		394	70/35		Hypertension
15	57	M	Oropharynx	T1N2a	188			188	60/30		
16	63	M	Oropharynx	T1N2aM0	170	170	170	510	70/35		
17	71	F	Oropharynx	T3N2b	160			160	70/35		Hypertension, Stroke
18	81	F	Hypopharynx	T3N0	58	58	40	156	70/35		
19	68	M	Oropharynx	T2N2bM0	200	200	130	530	70/35		Hypertension, Cardiomyopathy
20	58	M	Oropharynx	T2N2bM0	217	173		390	70/35		Hypertension, Gout
21	58	M	Oropharynx	T1N2a	219	219	219	219	70/35		Hypertension
22	52	M	Oropharynx	T1N3M0	187			187	70/35		
23	55	M	Oropharynx	cT3N2bM0	200	200		400	74/37		Hep C, Renal & liver dysfunction

* TNM staging criteria: refers to the size of the primary tumour (T), the extent of spread to nearby lymph nodes (N), and whether the cancer has metastasized to other organs of the body (M). 'X' indicates the primary tumour cannot be assessed, '0' indicates no evidence of primary tumour', while grading 1 – 4, 'a' and 'b' indicate increasing severity and spread, respectively.
** Patient received R-CHOP chemotherapy for Non-Hodgkin's Lymphoma in June 2008.
*** Patient had previous history of metastatic melanoma in 1983 requiring radical neck dissection.
Abbreviations: F, frusemide; NH, non-hodgkins; IDDM, insulin dependent diabetes mellitus

2.1.1 Treatment protocol

Patients were prescribed cranial irradiation therapy with concurrent cisplatin chemotherapy. Surgery was also employed where necessary. 18 patients received irradiation of 70 Gy in 35 fractions, four received a lower dose of 60 Gy in 30 fractions, and one received a dose of 74 Gy in 35 fractions. Cisplatin was typically charted for days 1, 22 and 43. Patients were required to be admitted overnight to allow for sufficient hydration. Cisplatin was administrated IV in 1000 ml of 0.9 saline at a rate of 1 mg cisplatin per minute. In conjunction, patients were given the following:

- 1000 ml 0.9 saline over one hour;
- Dexamethasone 16 mg in 1000 ml over one hour;
- 1000 ml 0.9 saline with 100 ml 15% Mannitol (osmotic diuretic) over one hour;
- 1000 ml 0.9 saline with 100 ml 15% Mannitol over four hours;
- 1000 ml 0.9 saline with 30 mmol KCL over six hours;
- 1000 ml 0.9 saline with 30 mmol KCL over six hours;
- three 8 mg doses of the anti-emetic Ondansetron were administered at 12 hour intervals.

The total cisplatin dose ranged from 188 mg to 657 mg with a mean dose of 413.6 mg. No other chemotherapy agents were administered.

2.2 Procedure

The protocol used in this study is described below. This protocol was based on previous findings in the literature with consideration to the equipment that was available for use.

Invitation letters were sent out to the 39 eligible individuals along with a response form and a preaddressed and stamped envelope. Individuals also had the option of contacting the author via email or phone as listed on the invitation letter. All 23 participants were contacted via their preferred communication mode as stated on their response form to arrange an appropriate appointment time. Prior to the assessments, a hand search of the Christchurch Audiology and Ear, Nose and Throat (ENT) Department oncology audiogram files was undertaken to match any previous audiograms to participating individuals.

At the appointment, all participants underwent diagnostic audiological assessment involving a case history, otoscopy, tympanometry, ipsilateral acoustic reflexes, standard pure-tone audiometry (0.25 to 8 kHz) and extended high frequency audiometry (9 to 16 kHz), speech audiometry, and distortion product otoacoustic emissions (DPOAEs). All testing was carried out in sound treated rooms in the Audiology Department at Christchurch Public Hospital. To ensure consistency, all testing was performed by the author. A more detailed outline of all procedures is presented below.

2.2.1 Pure-tone audiometry

Pure-tone thresholds in dB HL were ascertained using the modified Hughson-Westlake method (Carhart & Jerger, 1959). A calibrated Grason-Stadler GSI 61 Clinical Audiometer was used to generate pure tones that were presented to each ear via Etymotic Research ER-3A insert earphones for standard pure-tone audiometry, Sennheiser HDA 200 circum-aural headphones for extended high-frequency audiometry, and a Radioear B-71 bone conductor. In cases where insert earphones were contra-indicated, Telephonics TDH-59P headphones were used. Each participant's air conduction thresholds were measured in 5 dB steps at 0.25, 0.5, 1, 2, 3, 4, 6, 8, 9, 11.2, 12.5, 14 and 16 kHz in each ear. Bone conduction thresholds were measured from 0.5 – 4 kHz only, where air conduction thresholds were 20 dB HL or greater at the relevant frequency(s). Threshold was defined as the lowest intensity at which two reliable ascending responses were obtained. Pulsed tones were used as they are perceived as being easier to distinguish without adversely affecting the results (Burk & Wiley, 2004; Hamill & Haas, 1986), particularly for tinnitus sufferers (Mineau & Schlauch, 1997). Air conduction masking using a plateau method was applied to establish true audiometric thresholds when the air conduction thresholds of the test ear and of the non-test ear differed by at least the minimum inter-aural attenuation value for the test frequency. Specifically, the following values were used; 75 dB HL at 0.5 and 1 kHz, and 50 dB HL at frequencies above 1 kHz, where ER-3A earphones were used; 40 dB HL at 0.5 and 1 kHz, 45 dB HL at 2 kHz, and 50 dB HL at 4 kHz, where TDH-59P headphones were used. Bone conduction masking using the plateau method was also applied when there was an air-bone gap present equal to or greater than 15 dB HL.

2.2.2 Speech audiometry

Speech audiometry was performed using the New Zealand Recording of CVC (Revised AB) Word Lists (National Audiology Centre, Auckland, New Zealand). The word lists were presented using portable compact disc (CD) players (Sony D-EJ011 and Aistar ESP A5252) and a calibrated Grason-Stadler GSI 61 Clinical Audiometer, via ER-3A insert earphones or TDH-59P headphones. The maximum word recognition score was ascertained by recording the percentage of phonemes correctly repeated when the stimuli were presented 30 dB above the participant's pure-tone threshold average (PTA) of 0.5, 1 and 2 kHz where the hearing loss was relatively flat, or the two best thresholds at these frequencies if the audiogram was steeply sloping. If the maximum word recognition score was less than 90%, presentation of the stimuli was increased by 10 dB. The speech reception threshold (SRT), defined as the lowest intensity at which 50% of the phonemes can be correctly discriminated, was determined from a performance intensity (PI) function ascertained in 10 – 15 dB steps. Speech masking was applied to the contralateral ear when the presentation level of the speech stimuli exceeded the best bone conduction threshold of the non-test ear by the appropriate interaural attenuation value, depending

on the type of transducer used. Specifically, 55 dB HL where ER-3A earphones were used, and 45 dB HL where TDH-59P headphones were used.

2.2.3 Immittance audiometry

2.2.3.1 Tympanometry

Tympanometry was performed using a Grason-Stadler TympStar Middle-Ear Analyzer. A stimulus tone of 226 Hz was used, with a sweep rate of 50 daPa per second. The traces were compared to norms published by (American Speech-Language-Hearing Association, 1990) to determine tympanogram type. Type A tympanograms, consistent with normal middle ear pressure and compliance, were defined by ear canal volume of 0.6 – 1.5 cm^3, peak pressure between –100 and +100 daPa, and static admittance between 0.3 – 1.4 mmho. Traces with normal ear canal volume and peak pressure, but deviations in static admittance either above or below the normal range, were classified as Type Ad and Type As respectively. Traces with peak pressure less than –100 daPa were classed as Type C tympanograms, consistent with eustachian tube dysfunction and resulting in a retracted tympanic membrane. Where ear canal volume was normal and no peak pressure identified, traces were classed as Type B tympanograms, consistent with middle ear dysfunction. A Type B tympanogram with lower than normal ear canal volume was classed as a Type B-low, suggestive of wax occlusion or positioning of the probe tip against the EAC wall. A Type B tympanogram with higher than normal ear canal volume was classed as a Type B-high, consistent with tympanic membrane perforation or patent ventilation tube.

2.2.3.2 Acoustic reflexes

Ipsilateral acoustic reflexes (AR) were carried out using a Grason-Stadler TympStar Middle-Ear Analyzer. Stimuli were initially presented at 80 dBSPL, increasing in 5 dB steps until a significant compliance change was noted, equal or greater than 0.02 mmho. The stimulus was increased a further 5 or 10 dB to check for growth of the response. The acoustic reflex threshold (ART) was defined as the lowest intensity at which two reliable responses were obtained. ARTs were sought at 0.5, 1, 2 and 4 kHz bilaterally.

2.2.4 Distortion product otoacoustic emissions measurement

DPOAEs were evoked and recorded using a Grason-Stadler GSI 60 DPOAE System. The stimuli consisted of two primary pure-tones, f_1 and f_2, with an intensity level fixed at 65 dB SPL (L_1) and 55 dB SPL (L_2), respectively, and with a frequency ratio (f_2/f_1) of 1.22. An f_1/f_2 ratio of 1.22 has been shown to generate maximal distortion across all frequencies and subjects (Gaskill & Brown, 1990). The amplitude is also affected by the overall level and the level difference between the two primary tone levels ($L_1 – L_2$). High-intensity primaries elicit high amplitude DPOAEs but are thought to reflect passive cochlear processes as demonstrated by DPOAEs recorded from dead or damaged cochleae (Zurek, Clark, & Kim, 1982). It has been suggested that moderate level primaries, L_1 = 65 dB SPL

and L_2 = 55 dB SPL, are preferable for clinical use due to increased accuracy in distinguishing between normal and hearing impaired ears (Stover, Gorga, Neely, & Montoya, 1996).

The testing was performed for 16 ascending frequencies where f_2 varied from 2.0 to 9.25 kHz. DPOAE amplitude and noise floor were displayed for each frequency as DP-grams. An emission was considered present if the SNR was greater than 6 dB and the absolute amplitude greater than -10 dB SPL (Hall, 2000).

2.3 Statistical methods

All data were entered and analysed using Microsoft Excel 2007. The primary methods for analysis were measures of central tendency and measures of variability. Level of hearing was calculated as the PTA of 0.5, 1, 2, and 4 kHz for standard audiometry, and the PTA of 9, 10, 11.2 and 12.5 kHz for EHF audiometry. When determining whether a significant cochleotoxic change had occurred (American Speech-Language-Hearing Association, 1994), individual thresholds were analysed at each frequency. A Fisher's exact test was undertaken to investigate whether participants were able to accurately perceive a significant cochleotoxic change in their hearing. The Fisher's exact test was used due to the expected count of some cells being less than 5.

Due to the small sample size, many statistical tests were not appropriate. In addition, the focus of this study was to determine the *clinical* significance of the findings. For example, although a change in hearing thresholds may constitute a *statistically* significant result, if it falls within the ± 10 dB test-retest reliability it will have little relevance to the clinical management of the patient.

2.4 Ethical considerations

Ethical approval from the Upper South B Regional Ethics Committee was granted on 2 November 2009 (Ref: URB/09/41/EXP, see Appendix A). Written consent was obtained from each participant prior to audiological assessment (Appendix E), and patient confidentiality was maintained in accordance with the conditions of ethical approval from the above-named ethics committee.

3 Results

The results of this study will be reported in several sections. First, details of pre-treatment assessments obtained from patient files will be presented, followed by the audiometric data collected from the post-treatment assessments carried out by the author. The last section pertains to analysis of data with respect to the cochleotoxicity criteria stipulated by ASHA. This includes four case studies that were of particular interest.

3.1 Pre-treatment audiological assessment

From the total sample of 23 participants who were recruited for this study, 16 (69.6%) individuals had undergone pre-treatment audiological assessments. This is displayed in Figure 3.1. These assessments consisted of standard pure-tone audiometry for all 16 (100%) participants, and EHF audiometry for 14 (87.5%) participants.

The pre-treatment standard PTA of 0.5, 1, 2 and 4 kHz for both ears was calculated for each of these 16 individuals. The mean pre-treatment standard PTA across all 16 participants was 20.9 ± 11.3 dB HL for the left ear, and 20.9 ± 9.3 dB HL for the right ear. The mean PTA for both ears was 20.9 ± 10.2 dB HL. The extended high-frequency pure-tone average (EHF PTA) of 9, 10, 11.2 and 12.5 kHz was calculated for each individual. In cases where there was no response at the limit of the audiometer for a particular frequency, the PTA is reported as being *at least* the specified value. This signifies that the reported PTA is most likely an underestimation of the true PTA. The mean pre-treatment EHF PTA across all 16 participants was at least 50.7 ± 15.5 dB HL for the left ear, and at least 50.6 ± 14.5 dB HL for the right ear. The mean EHF PTA for both ears was at least 50.7 ± 14.7 dB HL. Mean pre-treatment pure-tone audiometry results are displayed in Figure 3.2 and Figure 3.3.

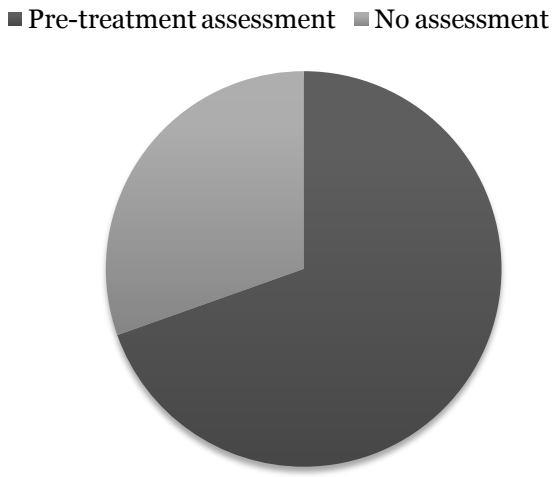

Figure 3.1: Proportion of participants who had undergone pre-treatment assessment (16 of 23 participants, or 69%).

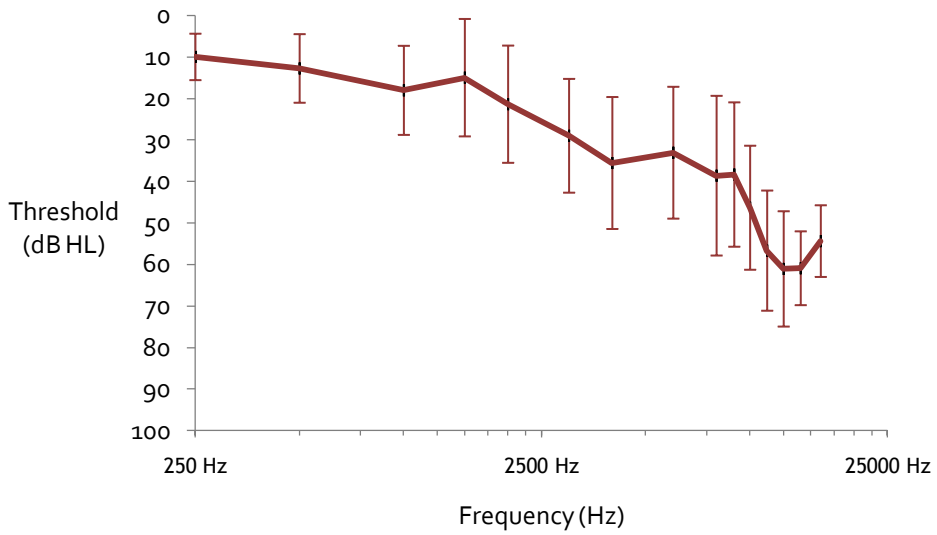

Figure 3.2: Mean e-treatment pure-tone air conduction thresholds in decibel hearing level (dB HL) in the right ear for 16 participants.

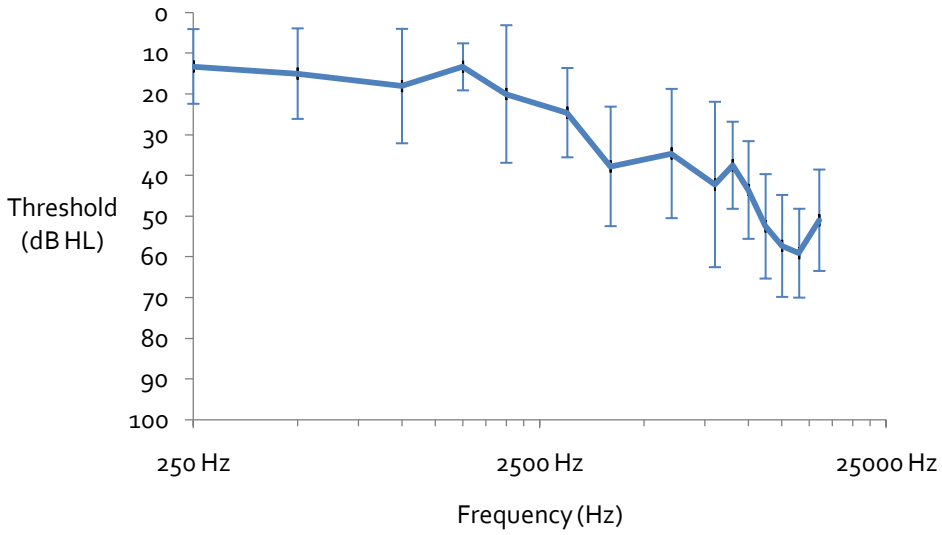

Figure 3.3: Mean pre-treatment pure-tone air conduction thresholds in decibel hearing level (dB HL) in the left ear for 16 participants.

Tympanometry was performed on 15 (93.8%) participants in total, with bilateral measurements for 14 (87.5%) participants and unilateral (right ear only) for one (6.3%) participant (participant 13). Of those 15 participants, ten (66.7%) participants had type "A" tympanograms bilaterally, indicating normal middle ear pressure and compliance. Participant 13 had a type "A" tympanogram in his right ear. One (6.7%) participant had type "C" tympanograms bilaterally, consistent with Eustachian tube dysfunction resulting in retracted tympanic membranes. One (6.7%) participant had a unilateral type "C" tympanogram. One (6.7%) participant had bilateral type "Ad" tympanograms while two (13.3%) participants had unilateral type "Ad" tympanograms, consistent with greater than normal compliance.

Ipsilateral ARs were performed bilaterally on one (6.3%) participant. Pre-treatment speech audiometry and DPOAEs were not performed on any of the 16 participants. Table 3.1 provides pre-treatment assessment details for each participant.

Table 3.1: Pre-treatment audiological assessment information for each of the 16 participants.

Participant	Age (years;months)*	Gender	Pure-tone average (dB HL)**		EHF Pure-tone average (dB HL) ***		Tympanogram type		Acoustic reflexes
			Left ear	Right ear	Left ear	Right ear	Left ear	Right ear	
1	62;5	Male	11.3	13.8	53.8	53.8	A	A	
4	54;2	Male	22.5	40			C	C	
5	60;6	Male	7.5	6.3	56.3	42.5	A	A	
6	51;9	Male	28.8	20	*63.8*	56.3	Ad	Ad	
7	52;7	Male	13.8	13.8	32.5	28.8	A	A	
8	51;2	Male	23.8	20	52.5	51.3	A	A	
9	66;2	Male	27.5	16.3	*91.3*	*83.8*	C	Ad	
11	50;9	Male	31.3	32.5	47.5	42.5	A	A	X
12	52;2	Male	11.3	12.5	31.3	47.5	A	A	
13	64;0	Male	27.5	28.8	36.3	41.3		A	
14	53;9	Male	23.8	25	53.8	41.3			
17	67;9	Female	51.3	35			A	A	
19	67;9	Male	16.3	21.3	55	53.8	A	A	
21	56;6	Male	7.5	11.3	56.3	58.3	A	A	
22	48;9	Male	20	20	45	72.5	A	Ad	
23	52;9	Male	11.3	17.5	35	35	A	A	

* Age at time of pre-treatment assessment
** Pure-tone average of 0.5, 1, 2 and 4 kHz
*** Pure-tone average of 9, 10, 11.2 and 12.5 kHz
EHF - extended high-frequency
N.B. Values in italics represent pure-tone averages where one or more of the component frequencies yielded a threshold that was considered to be no response at the limit of the audiometer.

3.2 Post-treatment audiological assessment

All 23 participants underwent post-treatment audiological assessments performed by the author. These involved case history, standard and EHF pure-tone audiometry, speech audiometry, DPOAEs and immittance audiometry. Information pertaining to the research aims is presented below. Comprehensive assessment details of each participant can be found in Appendix F.

3.2.1 Case history

3.2.1.1 Hearing loss

At the time of the post-treatment assessment, 20 (87%) participants out of the total sample (n = 23) felt that they had hearing loss in either one (10%) or both ears (90%). Of those 20 participants, nine participants (45%) believed that they had hearing loss pre-treatment but that their hearing had deteriorated further since receiving treatment for cancer, six (30%) participants reported that their hearing loss had come on as a result of treatment, while the remaining five (25%) participants felt that their hearing had not changed after treatment. Overall, 15 (65%) of the 23 participants reported hearing loss that they believed to be a direct result of their cancer treatment. The mean length of hearing loss was 10.47 ± 16.70 years. Of those 15 participants, 10 (66.7%) described the onset of their hearing loss as "gradual", four (26.7%) described it as "sudden" onset, while the remaining one (6.7%) participant was unsure. Of the 15 participants, 14 (93.3%) felt that the hearing loss they experienced affected both ears and one (6.7%) participant felt that it affected the right ear only.

Participants were asked what environments, if any, they experienced difficulty hearing in. Of the 20 participants who reported hearing loss, 19 (95%) said that noisy environments were difficult, 17 (85%) found group conversations a problem, 16 (80%) found they required the television or radio volume turned up, eight (40%) reported difficulty understanding speech when talking on the telephone, three (15%) participants experienced difficulty with conversations in quiet environments and when conversing with one other person. Of the 15 participants who reported hearing loss post-treatment, 14 (93.3%) found noisy environments difficult, 13 (86.7%) said they experienced difficulty with group conversations and when listening to the television and/or radio, seven (46.7%) described conversations on the telephone difficult, and three (20%) participants reported problems with conversations in quiet environments and when conversing with one other person.

3.2.1.2 Tinnitus

During questioning, 18 participants (78.3%) reported experiencing tinnitus at some stage during their life. While eight (44.4%) of these 18 participants were not sure of the duration of their tinnitus, the mean length of time tinnitus was experienced by the other

ten (55.6%) participants was 5.98 ± 5.99 years. Of those 18 participants, five (27.8%) participants experienced tinnitus prior to their cancer treatment and felt that there had been no change; three (16.7%) participants experienced tinnitus prior to treatment but felt that it had increased in severity at the time of treatment; eight (44.4%) participants reported the onset of tinnitus coincided with their treatment, with one experiencing temporary tinnitus lasting eight to nine months only; one (5.6%) participant felt that their tinnitus had been affected by the treatment but was unsure whether it had started or increased in severity; and one (5.6%) participant was unsure whether their tinnitus had been affected by the treatment. Of the total sample, 11 (47.8%) participants felt that their tinnitus had either begun or increased in severity as a result of treatment. Participant 15 received only one dose of cisplatin due to a significant increase in tinnitus severity.

Participants were asked to choose the best description of what their tinnitus sounded like; of the 18 participants who reported either a history of, or current tinnitus, seven (38,9%) described a "ringing" sound, three (16.7%) described a "buzzing" sound, two (11.1%) described a "hissing" sound, one (5.6%) described a sound like "crickets", and one (5.6%) described a "whistle" sound. Four (22.2%) participants chose the "other" description and included "zinging", "squeal" and "sea noise/waves". Participant six did not answer this question as he did not currently have tinnitus and was unable to remember what it sounded like.

3.2.1.3 Balance

Seven (30.4%) participants reported difficulties with their balance. Of these seven participants, two (28.6%) described problems relating to low blood pressure, one (14.3%) reported a history of benign paroxysmal positional vertigo (BPPV), while the remaining four (57.1%) described a feeling of imbalance that was noticed since receiving treatment.

3.2.1.4 Aural fullness

Seven (30.4%) participants described a feeling of aural fullness or pressure in one or both ears. Four participants reported the onset of these symptoms with treatment.

3.2.1.5 Facial weakness

Twelve (52.2%) participants reported facial numbness or weakness. All 12 (100%) participants believed this occurred as a direct result of surgery to remove either the tumour and/or affected lymph nodes.

3.2.1.6 Noise exposure

Twenty-one (91%) participants out of 23 reported exposure to significant noise either through their occupation or recreational activities. The mean length of exposure was 22.05 ± 12.91 years. Of these 21 participants, 9 (42.6%) participants reported wearing some form of hearing protection at least some of the time, while the remaining 12 (57.1%) did not wear hearing protection.

The percentage of participants who reported the three main ototoxic symptoms are presented in Figure 3.4 while case history information for each participant is detailed in Table 3.2.

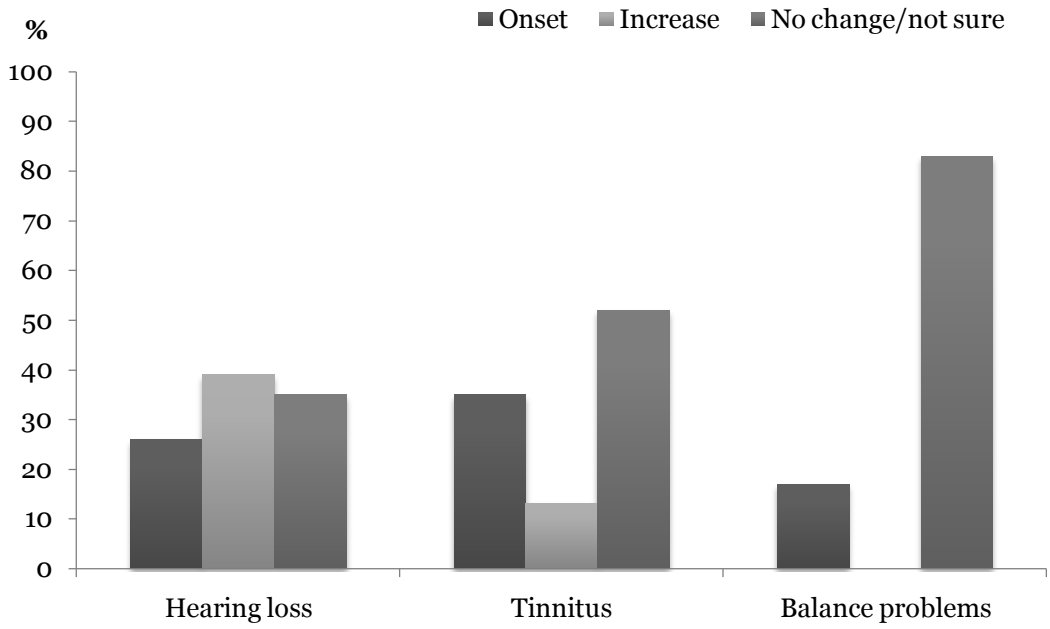

Figure 3.4: Percentage of participants who reported experiencing each symptom post-treatment (n=23).

Table 3.2: Case history information for each of the 23 participants. HL: hearing loss, Tx: treatment, Y: yes, N: no, NS: not sure, Q: quiet, NE: noisy, G: groups, P: phone, TV/R: TV/radio

Patient	HL	HL from Tx	Onset of HL	Ear	Problem situations	Tinnitus	Tinnitus from Tx	Tinnitus sound	Balance	Aural fullness	Facial numbness	Ear surgery	Noise exposure
1	Y	N	Gradual	Both	NE, G, TV/R	Y	N	Ringing	N	N	Y	N	Y
2	Y	Y	Gradual	Both	NE, G, P, TV/R	Y	Increased	Crickets	N	N	N	N	Y
3	Y	Y	Sudden	Both	NE, G, P, TV/R	Y	N	Buzzing	N	N	N	N	Y
4	Y	Y	Sudden	Both	Q, G, P	Y	N	Hissing	N	N	N	N	Y
5	Y	Y	Gradual	Both	NE, G, TV/R	Y	NS	Ringing	N	N	N	N	Y
6	Y	N	Gradual	Both	TV/R	Y	N		Y	N	Y	N	Y
7	Y	Y	Sudden	Both	NE, G, TV/R	Y	Increased	Whistle	N	Y	Y	N	Y
8	NS	N	Gradual	Left	NE, G	N			N	N	Y	N	Y
9	Y	Y	NS	Both	NE, P, TV/R	Y	Onset	Ringing	N	Y	N	N	Y
10	Y	Y	Gradual	Both	Q, NE, T, G, TV/R	N			N	N	Y	N	Y
11	N	N			TV/R	N			N	Y	Y	N	N
12	Y	N	Gradual	Both	NE, G, P	Y	N	Ringing	Y	N	Y	N	Y
13	Y	Y	Gradual	Both	Q, NE, G, TV/R	Y	Increased	Buzzing	N	N	N	N	Y
14	Y	Y	Gradual	Both	NE, G, P, TV/R	Y	Onset	Zinging	N	N	N	N	Y
15	Y	N	Sudden	Both	NE	Y	Onset	Squeal	Y	N	Y	N	Y
16	N	N				Y	Onset	Hissing	N	N	N	N	N
17	Y	Y	Gradual	Both	NE, T, G	N			N	N	Y	N	Y
18	Y	Y	Gradual	Both	NE, P, TV/R	N			Y	Y	Y	N	Y
19	Y	N	Gradual	Both	NE, G	Y	Onset	Ringing	N	Y	N	N	Y
20	Y	Y	Gradual	Right	NE, G, P, TV/R	Y	Onset	Squeal	Y	N	Y	N	Y
21	Y	Y	Gradual	Both	NE, G, TV/R	Y	Y	Waves	Y	Y	Y	N	Y
22	Y	Y	Sudden	Both	NE, G, TV/R	Y	Onset	Ringing	N	N	N	N	Y
23	Y	Y	Gradual	Both	NE, T, G, TV/R	Y*	Onset	Ring,Buzz	Y	Y	N	N	Y

3.2.2 Pure-tone audiometry

For this section please note that a threshold shift is considered clinically significant when there is a difference of 15 dB or greater between tests. This allows for ± 5 dB test-retest reliability. Fluctuations of thresholds between tests of 10 dB or less have therefore not been reported. In addition, the classification used when describing degree of hearing loss is that of Jerger and Jerger (1980) which states the following:

-10 to 20 dB HL	Normal hearing
21 to 40 dB HL	Mild hearing loss
41 to 55 dB HL	Moderate hearing loss
56 to 70 dB HL	Moderately-severe hearing loss
71 to 90 dB HL	Severe hearing loss
91+ dB HL	Profound hearing loss

The pure-tone threshold average (PTA) of 0.5, 1, 2 and 4 kHz for both ears was calculated for each of the 23 individuals. The mean PTA of the total sample was 31.8 ± 13.8 dB HL for the left ear, and 29.2 ± 9.7 dB HL for the right ear. The mean PTA for both ears was 30.5 ± 11.9 dB HL. The extended high-frequency pure-tone average (EHF PTA) of 9, 10, 11.2 and 12.5 kHz was calculated for each individual. The mean EHF PTA of the total sample was 70.9 ± 13.7 dB HL for the left ear, and 71.7 ± 12.6 dB HL for the right ear. The mean EHF PTA for both ears was 71.3 ± 13.0 dB HL. Post-treatment pure-tone audiometry results are displayed in Figure 3.5 and Figure 3.6.

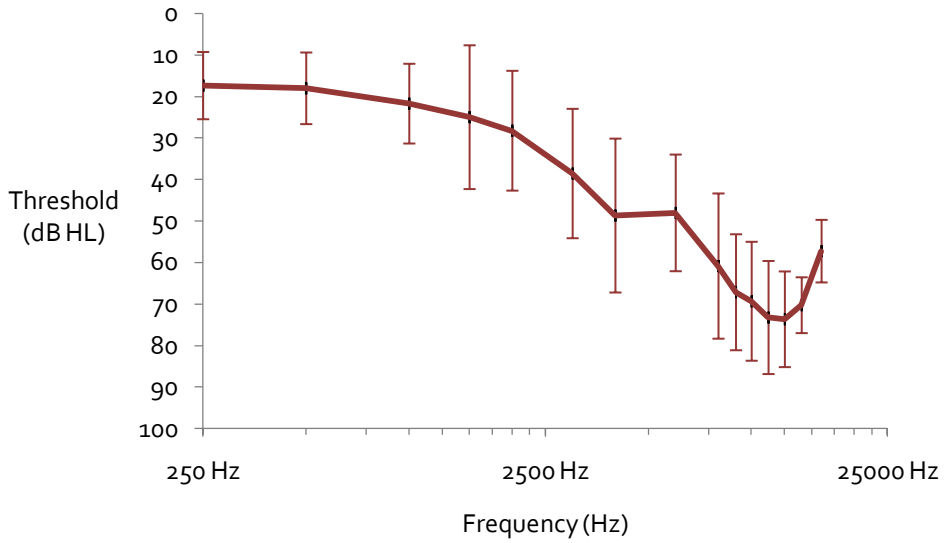

Figure 3.5: Post-treatment pure-tone air conduction thresholds in the right ear for all 23 participants

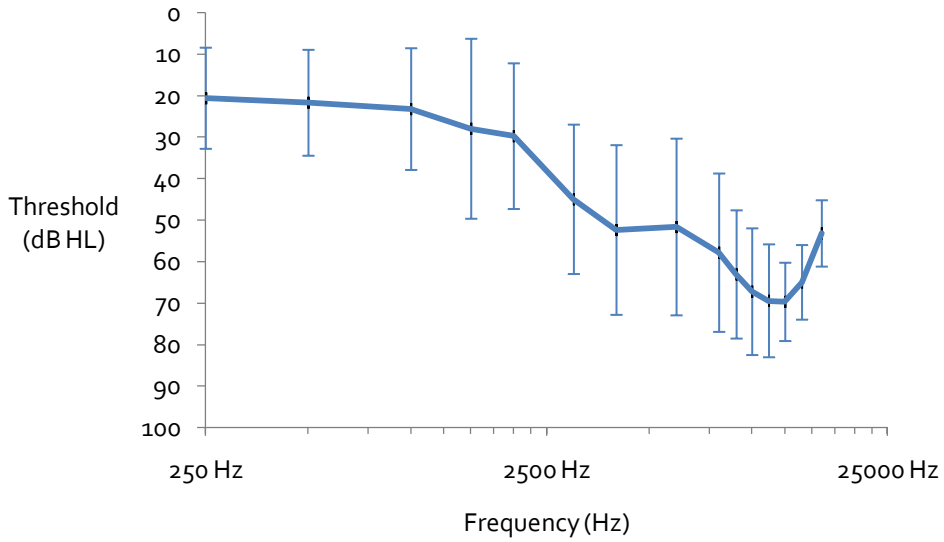

Figure 3.6: Post-treatment pure-tone air conduction thresholds in the left ear for all 23 participants

3.2.3 Speech audiometry

Speech audiometry was performed for all 23 participants and was consistent with the pure-tone audiogram (see Appendix F).

3.2.4 DPOAEs

DPOAEs were performed on 18 participants (78.3%). The remaining five participants were not assessed due to time constraints (participants 9, 10 and 23), unwillingness of the patients (participant 18) and because the equipment had been sent away for calibration

(participant 7). Participant 15 was assessed using another brand of equipment (Audera) that measured emissions at different frequencies to the GSI 60. Interpolation did not accurately represent OAE results and therefore the data collected from participant 15 are not included in the analysis. DPOAE data are displayed for each participant in Table 3.3.

3.2.5 Immittance audiometry

3.2.5.1 Tympanometry

Tympanometry was performed on 21 (91.3%) participants in total, with bilateral measurements for 19 (82.6%) participants and unilateral for two (8.7%) participants (participants 13 and 15). Of those 21 participants, 15 (71.4%) participants had type "A" tympanograms bilaterally, consistent with normal middle ear pressure and compliance. One (4.8%) participant (participant 13) had a type "A" tympanogram in his right ear. Type "Ad" tympanograms, consistent with greater than normal compliance, were measured bilaterally in one (4.8%) participant, and unilaterally in two (9.5%) participants (including participant 15). One (4.8%) participant had a unilateral type "As" tympanogram, consistent with reduced compliance, while the remaining participant presented with a unilateral type "C" tympanogram, consistent with Eustachian tube dysfunction resulting in retracted tympanic membranes.

3.2.5.2 Acoustic reflexes

Acoustic reflexes were measured for 14 (60.9%) participants in total, with bilateral measurements for 12 (85.7%) of those participants and unilateral measurements for the remaining two (14.3%) participants. ART values are displayed for each participant in Table 3.4.

Table 3.3: Distortion product otoacoustic emission (DPOAE) data from 18 participants. Hz: hertz, P: participant, L: left, R: right, ✓: present(SNR > 5 dB, ≥ 10 dB SPL)

P	Distortion product otoacoustic emission (DPOAE) F2 (Hz)																													
	2000		2250		2500		2750		3062		3375		3750		4062		4500		5000		5500		6125		6812		7500		8375		9250	
	L	R	L	R	L	R	L	R	L	R	L	R	L	R	L	R	L	R	L	R	L	R	L	R	L	R	L	R	L	R	L	R
1	✓	✓	✓	✓	✓	✓		✓				✓		✓				✓					✓				✓				✓	
2																		✓					✓	✓			✓				✓	
3	✓	✓	✓	✓	✓	✓				✓																				✓		
4		✓	✓																					✓			✓	✓				✓
5	✓	✓	✓	✓	✓	✓		✓		✓		✓		✓		✓	✓	✓		✓		✓		✓							✓	
6	✓		✓	✓			✓			✓			✓										✓	✓			✓					
8	✓	✓	✓	✓	✓	✓		✓		✓		✓						✓													✓	
9		✓				✓				✓																						✓
11			✓					✓	✓		✓		✓			✓	✓							✓							✓	✓
12	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓								✓		✓		✓	✓		✓				✓	✓	
13	✓	✓	✓	✓																								✓				
14	✓	✓	✓	✓	✓	✓																		✓								
16	✓	✓	✓	✓	✓	✓				✓														✓								✓
17											✓				✓												✓					
20		✓	✓	✓	✓	✓	✓	✓			✓	✓	✓											✓				✓	✓			✓
21	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓						✓					✓			✓	✓
22	✓	✓	✓		✓	✓				✓						✓	✓	✓		✓		✓	✓									

Table 3.4: Ipsilateral acoustic reflex thresholds for right and left ears of 14 participants

Participant	Right ear				Left ear			
	0.5 kHz	1 kHz	2 kHz	4 kHz	0.5 kHz	1 kHz	2 kHz	4 kHz
1	85	85	95	100↓	85	85	95	100↓
2	95	95	105↓	100↓				
3	105↓	105↓	105↓	100↓	100	105↓	105↓	100↓
4	95	95	105↓	100↓				
7	95	85	90	100↓	80	80	80	95
8	90	85	90	100↓	90	90	95	100↓
9	105↓	105↓	105↓	100↓	110↓	110↓	105↓	100↓
10	90	90	100	100↓	85	85	105↓	100↓
11	80	80	80	80	80	80	80	80
12	100	95	105	100↓	90	85	95	95
14	85	90	85	100↓	95	95	95	100↓
20	110	105	105↓	100↓	110↓	110↓	105↓	100↓
21	90	85	85	100↓	90	85	85	100↓
22	105↓	105↓	105↓	100↓	95	90	90	100↓

↓ Denotes "no response" either at the limit of the equipment or when the stimulus was too loud for the participant to tolerate.

3.3 Serial audiological assessment

Of the 16 participants who received a pre-treatment audiological assessment, 11 of them had at least one further assessment for the purposes of monitoring before the post-treatment assessment for this study. Two additional participants, who had not had a pre-treatment assessment, underwent audiological assessment during the treatment phase. Participant 15, who received only one dose of cisplatin due to a substantial increase in tinnitus severity, did not receive any form of audiological assessment prior to the post-treatment assessment carried out for the purpose of this research.

3.4 Cisplatin-induced hearing loss

The baseline data from the 16 participants who underwent audiological assessment prior to beginning treatment, was compared with the data from the post-treatment assessment. In particular, results were analysed to see whether a cochleotoxic threshold shift had occurred based on the ASHA criteria of: (1) ≥ 20 dB decrease at any one test frequency;

(2) ≥ 10 dB decrease at any two adjacent test frequencies; or (3) loss of response at three consecutive test frequencies where responses were previously obtained.

Overall, 15 (93.8%) of the 16 participants experienced a significant cochleotoxic change in thresholds. This was bilateral in 13 (86.7%) participants and unilateral in the remaining 2 (13.3%). Thirteen (81.3%) of the 16 participants experienced a change in thresholds in their left and/or their right ear that met the first ASHA criterion, 15 (93.8%) of the 16 participants experienced a change in their left and/or right ear that met the second ASHA criterion. Participants 5 and 21 experienced temporary shifts in thresholds that met the third ASHA criterion, but these had recovered by the final assessment. This is illustrated in Figure 3.7. Details for each of the 16 participants are displayed in Table 3.5.

The survey data revealed that of the 16 participants who had a pre-treatment audiogram, 10 participants had perceived deterioration in their hearing and had a measureable change (based on any of the three ASHA criteria), 5 participants had not perceived a deterioration in their hearing when there had in fact been a measureable change, and the remaining one participant had not perceived a change in hearing and had not had a measureable hearing loss. That is, all of the participants who perceived a loss of hearing actually had a measurable hearing loss.

If the 15 participants who had suffered a measurable hearing loss were simply guessing whether they had a hearing loss, one would expect 50% to indicate that they had perceived a hearing loss and 50% to indicate that they had not perceived a hearing loss. Fisher's exact test (Fisher, 1922) shows that the probability of 10 or more participants correctly perceiving a hearing loss by chance is 15.1%, which is more than the commonly used 5% threshold. While the data are not conclusive, they do indicate that participants tend to perceive correctly when they have experienced a measurable deterioration in their hearing.

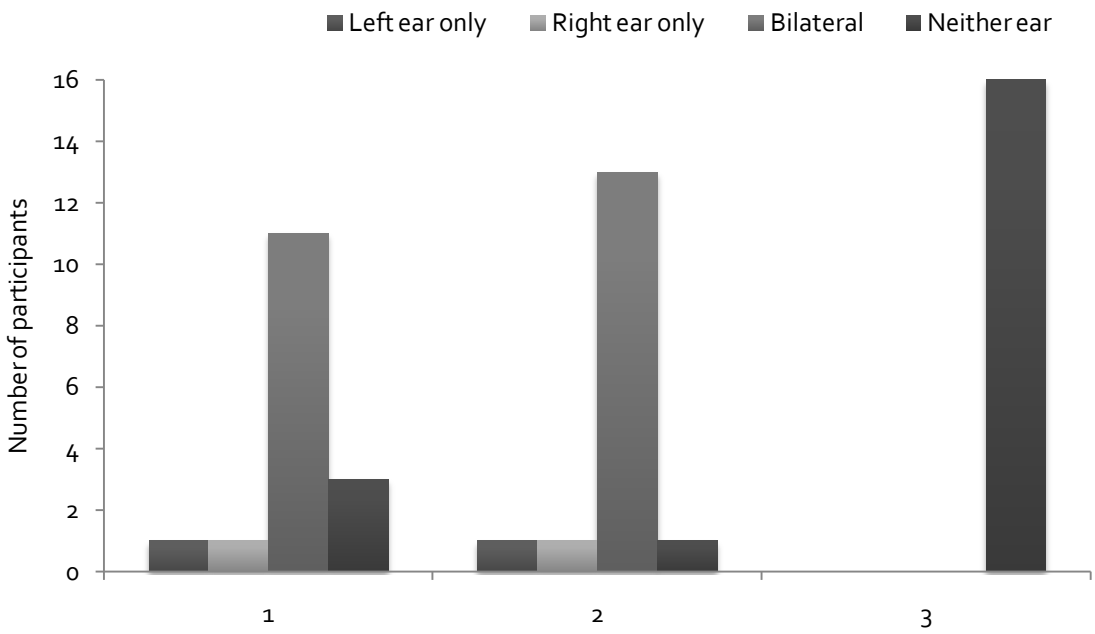

Figure 3.7: Number of participants (n=16) who experienced a significant long-term cochleotoxic deterioration in hearing thresholds based on the three ASHA criteria of (1) ≥ 20 dB decrease at any one test frequency; (2) ≥ 10 dB decrease at any two adjacent test frequencies; or (3) loss of response at three consecutive test frequencies where responses were previously obtained

Table 3.5: Standard and extended high-frequency pure-tone audiometry averages and ASHA cochleotoxicity criteria for each of the 16 participants

Participant	Pre-treatment assessment				Post-treatment assessment				ASHA cochleotoxicity criteria						Any
	PTA (dB HL)		EHF PTA (dB HL)		PTA (dB HL)		EHF PTA (dB HL)		1		2		3		
	Left ear	Right ear	Left ear	Right ear	Left ear	Right ear	Left ear	Right ear	Left ear	Right ear	Left ear	Right ear	Left ear	Right ear	
1	11.25	13.75	53.75	53.75	28.75	27.5	71.25	67.5	Yes	Yes	Yes	Yes	No	No	Both
4	22.5	40			43.75	37.5	86.25	78.75	Yes	No	Yes	No	No	No	Left
5	7.5	6.25	56.25	42.5	13.75	21.25	85	82.5	Yes	Yes	Yes	Yes	No	No	Both
6	28.75	20	*63.75*	56.25	16.25	13.75	56.25	48.75	No	No	No	No	No	No	No
7	13.75	13.75	32.5	28.75	26.25	21.25	71.25	66.25	Yes	Yes	Yes	Yes	No	No	Both
8	23.75	20	52.5	51.25	27.5	25	62.5	62.5	Yes	Yes	Yes	Yes	No	No	Both
9	27.5	16.25	*91.25*	*83.75*	53.75	23.75	86.25	90	Yes	Yes	Yes	Yes	No	No	Both
11	31.25	32.5	47.5	42.5	32.5	37.5	63.75	61.25	Yes	Yes	Yes	Yes	No	No	Both
12	11.25	12.5	31.25	47.5	10	16.25	42.5	52.5	No	No	Yes	Yes	No	No	Both
13	27.5	28.75	36.25	41.25	30	33.75	55	60	Yes	Yes	Yes	Yes	No	No	Both
14	23.75	25	53.75	41.25	30	30	60	63.75	Yes	Yes	Yes	Yes	No	No	Both
17	51.25	35	DNT	DNT	58.75	41.25	82.5	78.75	No	Yes	Yes	Yes	No	No	Both
19	16.25	21.25	55	53.75	28.75	35	71.25	75	Yes	Yes	Yes	Yes	No	No	Both
21	7.5	11.25	56.25	58.75	7.5	15	57.5	63.75	No	No	No	Yes	No	No	Right
22	20	20	45	72.5	32.5	30	56.25	86.25	Yes	Yes	Yes	Yes	No	No	Both
23	11.25	17.5	35	35	30	25	85	88.75	Yes	Yes	Yes	Yes	No	No	Both

** Pure-tone average (PTA) of 0.5, 1, 2 and 4 kHz, *** Pure-tone average (PTA) of 9, 10, 11.2 and 12.5 kHz. EHF, extended high-frequency; DNT, did not test

N.B. Values in italics represent pure-tone averages where one or more of the component frequencies yielded a threshold that was considered to be no response at the limit of the audiometer

3.4.1 Influencing variable

For the 16 participants there was considerable variation in the duration between pre- and post-treatment assessments. Given the mean age of the participants (60.2 years), the deterioration in hearing thresholds within this time period may be partly attributed to other factors such as presbycusis. Thresholds were calculated using the NAL percentage binaural hearing handicap {Macrae, 1976 #191} and adjusted for age. The mean pre-treatment percentage binaural hearing loss was 4.8 ± 4.4, and 4.0 ± 4.5 age corrected. The mean post-treatment percentage binaural hearing loss was 12.7 ± 8.8, and 11.3 ± 8.3 age corrected. The mean percentage binaural hearing loss that occurred between the pre- and post-treatment assessments were 6.2 ± 4.7 and 5.7 ± 4.5 age corrected. Individual results for the 16 participants are displayed in Table 3.6.

Table 3.6: Change in percentage binaural hearing loss adjusted for age and time elapsed between pre-and post-treatment assessments. Time in year;month. HL: hearing loss.

Participant	Time	Pre-Treatment		Post-Treatment		Overall
		% HL	Age adjusted	% HL	Age adjusted	Age adjusted
1	1;3	0.7	-1	9	6.9	7.9
4	2;8	8.3	8.3	18.9	18.9	10.6
5	1;2	0	-1	2.7	1.3	2.3
6	1;4	5.7	5.7	0.9	0.9	-4.8
7	2;5	0.8	0.8	12.1	12.1	11.3
8	0;11	3.2	3.0	7.2	7.2	4
9	3;2	4.6	1.2	13.9	8.9	7.7
11	0;7	9.9	9.9	16.4	16.4	6.5
12	4;2	1.8	1.8	0.8	0.	-1
13	3;1	8.5	6	15.7	11.8	5.8
14	1;7	6.9	6.9	13.1	13.1	6.2
17	3;10	16	15.7	29.9	28.9	13.2
19	0;11	6	2.1	14.2	9.8	7.7
21	1;6	1.5	1.5	1.4	0.9	0.6
22	4;1	2.9	2.9	9.8	9.8	6.9
23	2;6	0.3	0.3	8.9	8.9	8.6

3.5 Case studies

Two of the 15 participants who experienced a significant cochleotoxic threshold shift were noted to have acute renal failure that prevented them from receiving the third dose of cisplatin. One participant received only the first dose of cisplatin due to a significant deterioration in hearing. Pre- and post-treatment data for these participants, along with that of the participant who received the largest total dose of cisplatin, are presented in detail.

3.5.1 Participant 5

Participant 5 is a 61;8 year old male who was diagnosed with SCC of the hypopharynx in 2008. The participant was aged 60;6 years at the time of beginning concurrent cisplatin and irradiation therapy. One day prior to commencing treatment, the participant underwent baseline audiological assessment that included standard pure-tone audiometry, EHF pre-tone audiometry and tympanometry. Standard pure-tone audiometry showed normal hearing sloping to a mild loss at 8 kHz bilaterally. The PTA was 7.5 dB HL in the left ear, and 6.25 dB HL in the right ear. EHF pure-tone audiometry showed a moderate to severe sloping hearing loss in the left ear, with a loss of response at 16 kHz, and a mild to moderately severe hearing loss in the right ear. EHF PTA was 56.25 dB HL in the left ear and 42.5 dB HL in the right ear. Tympanometry yielded a type "A" tympanogram bilaterally, consistent with normal middle ear pressure and compliance.

Participant 5 received one dose of 180 mg cisplatin on day one of the treatment protocol. On day 23, the participant underwent a follow-up audiological assessment prior to receiving the second dose. Standard pure-tone audiometry showed deterioration of high-frequency thresholds with a decrease of 25 dB at 4 kHz, 35 dB at 6 kHz and 55 dB at 8 kHz in the left ear, and15 dB at 4 kHz, and 25 dB at 8 kHz in the right ear. Bone conduction suggested a conductive component at 4 kHz bilaterally. EHF pure-tone audiometry showed a 35 dB decrease at 9 kHz, 10 kHz and 11.2 kHz, with a loss of response at 12.5 kHz, 14 kHz and 16 kHz in the left ear. EHF pure-tone audiometry also showed a 45 dB decrease at 9 kHz, 35 dB at 10 kHz, 45 dB at 11.2 kHz and loss of response at 12.5 kHz in the right ear. Analysis of thresholds in relation to the ASHA criteria indicated a significant cochleotoxic change, fulfilling all three criteria bilaterally. Tympanometry remained stable indicating no middle ear effusion. It was also noted in the patient file that participant 5 had signs of renal dysfunction and had experience significant nausea and vomiting. For these reasons, the second cisplatin dose was reduced by 25% to 130 mg. The third dose was withheld due to acute renal failure. No further monitoring audiological assessments were carried out.

Post-treatment assessment was carried out for the purpose of this research in January 2010. During questioning, the participant reported a gradual bilateral hearing loss prior to beginning treatment but noted a significant deterioration since treatment. He reported

difficulty hearing in group situations and in environments with background noise. He commented that he now turns the television volume up to a level that his wife is not comfortable with. Participant 5 reported experiencing a high pitched, ringing tinnitus although he was unsure of the time of onset and whether it had changed since undergoing treatment. He reported a 10 year history of occupational noise exposure for which he wore hearing protection. Standard pure-tone audiometry showed normal hearing sloping steeply to a severe hearing loss bilaterally. Bone conduction results indicate a conductive component at 4 kHz in the left ear, and at 1, 2, and 4 kHz in the right ear. Standard PTA was 13.75 dB HL in the left ear, and 21.23 dB HL in the right ear. EHF pure-tone audiometry showed a severe rising to a moderately-severe hearing loss in the left ear and a severe to moderately-severe flat hearing loss in the right ear. EHF PTA was 85 dB HL in the left ear, and 82.5 dB HL in the right ear. Analysis of thresholds in relation to the ASHA criteria indicated a significant cochleotoxic change, fulfilling criteria 1 and 2 bilaterally. Otoscopy showed significant wax in the right ear. Tympanometry yielded type "A" tympanograms bilaterally, consistent with normal middle ear pressure and compliance. Speech audiometry at a presentation level of 45 dB HL in the left ear and 50 dB HL in the right ear yielded 97% and 100% respectively. Speech presentation at 30 dB HL gave 94%, and 63% at a level of 20 dB HL in the left ear. In the right ear, a presentation level of 35 dB HL and 25 dB HL gave 100% and 88% respectively. DPOAEs were present in the left ear at 2, 2.25, 2.5, 4.5 and 9.25 kHz and from 2 to 6.125 in the right ear. Ipsilateral acoustic reflexes were unable to be tested due to difficulty maintaining a hermetic seal. Audiometric data for participant 5 are detailed in Figure 3.8.

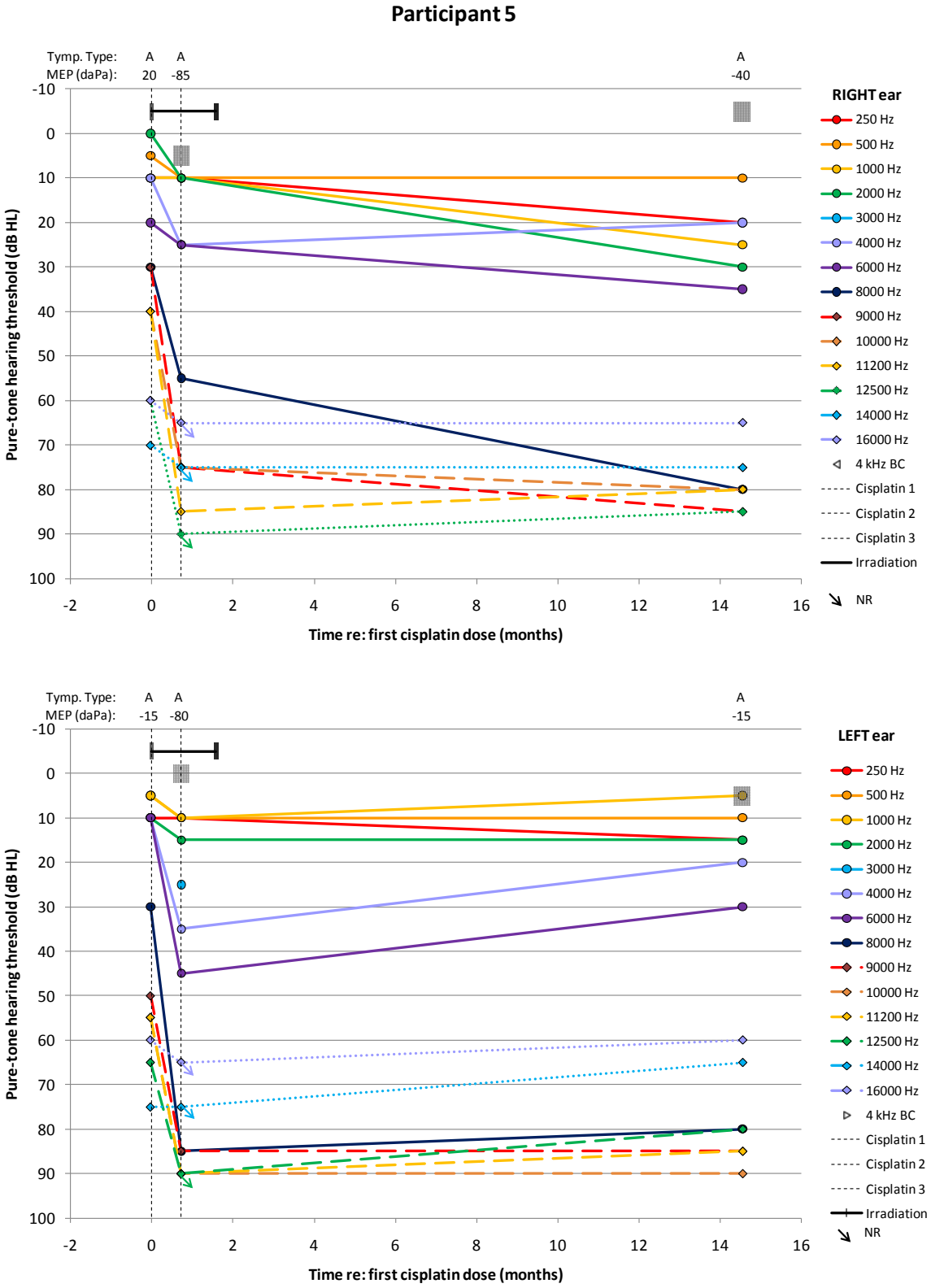

Figure 3.8: Illustration of hearing thresholds in decibel hearing level (dB HL) at 0.25 to 16 kHz for the right ear (top) and left ear (bottom). Thresholds are shown as a function of time from the initial cisplatin dose (0 months) to post-treatment assessment. The vertical lines indicate cisplatin doses. Horizontal bar indicates period of irradiation. Dashed coloured lines indicate extended high-frequency thresholds. No response at the limits of the audiometer is indicated by an arrow, with those intensities joined by dotted lines.

3.5.2 Participant 21

Participant 21 is a 58;0 year old male who was diagnosed with SCC of the oropharynx in 2008. The participant was aged 56;6 years at the time of beginning concurrent cisplatin and cranial irradiation therapy. Two days prior to commencing treatment, the participant underwent audiological assessment that involved standard pure-tone audiometry, EHF pure-tone audiometry, and tympanometry. Standard pure-tone audiometry showed normal hearing sloping to moderate hearing loss bilaterally. Bone conduction results indicate a conductive component at 4 kHz. The PTA was 7.5 dB HL in the left ear and 11.25 dB HL in the right ear. EHF pure-tone audiometry showed a moderate to moderately-severe relatively flat loss bilaterally. The EHF PTA was 56.25 dB HL in the left ear and 58.75 dB HL in the right ear. Tympanometry yielded type "A" tympanograms bilaterally, consistent with normal middle ear pressure and compliance.

Participant 21 received one dose of 219 mg cisplatin on day one of the treatment protocol. On day 22, he received the second 219 mg dose of cisplatin. The day following (day 23) he underwent repeat audiological assessment consisting of standard pure-tone audiometry, EHF pure-tone audiometry and tympanometry. Standard pure-tone audiometry showed a 15 dB deterioration at 4 kHz in the right ear. Bone conduction results were consistent with a conductive component. EHF pure-tone audiometry showed a deterioration of 15 dB at 11.2 kHz, 25 dB at 12.5 kHz and loss of response at 14 kHz and 16 kHz in the right ear. EHF pure-tone audiometry also showed a 15 dB deterioration at 14 kHz and a loss of response at 16 kHz in the left ear. Tympanometry yielded a type "A" tympanogram in the left ear, consistent with normal middle ear pressure and compliance, and a type "C" tympanogram in the right ear, consistent with negative middle ear pressure and resulting in a retracted tympanic membrane. Analysis of thresholds in relation to the ASHA criteria indicated a significant cochleotoxic change bilaterally, fulfilling criterion 2 for the left ear and both criteria 1 and 2 for the right ear. On day 42, participant 21 received his third and final dose of 219 mg cisplatin, bringing the total dose to 657 mg. This is the highest dose received by any of the 23 participants involved in this study. The irradiation therapy ceased 7 days later.

Approximately three months later in February 2009, participant 21 underwent a follow-up audiological assessment involving standard pure-tone audiometry, EHF pure-tone audiometry, and tympanometry. Standard pure-tone audiometry did not show any significant change in the left ear. In the right ear, there was a significant deterioration of 15 dB HL at 0.25 kHz and 3 kHz, 20 dB HL at 4 kHz, and 15 dB HL at 6 kHz and 8 kHz. Bone conduction at 4 kHz in the right ear suggested a conductive component and was not significantly different from the previous test. EHF pure-tone audiometry in the left ear showed a deterioration of 20 dB HL at 9 kHz, and 15 dB HL at 10 kHz. There was a significant improvement of hearing thresholds at 14 kHz and 16 kHz, with an improvement of 15 dB HL and at least 25 dB HL respectively. In the right ear, there was a

35 dB HL deterioration at 9 kHz and 10 kHz, 15 dB HL at 11.2 kHz, and a loss of response at 12.5 kHz and 14 kHz. Tympanometry results were similar to the previous test with a type “A” tympanogram in the left ear, and a type “C” tympanogram in the right ear. Analysis of thresholds in relation to the ASHA criteria indicated a significant cochleotoxic change bilaterally, this time fulfilling criteria 1 and 2 in the left ear, and all three in the right ear. It is important to emphasise that, although there was middle-ear dysfunction which probably influenced the right ear thresholds, the 4 kHz bone conduction results show a 15 dB shift, although this is still not enough to fulfil the first ASHA criterion at that frequency.

Further audiological assessment was carried out for the purpose of this research in March 2010. The participant reported a gradual hearing loss since receiving treatment. He reported difficulty hearing in group situations and in noisy environments he relies on lipreading. He also described significant difficulty watching the television. Participant 21 reported unilateral tinnitus in his right ear that sounds like a “low pitch sea noise”. He was unsure of the onset but had noticed an increase in severity since starting treatment. He also reported an occasional feeling of being on uneven ground that he first noticed after treatment. He did not describe any symptoms of vertigo or nausea. In addition, participant 21 described a feeling of aural pressure or fullness in his right ear that he believed developed whilst having treatment and lasted approximately three to four months. This was thought to be caused by otitis media with effusion. He reported a 15 year history of occupational noise exposure during which time he wore hearing protection. Standard pure-tone audiometry showed normal hearing sloping to a mild hearing loss in the left ear, and normal hearing sloping to a moderate loss in the right ear. Bone conduction results indicate a conductive component at 4 kHz in the right ear. Standard PTA was 7.5 dB HL in the left ear and 15 dB HL in the right ear. EHF pure-tone audiometry showed a moderate to moderately-severe flat loss bilaterally. EHF PTA was 57.5 dB HL in the left ear, and 63.75 dB HL in the right ear. Tympanometry yielded a type “A” tympanogram in the left ear, consistent with normal middle ear pressure and compliance, and a type “C” tympanogram in the right ear, indicating negative middle ear pressure and resulting in a retracted tympanic membrane. Speech audiometry at a presentation level of 35 dB HL in the left ear and 40 dB HL in the right ear yielded 94% and 100% respectively. Speech presentation at 20 dB HL resulted in 80% and 13% at 10 dB HL in the left ear. In the right ear, speech presentation at 25 dB HL and 15 dB HL resulted in 84% and 33% respectively. DPOAEs were present from 2 to 4.5 kHz and at 6.125 kHz and 9.250 kHz in the left ear. In the right ear they were present from 2 to 4.062 kHz, and at 7.5 kHz and 9.250 kHz. Ipsilateral acoustic reflexes were present at normal presentation levels from 0.5 to 2 kHz and absent at 4 kHz bilaterally. Analysis of thresholds in relation to the ASHA criteria indicated a significant cochleotoxic change in the right ear only, fulfilling criterion 2 only. Audiometric data for participant 21 are detailed in Figure 3.9.

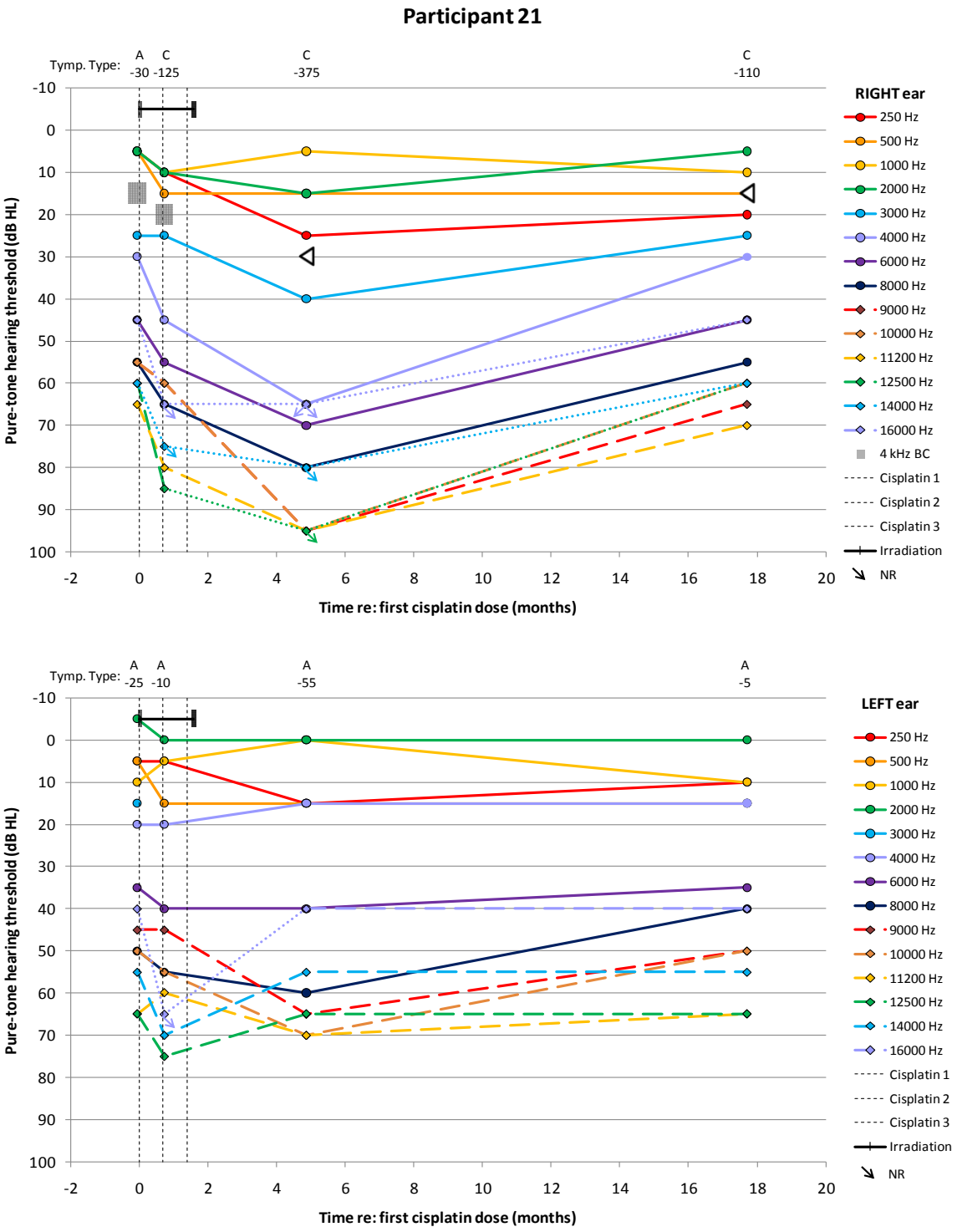

Figure 3.9: Illustration of hearing thresholds in decibel hearing level (dB HL) at 0.25 to 16 kHz for the right ear (top) and left ear (bottom). Thresholds are shown as a function of time from the initial cisplatin dose (0 months) to post-treatment assessment. The vertical lines indicate cisplatin doses. Horizontal bar indicates period of irradiation. Dashed coloured lines indicate extended high-frequency thresholds. No response at the limits of the audiometer is indicated by an arrow, with those intensities joined by dotted lines.

3.5.3 Participant 22

Participant 22 is a 52;10 year old male who was diagnosed with SCC of the oropharynx in 2005. The participant was aged 48;9 years at the time of beginning concurrent cisplatin and irradiation therapy. Eight days prior to commencing treatment, the participant underwent audiological assessment that involved standard pure-tone audiometry, EHF pure-tone audiometry and tympanometry. Standard pure-tone audiometry showed normal hearing sloping to a moderate mixed loss in the left ear, and normal hearing sloping to a mild sensorineural hearing loss in the right ear. The PTA was 20 dB HL bilaterally. EHF pure-tone audiometry showed a moderate to moderately-severe hearing loss with a loss of response above 14 kHz in the left ear. In the right ear, testing showed a moderate sloping to a severe hearing loss with a loss of response above 12.5 kHz in the right ear. Tympanometry yielded a type "A" tympanogram in the left ear, consistent with normal middle ear pressure and compliance, and a type "Ad" in the right ear, consistent with greater than normal compliance.

Participant 22 received one dose of 187 mg cisplatin on day one of the treatment protocol. Twenty days later the participant complained of hearing loss and was subsequently sent for audiological assessment. Standard pure-tone audiometry showed deterioration of high-frequency thresholds with a decrease of 15 dB at 8 kHz in the left ear, and 15 dB at 4 kHz, 30 dB at 6 kHz and 40 dB at 8 kHz in the right ear. EHF pure-tone audiometry showed a 20 dB decrease at 10 kHz and 11.2 kHz in the left ear, and a 15 dB decrease at 9 kHz and 10 kHz and loss of response at 11.2 and 12.5 kHz in the right ear. Tympanometry remained stable, indicating no middle ear effusion. Analysis of thresholds in relation to the ASHA criteria indicated a significant cochleotoxic change, fulfilling criteria 1 and 2 bilaterally. Due to this change in hearing, the second dose was withheld. Twenty one days later the participant was reassessed prior to the scheduled third cisplatin dose. Standard audiometry indicated further deterioration in the right ear only, with an additional decrease of 15 dB at 0.25 kHz and 0.5 kHz, 20 dB at 2 kHz and 15 dB at 4 kHz. Bone conduction results indicated this was a mixed hearing loss. EHF audiometry did not show any significant change (≥ 15 dB) in hearing thresholds in either the left or right ear. Tympanometry remained stable in the right ear but suggested reduced compliance in the left ear (type "As" tympanogram). Analysis of thresholds in relation to the ASHA criteria continued to indicate a significant cochleotoxic change, fulfilling criteria 1 and 2 bilaterally The third dose was also withheld due to the further deterioration in hearing on the right side.

Post-treatment assessment was carried out for the purpose of this research in January 2010. The participant reported sudden hearing loss, particularly in his right ear that he believed developed with cisplatin treatment. He reported difficulty hearing in group situations and when there is background noise. He felt that he had the television and radio turned up louder than other family members would like. Participant 22 also

reported unilateral tinnitus in his left ear, the onset of which coincided with the single dose of cisplatin. He described it as a high pitch ringing that was of minimal annoyance. He had a history of occupational noise exposure of approximately 20 years duration, but did not wear hearing protection. Standard pure-tone audiometry showed a mild to moderate sloping sensorineural hearing loss in the left ear, and a mild to moderately-severe sloping mixed hearing loss in the right ear. Standard PTA was 32.5 dB HL for the left ear and 30 dB HL for the right ear. EHF pure-tone audiometry showed a moderate to moderately-severe flat hearing loss in the left ear and a severe to profound hearing loss in the right ear. EHF PTA was 56.25 dB HL in the left ear and 86.25 dB HL in the right ear. Tympanometry yielded a type "A" tympanogram in the left ear, consistent with normal middle ear pressure and compliance, and a type "Ad" tympanogram in the right ear, consistent with increased compliance. Speech audiometry at a presentation level of 65 dB HL yielded 94% in the left ear and 100% in the right ear. Speech presentation at 55 dB HL and 40 dB HL in the left ear yielded 74% and 54% respectively. Speech presentation at 50 dB HL and 35 dB HL in the right ear yielded 80% and 21% respectively. DPOAEs were present in the right ear at 2, 2.5, 3.062, 4.062, 4.5 and 5.5 kHz, and in left ear at 2, 2.25, 4.5 and 6.125 kHz. Ipsilateral acoustic reflexes were present at normal presentation levels in the left ear from 0.5 to 2 kHz and absent at 4 kHz. Reflexes were absent from 0.5 to 4 kHz in the right ear. Analysis of thresholds in relation to the ASHA criteria indicated a significant cochleotoxic change, fulfilling criteria 1 and 2 bilaterally. Audiometric data for participant 22 are detailed in Figure 3.10.

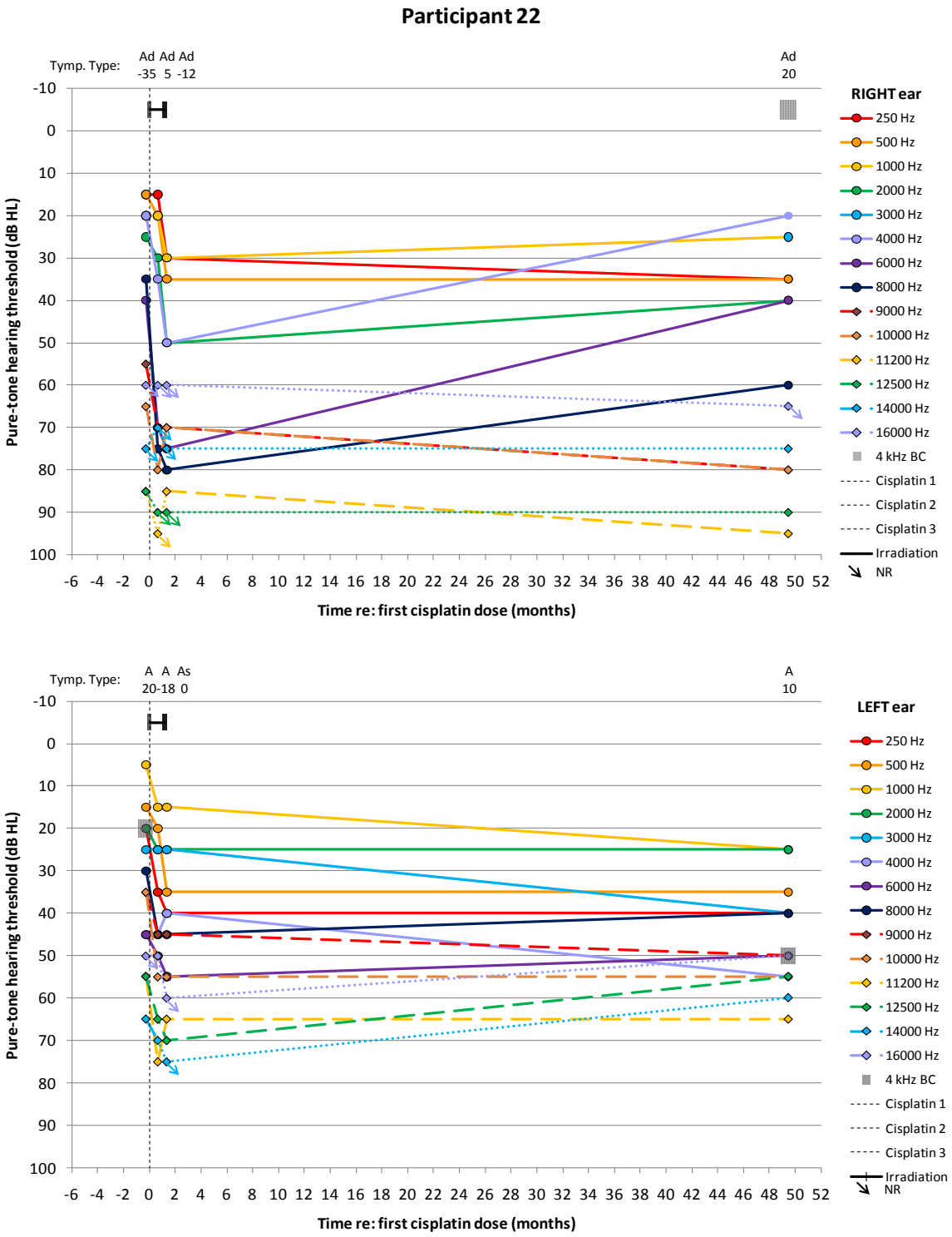

Figure 3.10: Illustration of hearing thresholds in decibel hearing level (dB HL) at 0.25 to 16 kHz for the left ear (top) and right ear (bottom). Thresholds are shown as a function of time from the initial cisplatin dose (0 months) to post-treatment assessment. The vertical lines indicate cisplatin doses. Dashed coloured lines indicate extended high-frequency thresholds. No response at the limits of the audiometer is indicated by an arrow, with those intensities joined by dotted lines.

3.5.4 Participant 23

Participant 23 is a 55;3 year old male who was diagnosed with SCC carcinoma of the oropharynx at Christchurch Public Hospital in 2007. The participant was aged 52;9 years old at the time of beginning concurrent cisplatin and irradiation therapy. Prior to commencing treatment, the participant underwent audiological assessment that involved standard pure-tone audiometry, EHF pure-tone audiometry and tympanometry. Standard pure-tone audiometry showed normal hearing bilaterally with a PTA of 11.25 dB HL in his left ear and 17.5 dB HL in his right ear. EHF pure-tone audiometry showed a mild hearing loss bilaterally sloping to a moderate hearing loss in the right ear, and a moderately-severe loss in the left ear. EHF PTA was 35 dB HL bilaterally. Tympanometry yielded type "A" tympanograms bilaterally, consistent with normal middle ear pressure and compliance.

Participant 23 received two doses of 200 mg cisplatin, giving a total dose of 400 mg. The participant did not receive the scheduled third dose due to a significant deterioration in his health including septicaemia, neutropenia, respiratory failure and acute renal failure. The participant received a total irradiation dose of 74 Gy in 37 fractions (2 Gy per fraction). The participant had a history of chronic Hepatitis C.

Post-treatment assessment was carried out for the purpose of this research in January 2010. The participant reported gradual hearing loss that he first noticed since undergoing treatment for cancer. He believed he had experienced hearing loss in both ears and reported difficulty hearing when engaged in two-person conversations and group conversations, when watching television and when in situations with background noise. Standard pure-tone audiometry showed normal hearing steeply sloping to a severe sensorineural hearing loss bilaterally with a PTA of 30 dB HL in his left ear and 25 dB HL in his right ear. EHF pure-tone audiometry showed a severe hearing loss bilaterally with a loss of response at 12.5, 14 and 16 kHz in the left ear and at 16 kHz in the right ear. EHF PTA was 85 dB HL in the left ear and 88.75 dB HL in the right ear. Tympanometry was not performed due to significant wax and debris bilaterally. Speech audiometry at a presentation level of 45 dB HL yielded 100% in the right ear and 87% in the left ear. Speech presentation at 30 dB HL yielded 63% in the right ear and 50% in the left ear. Acoustic reflexes and DPOAEs were unable to be performed due to time constraints. Analysis of thresholds in relation to the ASHA criteria indicated a significant cochleotoxic change, fulfilling criteria 1 and 2 bilaterally. Audiometric data for participant 23 are detailed in Figure 3.11.

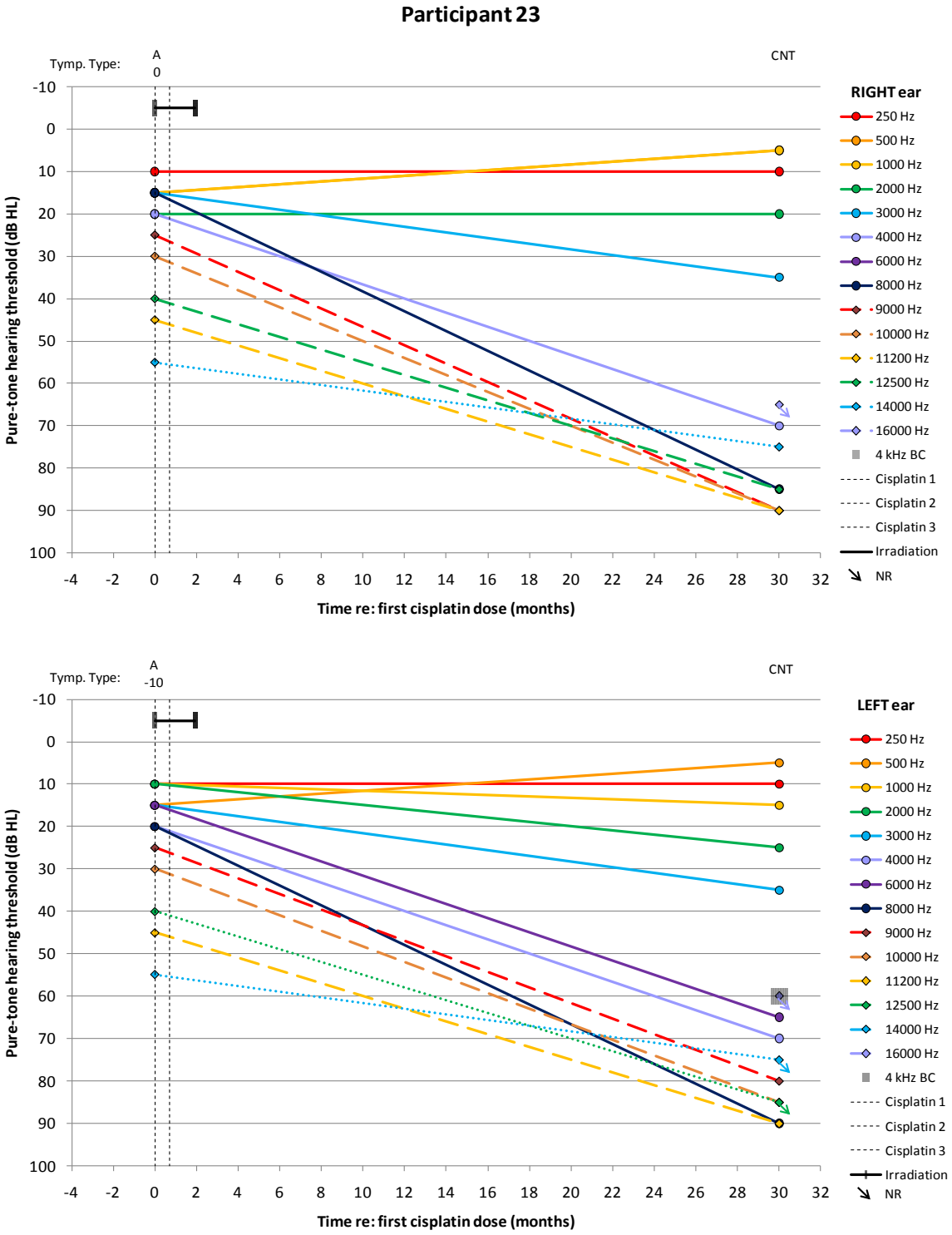

Figure 3.11: Illustration of hearing thresholds in decibel hearing level (dB HL) at 0.25 to 16 kHz for the left ear (top) and right ear (bottom). Thresholds are shown as a function of time from the initial cisplatin dose (0 months) to post-treatment assessment. The vertical lines indicate cisplatin doses. Dashed coloured lines indicate extended high-frequency thresholds. No response at the limits of the audiometer is indicated by an arrow, with those intensities joined by dotted lines.

4 Discussion

Cisplatin-induced ototoxicity is a significant clinical problem that can result in vocational, educational and social consequences. Currently there is no clinically-proven method to reduce or prevent this from occurring. In the present study, detailed post-treatment audiological assessment was performed in 23 patients who had previously received concurrent cisplatin and cranial irradiation therapy for the treatment of head and neck cancer. In addition, audiology files were examined and any previous audiometric data for the patients were analysed. The aims of this study were:

1. To investigate the prevalence of ototoxicity in head and neck oncology patients who received cisplatin in combination with cranial irradiation; and
2. Examine the current state of audiological monitoring for this population at a major New Zealand hospital.

It is the author's hope that this study will increase audiologists' awareness of the impact of ototoxicity and the importance of comprehensive audiological monitoring with the potential of improving quality of life for oncology patients.

A summary of the findings is provided below and is discussed in relation to the relevant literature. Following that, the clinical implications are presented, as well as limitations of the study and directions for future research.

4.1 Cisplatin-induced ototoxicity

Significant changes in hearing resulting from exposure to ototoxic agents, defined by the ASHA criteria of (1) ≥ 20 dB decrease at any one test frequency; (2) ≥ 10 dB decrease at any two adjacent test frequencies; or (3) loss of response at three consecutive test frequencies where responses were previously obtained, were observed in this study. In total, 93.8% of the participants who had undergone a baseline audiological assessment experienced significant cochleotoxic deterioration in hearing thresholds. This is comparable to previous studies which have reported rates as high as 75 – 100% (McKeage, 1995), although rates as low as 9% have also been noted (Rybak, 1981). The observed variability in the reported incidence of cisplatin ototoxicity may be influenced by treatment and patient-related factors. Factors such as larger cumulative dose (Brock, et al., 1991), younger and older age (Helson, et al., 1978; Li, et al., 2004), renal dysfunction (Rybak, Huang, et al., 2007), noise exposure (Bokemeyer, et al., 1998) and cranial irradiation (Low, et al., 2006) have been cited as variables that increase an individual's risk of ototoxicity. The influences of such factors are discussed in the following sections. In addition, differences in the criteria used to define ototoxicity may also affect the reported incidence. The ASHA (American Speech-Language-Hearing Association, 1994) criteria are the most widely used criteria used for determining a shift in pure-tone

thresholds. Clinical trials, however, list ototoxicity as an adverse event based on a grading system. The two most widely used grading scales in this respect are Brock's Hearing Loss Grades (Brock, et al., 1991) and the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) Ototoxicity Grades. Caution should be exercised when comparing incidence rates across studies, particularly those that do not use one of the aforementioned criteria, as differences may be attributed to false positive results due to criteria that are too stringent.

4.1.1 The influence of cumulative and total dose

There is agreement in the literature that cumulative doses greater than 400 mg/m^2 places the patient at higher risk of developing ototoxicity. These studies are, however, often based on children and young adults with common paediatric malignancies such as osteosarcoma, medulloblastoma and neuroblastoma (Knight, Kraemer, & Neuwelt, 2005). Reports of hearing deterioration from smaller doses are not uncommon (Rybak, 1981). Helson et al., (1978) found high-frequency SNHL in patients receiving cisplatin in excess of 200 mg total dose while Schaefer et al., (1985) studied ototoxicity in a sample of 100 head and neck cancer patients ranging in age from 51 to 69 years. They concluded that patients receiving a total dose more than 400 mg of cisplatin over a period of six weeks or longer are at risk of developing ototoxicity and should be routinely screened. In the current study, the maximum cumulative dose for any participant was 300 mg/m^2. Fourteen participants, however, received a total dose of 400 mg or more over a period of six weeks, placing them at higher risk of developing ototoxicity. From the group of 16 participants who had a pre-treatment assessment, it was noted that there were similarly high proportions of cochleotoxicity (based on any one of the three ASHA criteria being met) between those who had received a total dose of 400 mg or more and those who received less than 400 mg. Specifically, all 6 participants who received under 400 mg experienced significant hearing deterioration, while 9 out of the 10 participants who received 400 mg or greater experienced significant hearing deterioration. This indicates that there is no significant effect of total cisplatin dose observed in this study, but this may be due to the small sample size.

4.1.2 The influence of renal dysfunction

Two participants (participant 5 and participant 23) were noted to have renal dysfunction during their treatment, and both experienced significant cochleotoxicity based on the ASHA criteria. The literature indicates patients with renal function have poor creatinine clearance which leads to increased serum active cisplatin levels. In contrast, a recent study has found plasma cisplatin concentration in patients with renal dysfunction about the same as patients with normal renal function (Matsumoto, 2008).

4.1.3 The influence of noise exposure

In the present study, over 90 percent of participants reported exposure to significant levels noise through their occupation. NIHL is the second most common SNHL after

presbycusis, and has become one of the most important occupational problems since the industrial revolution (Konings, Van Laer, & Van Camp, 2009). There are three types of changes in hearing status that may occur following exposure to either recreational or occupational noise. These are referred to as temporary threshold shift (TTS), permanent threshold shift (PTS) and acoustic trauma (Feuerstein, 2002). TTS is a temporary reduction in hearing sensitivity resulting from exposure to sound above 85 dBA, and represents transient hair cell dysfunction (Rabinowitz, 2000). Other symptoms may include a subjective feeling of aural fullness and tinnitus (Feuerstein, 2002). This temporary hearing loss typically recovers within 16 to 24 hours of the noise exposure (Thorne et al., 2008), and is attributed to the synaptic repair and reconnection of inner hair cells via new dendritic processes (Prasher, 1998). PTS occurs with chronic noise exposure and can result from incomplete recovery of TTS. Damage to the cochlear results from metabolic decompensation (Konings, et al., 2009) and includes disruption to the stereocilia, swollen nuclei, swollen mitochondria, cytoplasmic vesiculation and vacuolization. Progressive damage may lead to degeneration of nerve fibres and changes within the central auditory system (Feuerstein, 2002). Acoustic trauma occurs following acute exposure to noise intensities above 130 dB SPL, causing mechanical destruction of the organ of Corti (Konings, et al., 2009). Damage may also extend to tympanic membrane perforation and ossicular fractures (Feuerstein, 2002). It appears there is large individual susceptibility to NIHL. This individual variability is an indication that NIHL does not have a single causative factor, but is in fact, a complex condition caused by an interaction of environmental and genetic factors. Environmental factors have been well researched and include exposure to organic solvents and heavy metals (Morata, Dunn, & Seiber, 1994), age (Rosenhall, 2003), extreme temperatures, and vibration (Prasher, 1998). Genetic factors associated with NIHL are less well known. Research into this area has examined the role of oxidative stress, K-recycling pathway, and heat shock proteins (Konings, et al., 2009).

It has been noted that concurrent noise exposure may potentiate the ototoxicity of cisplatin. Using a chinchilla model, (Boettcher, Henderson, Gratton, Danielson, & Byrne, 1987) showed that even mild noise exposure during treatment significantly increases the risk of permanent hearing loss (ANOVA: $p < 0.0001$). In particular, the interaction between noise and cisplatin was found to occur even in cases where cisplatin administration alone did not result in deterioration of thresholds. This is supported by Gratton, Salvi, Kamen and Saunders (1990) who demonstrated an increased risk of hair cell damage with noise exposure between 70 – 85 dB SPL. Initially noted at the highest test frequency, as noise level increases, cochlear damage spreads upwards to affect the mid-frequencies. The effect of prior noise exposure on thresholds is somewhat controversial with Laurell and Borg (1986) showing no effect. This finding may potentially be due to maximal OHC dysfunction already occurring as a result of noise exposure and therefore cisplatin administration may not result in further damage unless

the dose is high enough to begin causing damage to IHCs. In contrast, however, a history of noise exposure has been independently correlated with both subjective and objective hearing loss resulting from cisplatin treatment (Bokemeyer, et al., 1998).

In the present study, participants were questioned about their history of noise exposure but were not asked whether they had continued to have significant noise exposure during or directly following treatment. It is therefore difficult to draw any conclusions about the possible effect of noise exposure on the high prevalence of cisplatin-induced ototoxicity found in this study.

4.1.4 The influence of cranial irradiation

Due to the nature of the treatment protocol, all 23 participants received cranial irradiation. Eighteen of the 23 participants received a total irradiation dose of 70 Gy in 35 fractions (2 Gy per fraction). This dosage of cranial irradiation alone has been shown to induce ototoxicity in at least 33% of patients (Raaijmakers & Engelen, 2002) and it has been shown that patients receiving concurrent cisplatin chemotherapy have a greater risk than those receiving only irradiation treatment (Low, et al., 2006). Of the 16 participants who had a pre-treatment assessment, 11 received 70 Gy in 35 fractions, while 3 participants received a lower dose of 60 Gy in 30 fractions. A comparison between the two groups showed that both groups yielded similarly high proportions of participants who experienced cochleotoxicity based on any one of the three ASHA criteria. Specifically, all three participants who received the lower irradiation dose experienced cochleotoxicity, while 11 of the 12 participants who received the higher dose of irradiation experienced cochleotoxicity. Once again, this indicates that there is no significant effect of total irradiation dose observed in this study. This may be due to the small sample size, and also due to the common effect of the cisplatin therapy.

4.1.5 The influence of loop diuretics

Three of the participants (participants 2, 10 and 12) were given a single dose of the loop diuretic furosemide. This was administered to ameliorate facial swelling that had resulted from the irradiation therapy and prevented the correct fit of the treatment mask. Loop diuretics in isolation are known to produce a dose-related, usually reversible ototoxicity in 6–7% of patients, primarily affecting those with renal dysfunction (Mudd, Edmunds, Glatz, Campbell, & Rybak, 2008). This occurs by inhibiting potassium transport, causing edema of the epithelium of the stria vascularis (Jordan & Roland, 2000). There is some evidence to suggest loop diuretics may augment cisplatin cochleotoxicity (Brummett, 1980). Furosemide ototoxicity typically occurs with total daily IV doses greater than 240 mg, and serum concentrations greater than 50 mg/L. (Seligmann, et al., 1996). In patients with renal dysfunction, oral administration of furosemide doses between 160 to 800 mg/day has resulted in ototoxicity (Keefe, 1978). Furosemide ototoxicity is also dependent on the rate of infusion. IV administration of large doses (>120 mg) at a rate not exceeding 4 mg/min has been shown to avoid hearing loss (Rybak, 2007). In this

study, the administered doses of furosemide are considered low and therefore would not be expected to affect hearing thresholds in the short or long term. The rate of administration that was used in these patients, however, is unclear.

4.1.6 Tinnitus

In the present study, almost half of the sample reported tinnitus that had either begun or increased in severity as a result of treatment. This is higher than previously reported prevalence rates of 12–37% in other studies of cisplatin-induced ototoxicity (Bokemeyer, et al., 1998). The prevalence of chronic tinnitus in adults in the general population is estimated to fall in the range of 10–15% (Henry, Dennis, & Schechter, 2005) affecting a higher proportion of adults aged over 60 years compared with younger adults aged 20 – 30 years (Eggermont & Roberts, 2004). There also appears to be a relatively equal distribution between males and females (Crummer & Hassan, 2004). Most cases of chronic tinnitus are associated with hearing loss that is induced by noise exposure or the aging process, although medications are frequently associated with temporary or permanent tinnitus. The mechanism responsible for tinnitus is poorly understood even in cases when a causal event seems obvious. It is thought that exposure to ototoxic agents may affect hair cells, the vestibulocochlear nerve, or their central nervous connections (Crummer & Hassan, 2004). There is some evidence that tinnitus is the result of changes in spontaneous activity in the auditory system (Eggermont & Roberts, 2004). Cisplatin administration in hamsters has been associated with an increase in spontaneous neural activity (hyperactivity) in the dorsal cochlear nucleus DCN (Kaltenbach et al., 2002). In particular, animals with severe OHC loss displayed well-developed hyperactivity, mainly in the medial (high-frequency) half of the DCN. This pattern is consistent with OHC loss occurring mainly in the basal half of the cochlea.

In addition, there is a strong psychological component to tinnitus. This is illustrated in cases where the emergence of intrusive tinnitus occurs after the underlying medical condition and is triggered by seemingly unrelated factors such as emotional stress, psychological factors, bereavement, unemployment or various physical or mental illnesses (Henry, et al., 2005). These factors may also impact upon the perceived severity of the tinnitus. There is little doubt that undergoing treatment for cancer is a particularly stressful time, both emotionally and physically, and this aspect cannot be excluded as a contributing factor to the relatively high rate of tinnitus experienced in the study sample.

4.1.7 Time course of cochleotoxicity

Cisplatin-induced ototoxicity typically manifests as irreversible, progressive, bilateral, high frequency SNHL associated with tinnitus (Daldal, et al., 2007). Progression of hearing loss has been reported in 21% of patients, with deterioration continuing for up to 26 months after the completion of cisplatin therapy (Knight, et al., 2005). Bertolini et al., (2004) investigated the severity and evolution of hearing loss in 120 survivors of childhood cancer. Median follow-up pure-tone audiometry was 7 years post treatment

and showed deterioration of hearing in 37% of patients treated with cisplatin, and in 43% of patients treated with cisplatin plus carboplatin. Progression of hearing loss was seen up to 136 months after the completion of therapy. Interestingly, hearing loss was noted in patients who had normal hearing immediately post treatment. The period of time in which stabilisation of hearing thresholds occur is unknown, however, cisplatin has been detected in plasma proteins up to six months after completion of therapy (Mudd, et al., 2008). Participant 22 displayed continuing deterioration of hearing thresholds for approximately two months after the cessation of treatment (Figure 3.10). Participant 22 did not receive doses 2 and 3 due to significant changes in hearing that were measured approximately 3 weeks apart. Unfortunately no subsequent assessments were made in the period following and so it is uncertain whether his hearing stabilised shortly after the two month period or whether it continued to decline over a longer interval. Participant 23 also showed deterioration between the pre- and post-treatment assessments (Figure 3.11), however, due to the lack of follow-up assessment it is uncertain over what period of time this occurred. During the case history, participant 23 reported the gradual onset of hearing loss post treatment.

Although the auditory deficits are usually permanent, limited recovery has been observed both clinically and experimentally. Comparison of audiograms obtained from 50 male genitourinary cancer patients from baseline to the 52nd week of cisplatin treatment showed complete recovery of thresholds in 2% of patients, partial recovery in 26% and no recovery in 54% (Aguilar-Markulis, Beckley, Priore, & Mettlin, 1981). Bokemeyer et al., (1998) also reported partial or complete reversibility of subjective and/or objective hearing loss. Results from Klis et al., (2002) show that the loss and recovery of cochlear sensitivity coincides with loss and recovery of the endocochlear potential. These fluctuations do not occur for every patient, with studies not showing any change for a period of five years (Brock, et al., 1991). In this study, participant 5 and participant 21 experienced a temporary decline in hearing that fulfilled the third ASHA criteria but had recovered significantly before the post-treatment assessment.

4.1.8 Vestibulotoxicity

The cochleotoxicity of cisplatin is well documented in the literature, however, there are few reports concerning vestibular dysfunction resulting from cisplatin administration. In the present study, 17.4% of participants reported experiencing balance disturbances since receiving treatment. Clinically, cisplatin vestibulotoxicity is controversial. Vestibular complaints may be subtle or masked by symptoms commonly seen in patients receiving chemotherapy, such as nausea, vomiting and/or ataxia. Both temporary (Black, Gianna-Poulin, & Pesznecker, 2001) and permanent (Schaefer, Wright, Post, & Frenkel, 1981) vestibular dysfunction in humans has been demonstrated by caloric testing. The targets of cisplatin vestibulotoxicity have been investigated in albino guinea pigs using the vestibulo-ocular reflex (VOR) (Sergi, Ferraresi, Troiani, Paludetti, & Fetoni, 2003).

Significant decreases in VOR gain have been observed ($p = 0.014$) and are attributable to both crista and macular hair cell damage. Histological preparations confirm this hypothesis showing slight vestibular hair cell loss in both macular and semicircular canal organs (Sergi et al., 2004). In contrast, transmission electron microscopy of cisplatin-treated animals showed normal type I and type II hair cells with no evidence of blebbing, vacuolisation, loss of sterocilia and kinocilia or supporting cell damage (Schweitzer, Rarey, Dolan, Abrams, & Sheridan, 1986). Recently, proinflammatory cytokines are suggested to play a critical role in the pathogenesis of cisplatin-induced vestibulotoxicity (H. J. Kim et al., 2008). Overall, the vestibular epithelium appears more resistant to cisplatin injury although the reasons for this remain unknown. It appears that the slight vestibular dysfunction observed is consistent with the relatively low proportion of patients who experience vestibular symptoms.

In addition, the vestibulotoxicity of irradiation should be considered. Cranial irradiation for the treatment and/or management of various head and neck cancers may involve parts of the ear. Vestibular function was investigated in 25 patients who had received between 28 and 51.2 Gy to the vestibular system (Gabriele, Orecchia, Magnano, Albera, & Sannazzari, 1992). Five patients experienced subjective vertigo or dizziness, while 11 (44%) patients displayed vestibular abnormalities during assessment by electronystagmography (ENG). The amount of irradiation that the inner ear received in this study is unknown.

4.2 The current state of audiological monitoring

The results from this study showed that 30.4% of the individuals in this study did not have an audiological assessment prior to beginning their cisplatin treatment. One of the basic principles of cochleotoxicity monitoring is obtaining valid baseline data to measure any change in future thresholds (American Speech-Language-Hearing Association, 1994). Evidence in the literature indicates that the sensitivity of monitoring programmes are greatly increased by measuring EHF thresholds (Fausti, et al., 1993; Knight, et al., 2007). In this study, 87.5% of the participants who had baseline testing (i.e. 60.9% overall) had EHF audiometry included in the test battery. None of the baseline assessments included OAEs, acoustic reflexes or speech audiometry. Although not originally included in the ASHA cochleotoxicity criteria, investigations since have found that DPOAEs are particularly valuable for monitoring ototoxicity in patients who are unable to provide reliable behavioural thresholds due to age (Knight, et al., 2007) or illness (Reavis, et al., 2008).

Of the participants who received a pre-treatment assessment, 31.3% did not have any other follow-up assessments either during or after cisplatin therapy. It is recommended that participants undergo repeat assessments prior to each dose of cisplatin and then again at the completion of therapy to confirm any changes in hearing status (American Speech-Language-Hearing Association, 1994). Participant 21 only received one dose of

cisplatin due to significant deterioration in his hearing. He subsequently received a further two follow-up assessments, however, there was no repeat assessment to ascertain whether the hearing loss had stabilised or not. Participant 15 declined further doses of cisplatin due to a significant increase in tinnitus severity. Although tinnitus is associated with cisplatin-induced ototoxicity, the participant did not receive an audiological assessment at any stage.

The results of this study showed that although the participants who perceived a change in their hearing were accurate; that is, there was a measureable change in thresholds based on ASHA criteria, some participants were unable to perceive a deterioration in their hearing when there had been a significant change. This highlights the importance of having an effective monitoring protocol in place rather than relying solely on patient report. Unfortunately, it is often communication difficulties that alert people to a decline in hearing, by which stage the ototoxic damage has infiltrated the frequency range considered important for speech. Fluent communication is particularly important for patients with life-threatening diseases such as cancer, and is a central quality of life issue.

4.3 Other findings

4.3.1 Impact of OHCs on threshold shifts

In the present study, the greatest threshold shifts observed between pre- and post-treatment audiograms occurred at 9 kHz for both the left and right ear. The smaller measured threshold shifts for frequencies 10 kHz and above may be explained by the presence of pre-treatment cochlear hearing loss in the higher frequencies as a result of factors such as aging and noise exposure (Barr-Hamilton, et al., 1991). Cochlear hearing loss can involve damage or loss of function of the OHCs, IHCs or both. These are referred to as motor losses, sensory losses or mixed hair cell losses, respectively. The OHCs play an active role in the cochlea, enhancing cochlear vibration approximately 1000-fold, equivalent to 60 dB (Patuzzi, 2009). Therefore, losses greater than 60-70 dB often indicate some loss of effective IHC or neural function (Vinay & Moore, 2007). The pattern of high-frequency loss typically observed in cases of cisplatin ototoxicity can be explained by the increased vulnerability of OHCs to free-radical damage at the base of the cochlea compared to OHCs at the apex of the cochlea. This is possibly due to lower levels of the cellular antioxidant glutathione (Sha, Taylor, Forge, & Schacht, 2001), and may increase the susceptibility of basal OHCs to the action of ROS. This theory may also apply to noise-induced hearing loss (NIHL), where the formation of ROS has been shown to occur in response to noise trauma. The level of ROS has been shown to correspond with the intensity of exposure (Le Prell et al., 2003). In addition, BM vibration nearer the apex may be less affected by toxicity in the cochlea due to the reduced importance of the active process at lower frequencies. The minimal threshold changes at frequencies 10 kHz and above observed in this study may therefore be explained by prior damage and/or loss of

OHCs due to other factors such as noise exposure and possibly aging. In effect, the participants had already lost a large proportion of their active process at these EHF prior to cisplatin treatment, and so further cisplatin-induced injury through the formation of ROS had little impact on thresholds. At frequencies below 10 kHz, however, there was less OHC damage prior to treatment and therefore a greater effect was noted. These findings are in contrast to studies with samples consisting of children and young adults where threshold shifts are greatest with increasing frequency (e.g. de Almeida, Umeoka, Viera, & de Moraes, 2008), which is most likely due to these populations having intact OHCs prior to treatment.

4.3.2 Effect of medical factors

Hearing loss from ototoxicity is a complex disorder as there are often contributing factors such as age-related hearing loss, and noise exposure. In addition, certain medical conditions may also impact on the hearing loss observed, including cardiovascular disease (CVD), diabetes mellitus (DM), and head trauma. Other factors such as smoking and alcohol abuse have also been associated with hearing loss (Rosenhall, Sixt, Sundh, & Svanborg, 1993), however, as data were not collected on these determinants, they will not be discussed here.

4.3.2.1 Cardiovascular disease

In the present study, just under one third of the participants had at least one form of CVD including hypertension, cardiomyopathy, stroke and arrhythmia. A study by Gates, Cobb, D'Agostino and Wolf (1993) has shown a statistically significant association between CVD and hearing loss. This effect was noted to be greater for woman than men, and was more pronounced in the lower frequencies. Interestingly, metabolic presbycusis is associated with low-frequency hearing loss and is thought to result from microvascular disease leading to atrophy of the stria vascularis (Demeester, et al., 2009). A gender specific association has been observed, with middle-aged to elderly women with a self-reported history of myocardial infarction have been shown to be twice as likely to have cochlear impairment as women without a history of myocardial infarction (Torre, Cruickshanks, Klein, Klein, & Nondahl, 2005). This association was not observed in men. Over a quarter of the participants in this study had previously been diagnosed with hypertension. Hypertension and systolic (peak) blood pressure have also been associated with presbycusic changes in auditory status (Brant et al., 1996). A hypothesis put forward by Dai et al. (2004) proposes the role of hypoxia in the cochlea related to CVD events. Narrowing of the blood vessels that supply the cochlea may cause hypoxia of the inner ear and initiate a chain of events such as ischemia in the inner ear, malfunction of oxygen metabolism, reduction in the level of mitochondrial oxidative phosphorylation, elevation of free radicals and an accumulation of mitochondrial mutations. This may result in accelerated degeneration or death of cells in the organ of Corti and the nerve fibres of the inner ear, ultimately leading to decreased function of the acoustic neural system.

4.3.2.2 *Diabetes*

One participant in the present study had type II insulin-dependent diabetes mellitus (IDDM). Unfortunately, this participant did not receive a pre-treatment assessment. In addition, the participant received follow-up assessments at another South Island hospital where EHF audiometry was not tested. Despite this, the post-treatment assessment showed that the participant did experience significant cochleotoxicity bilaterally, based on the earliest assessment that was carried out. The relationship between DM and SNHL has been examined for more than a century, although no lesions have been located and the underlying mechanism is currently unknown. Diabetes is associated, however, with an increased risk of hearing loss, particularly in adults under 50 years old (Austin et al., 2009). Histological changes observed within type II diabetic cochleae include thickened vessels of the stria vascularis and BM, atrophy of the stria vascularis and loss of OHCs (Fukushima et al., 2006). These changes were greater in IDDM cochleae than those with the less severe noninsulin-dependent diabetes mellitus (NIDDM).

4.3.2.3 *Head trauma*

In the present study, 40% of participants reported significant head trauma during their life that rendered them unconscious and/or required admission to hospital. Hearing loss is a well-recognised consequence of head trauma. Although hearing loss is usually most pronounced in the high frequencies, the entire frequency range may be affected (Rosenhall, et al., 1993). Damage to the inner ear may include disruption to the membranous portion of the cochlea, disturbances in the circulatory system of the cochlea, or to haemorrhage into the fluids of the inner ear (Fitzgerald, 1996). Both peripheral and central damage has been illustrated in a rabbit model, with reduced DPOAE amplitudes and increased ABR wave I – III latencies (Danielidis et al., 2007). In addition, histopathologic examination of the temporal lobe and brainstem showed multiple haemorrhagic and necrotic areas, with oedema in the surrounding region, and severe damage to the vestibulocochlear nerve. Generally, hearing loss occurs immediately following the trauma and recovers somewhat over the next six months (Fitzgerald, 1996). In the present study, a single participant reported experiencing unilateral hearing loss following a blow to the head approximately 60 years earlier. Unfortunately, as there was no record of audiological assessment prior to the post-treatment assessment carried out for the purpose of this study, the magnitude of the hearing loss could not be quantified.

4.3.3 4 kHz air-bone gap

During the post-treatment assessment an air-bone gap equal to or greater than 15 dB at 4 kHz was noted in six of the participants. In each case there was no other indication of a conductive component to their hearing loss; that is, no air-bone gap at other frequencies and type “A” tympanograms, consistent with middle ear pressure and compliance. This phenomenon has been discussed in the literature, with speculation it is caused by acoustic radiation from the bone conductor reaching the test ear via air conduction thus increasing

the signal to the cochlea resulting in a better bone conduction threshold (Margolis, 2008). A study by Frank and Holmes (1981) found only a 1 dB difference between mastoid bone conduction thresholds at 4 kHz with the EAC plugged and unplugged. More recently, Stenfelt and Reinfeldt (2007) found that having the EAC plugged does in fact reduce ear canal pressure above 2 kHz, but does not affect bone conduction thresholds. Currently, the source of the aberrant 4 kHz air-bone gap is not thought to result from acoustic radiation, and remains unknown.

4.4 Clinical implications

Based on the results of the present study, there are two main clinical implications that are discussed below: participant's eligibility to receive funding for rehabilitation, and guidelines for the establishment of an ototoxicity monitoring programme.

4.4.1 Hearing aid funding

Obtaining baseline audiometric data and ensuring effective monitoring of hearing thresholds may impact upon an individual's ability to have a claim accepted by the Accident Compensation Corporation (ACC). Under ACC legislation, all New Zealand residents and visitors to New Zealand are eligible for comprehensive, no-fault personal injury cover provided by the Crown organisation. This includes cover for treatment injury (previously referred to as medical misadventure) which is defined as "personal injury that is — suffered by a person — seeking treatment... receiving treatment from, or at the direction of, 1 or more registered health professional...; and (b) caused by treatment..." (Parliamentary Counsel Office, 2001, p. pg. 70). It might be argued that hearing loss resulting from cisplatin therapy constitutes a treatment injury. In the case of participant 2, a claim for hearing loss as a treatment injury was submitted to ACC but was declined, apparently on the basis of having no pre-treatment audiometric data to confirm that there had been a decline in hearing thresholds as a result of cisplatin treatment. It does seem, however, that cisplatin-induced ototoxicity may not constitute a treatment injury. Further examination of the ACC act reveals that treatment injury is "not a necessary part, or ordinary consequence, of the treatment, taking into account all the circumstances of treatment, including — the clinical knowledge at the time of treatment" (Parliamentary Counsel Office, 2001, p. pg. 70). Ototoxicity has long been recognised as a side effect of cisplatin treatment, and so could be conversely argued that the resulting hearing loss is in fact, an ordinary consequence of cisplatin treatment. The ambiguity of this definition and effect of cisplatin means that a case could, in theory, be argued either way and is very much dependent on the availability of evidence illustrating any change in hearing.

Another important consideration is the potential impact of cisplatin-induced ototoxicity on an individual's ability to have a future claim accepted by ACC for NIHL. Individuals who have been exposed to high levels of noise may be eligible for complete funding of hearing aids and related consumables through ACC. Establishing that personal injury has

occurred as a result of noise exposure may prove difficult in individuals with no pre-treatment audiogram.

4.4.2 Recommendations for an ototoxicity monitoring programme

This study indicates that monitoring for cochleotoxicity is not happening for all patients receiving treatment with cisplatin chemotherapy at Christchurch Hospital. Overall, this group of patients appear to be suffering substantial deterioration of their hearing as a result of their cancer treatment. Currently, the governing body for audiologists in New Zealand, the NZAS, do not have any standards of practice for ototoxicity monitoring (E. Hunter, personal communication, 20 May, 2010). This also appears to be the case for the Audiological Society of Australia and the British Society of Audiology. Recently, the American Academy of Audiology (AAA) developed a position statement and practice guidelines for ototoxicity monitoring (American Academy of Audiology, 2009).

Over 90% of the participants for whom analysis of ototoxicity was possible, experienced a clinically significant deterioration of hearing thresholds as a result of concurrent cisplatin and cranial irradiation therapy. Data collected from patient files suggest that monitoring for ototoxicity is not currently routine procedure at Christchurch Hospital, with just under 70% of patients in the current study undergoing a baseline audiogram prior to commencing treatment. The purpose of this section is to clarify the clinical audiologist's role in ototoxicity monitoring, and suggest guidelines for the implementation of such a programme.

4.4.2.1 Audiologists role in ototoxicity monitoring

As discussed in the first chapter, the primary purpose of ototoxicity monitoring is early detection of hearing loss that may allow for appropriate intervention to minimise the effects and impact of hearing loss on the individual. For this to occur, it requires coordination with other medical personnel such as oncologists, radiologists and oncology nurses and may take the audiologist outside of their typical role. The position statement by AAA (2009) emphasises the role of the audiologist in the establishment and management of the programme particularly in the role of in-service education and interpretation of the results. In cases where ototoxicity is detected, the audiologist should be involved with the non-medical management side of the hearing loss. Assistance can include counselling, communication strategies, and prescribing amplification and/or assistive listening devices. Where amplification is not provided through the local hospital, patients should be made aware of the services provided by independent audiology clinics.

4.4.2.2 Potential test battery

There are three main approaches to ototoxicity monitoring which includes standard pure-tone audiometry, EHF pure-tone audiometry, and OAE measurement (American Academy of Audiology, 2009). OAEs have gained in popularity as both a screening and diagnostic tool and there is increasing evidence supporting the clinical application of

OAEs in ototoxicity monitoring. DPOAEs provide a non-invasive, objective measure of cochlear function (Reavis, et al., 2008), are time efficient, have good test-retest reliability and are able to be carried out at a patient's bedside. Loss of DPOAE response indicates damage to OHCs before it is able to be detected with standard pure-tone audiometry (Ress, et al., 1999). Unlike pure-tone audiometry, however, there is no universally accepted criterion that indicates a significant decline in OHC function. A study by Knight et al., (2007) used a criterion of an 8 dB SPL decrease, based on Beattie, Kenworthy and Luna (2003) who reported that differences in DPOAE amplitudes must exceed 7 dB SPL at 1 to 4 kHz to be statistically significant at the 0.05 level. The same study by Knight et al., (2007) found that EHF pure-tone audiometry was more sensitive in detecting ototoxic changes than DPOAEs and standard pure-tone audiometry. DPOAEs were shown to detect changes before standard pure-tone audiometry, however. One consideration in selecting OAEs for testing is the restricted test frequency range of most OAE systems that is able to be measured. The equipment used in the present study tested up to 9.25 kHz. As per ASHA guidelines (American Speech-Language-Hearing Association, 1994), both immittance testing and speech audiometry should also be included, particularly in the baseline assessment and again at the post-treatment follow-up.

4.4.2.3 Test protocol

When deciding on a test protocol, in addition to test sensitivity and specificity, consideration must be given to the status of the patient (their ability to perform certain tasks and their pre-exposure hearing sensitivity), the time required to carry out the test and its analysis, the costs involved in performing and interpreting the test, and availability of equipment (Konrad-Martin et al., 2005). Patient responsiveness can be determined by physician or nurse reports, and can be classed into three general groups: responsive, limited responsive and non-responsive (American Speech-Language-Hearing Association, 1994). Responsive patients tend to be adults and older children who do not fatigue easily and are able to provide reliable behavioural responses. Limited responsive patients can only provide reliable behavioural responses for a limited period of time due to fatigue, illness and age-related factors. Small children may be classed as limited responsive. Non-responsive patients are those who are unable to provide behavioural responses and require assessment via objective measures only, such as DPOAEs and/or ABR testing. It is important to note that patients may fluctuate between these categories throughout the treatment and recovery phase and therefore it is important to include objective measures of auditory status in baseline evaluation for all patients. The following flow chart has been proposed by the National Center for Rehabilitative Auditory Research (Gordon, 2009).

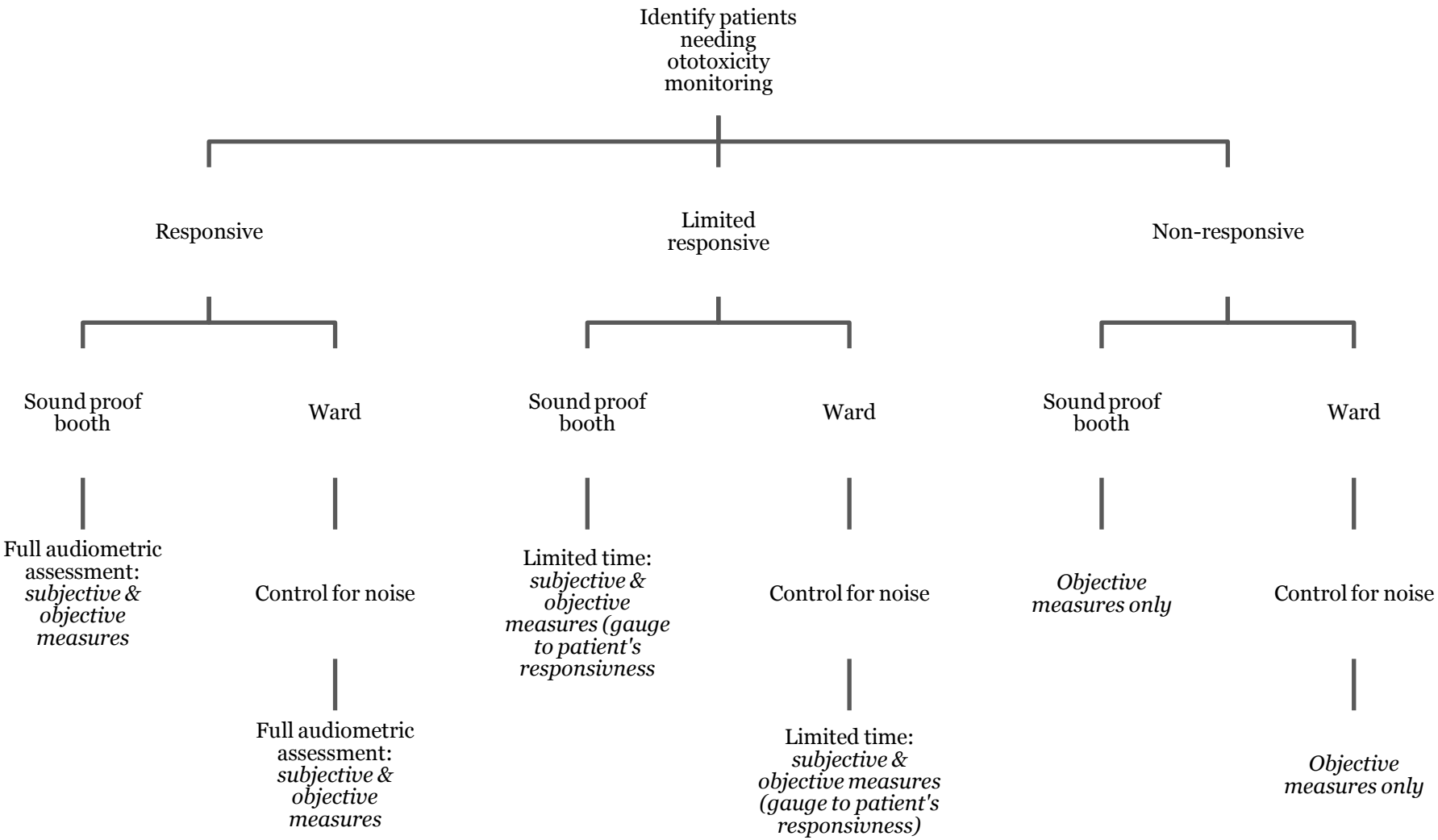

Figure 4.1: Proposed protocol for ototoxicity monitoring (Gordon, 2009)

4.4.2.4 *Tinnitus*

Tinnitus is a common side effect of many ototoxic drugs, including cisplatin (Seligmann, et al., 1996). In the current study, almost 50% of participants reported the onset or increase in severity of tinnitus. There is, however, no formal tinnitus monitoring procedures for use in an ototoxicity monitoring programme. In addition, tinnitus assessment methods are rarely reported in the literature. Self-report measures have been developed such as the Tinnitus Handicap Inventory (Newman, et al., 1996) and the TOMI (Fausti, et al., 2007). These surveys aim to quantify the impact of tinnitus on daily living and could be incorporated into a monitoring programme.

4.4.2.5 *Vestibulotoxicity monitoring*

The vestibulotoxicity of some drugs, such as particular aminoglycosides, is well established in the literature (Seligmann, et al., 1996). Despite this, there are no widely accepted guidelines for vestibulotoxicity monitoring. Like tinnitus, self-report measures such as the Dizziness Handicap Inventory (DHI) are available to provide a method of potentially detecting vestibulotoxicity (Jacobson & Newman, 1990).

4.5 Limitations of the current study

The criteria formulated by ASHA (1994) specify that any audiometric changes must be confirmed by a repeat assessment. This reliability check was not carried out in the current study for a number of reasons. Firstly, the period of data collection was limited considerably due to the significant delays involved with the initial research topic. Secondly, due to the large catchment area that Christchurch Hospital services for head and neck cancer, many of the participants did not reside locally making follow-up more difficult. The post-treatment assessments that were carried out were often scheduled for the same day as the patient's follow-up ENT and/or oncology appointment. This reduced additional travel and associated expense, particularly for participants who lived outside of Christchurch.

It is important to consider the potential limitations of the study sample. Human populations tend to be heterogenous by nature. Consequently, in order to make generalisations and draw valid conclusions, a large sample size is needed to ensure the variations that exist in behavioural, psychological or physical attributes are present in the sample. In the current study, invitation letters were sent to 39 individuals who fulfilled the inclusion criteria as stated previously in the method chapter. Although the response rate (66.7%) achieved was above the average response rate of 61% for postal surveys and correspondence (de Vaus, 2002), there is the possibility that the individuals who responded may have done so because they were having difficulty with their hearing and were more interested in undergoing an audiological assessment. This may have led to a biased sample, with an overrepresentation of people who had perceived a decline in their hearing since treatment. In addition, the sample primarily consists of male participants (21 males and 2 females). Although this is representative of the male predominance in

head and neck cancers (Argiris, et al., 2008), it may have influenced the mean pre-treatment hearing thresholds. Specifically, pure-tone thresholds may be elevated more so than if the sample consisted of an equal distribution of males and females, as males have greater hearing loss than their age-matched females with respect to age-related hearing loss (Van Eyken, et al., 2007).

Another limitation of this study is the lack of information provided about the prior assessments. In most cases, the reliability of the patient, type of transducer used and observations from otoscopy were not reported. This may reduce the validity of comparing pre- and post-treatment assessments. It is also important to consider variability between pre- and post-treatment assessments that may be due to patient factors such as attention, wellness, and fatigue.

A general limitation of ototoxicity monitoring is criteria that is used to define cochleotoxicity and is based on air conduction results alone. A limitation of this is that it does not account for fluctuations in middle ear status such as otitis media in paediatric populations or those undergoing cranial irradiation. In cases where no low frequency conductive component was measured, we have assumed there to be no significant conductive component in the EHF and therefore the thresholds were taken to represent cochlear function.

4.6 Directions for future research

The present study leads into a Phase III clinical trial to take place at Christchurch Hospital. This trial aims to investigate potential protective effects of IT dexamethasone administration against cisplatin-induced ototoxicity while preserving the chemotherapeutic actions. This trial will recruit patients diagnosed with some form of head and neck cancer who require at least two cycles of cisplatin therapy and concurrent cranial irradiation. 12 hours prior to the initial dose of cisplatin, all patients will have a baseline diagnostic audiological assessment including standard pure-tone audiometry (0.25 to 8 kHz), extended high-frequency audiometry (9 to 16 kHz), speech audiometry, tympanometry, DPOAEs, and evaluation of tinnitus using the TOMI. Approximately one hour before the administration of cisplatin, patients will receive IT injections of 24 mg dexamethasone and 0.9% saline into separate ears via bilateral myringotomies. Both the audiological assessment and IT injections will occur before each subsequent dose of cisplatin. At the completion of cisplatin therapy, the patients will undergo repeat audiological assessment at regular intervals to monitor any changes in their hearing status.

This future research has the potential to affect hearing outcomes for patients receiving cisplatin therapy and cranial irradiation. The present study has shown this particular subset of patients to have relatively high rates of ototoxicity. The upcoming trial also has the potential to ameliorate the dose-limiting effect of ototoxicity. As illustrated in the

present study, cisplatin therapy has to be withheld because of deteriorating hearing or tinnitus. If IT dexamethasone is shown to exert a protective effect, it may allow patient who would otherwise have had their cisplatin therapy reduced or stopped, to continue with the standard dose of cisplatin, thus potentially improving outcome from treatment.

5 Summary

Cisplatin –induced ototoxicity constitutes a significant clinical problem that can have far-reaching consequences. In this study, over 90% of participants experienced significant deterioration of their hearing thresholds based on an internationally recognised criteria. This is at the higher end of the values reported in the literature and may be due to the relatively high dose of cisplatin administered and exposure to a well known risk factor, cranial irradiation. Along with hearing loss, nearly half of the participants suffered from onset of tinnitus, or a noticeable increase in the severity of their tinnitus. Balance disturbances were less reported and in line with current literature.

This study found that despite the high proportion of patients experiencing ototoxicity, not all are receiving appropriate assessment and follow-up. Fluent communication is vital, particularly for a group of patients for whom quality of life is already compromised due to illness and fatigue. Consideration must be given, however, to the emphasis placed on carrying out a vigorous monitoring protocol for patients whom are already facing significant physical and emotional challenges. For a successful protocol to be established it requires an interdisciplinary approach with coordination between key personnel such as oncologist, radiologists, nurses, pharmacists and audiologists.

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Appendix A

Ethical approval letter from the Upper South B Regional Ethics Committee

Health and Disability Ethics Committees

Upper South B Regional Ethics Committee
Ministry of Health
4th Floor, 250 Oxford Tce
PO Box 3877
Christchurch
Phone (03) 372 3018
Fax (03) 372 1015
Email: uppersouth_ethicscommittee@moh.govt.nz

2 November 2009

Dr David Gibbs
Oncology Services
Christchurch Hospital
Private Bag 4710
Christchurch

Dear Dr Gibbs

Ethics Reference Number: URB/09/41/EXP
Follow up audiological assessment of adult head and neck cancer patients treated with chemoradiation in the Christchurch area

The above study has been given ethical approval by the **Chairperson** of the Upper South B Regional Ethics Committee.

Approved Documents
Study Protocol
Letter to participants version 1.0, dated 12 October 2009
Consent Form version 1.0, dated 12 October 2009

Final Report
The study is approved until **31 March 2010**. A final report is required at the end of the study and a report form to assist with this is available at http://www.newhealth.govt.nz/ethicscommittees. If the study will not be completed as advised, please forward a report form and an application for extension of ethical approval one month before the above date.

Amendments
It is also a condition of approval that the Committee is advised if the study does not commence, or is altered in any way, including all documentation eg advertisements, letters to prospective participants.

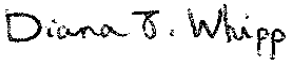
Please quote the above ethics committee reference number in all correspondence.

It should be noted that Ethics Committee approval does not imply any resource commitment or administrative facilitation by any healthcare provider within whose facility the research is to be carried out. The

organisation may specify their own processes regarding notification or approval.

On behalf of the committee, I would like to take this opportunity to wish you all the best with your research.

Yours sincerely



Mrs Diana Whipp
Upper South B Regional Ethics Committee Administrator

Appendix B

Invitation letter to eligible individuals

Canterbury
District Health Board
Te Poari Hauora ō Waitaha

Date

Patient name
Street address
Suburb
Town/city

Dear *(patient name inserted here)*,

You have had treatment for head and neck cancer that involved you having radiation treatment and chemotherapy with cisplatin. We are studying the effects that this treatment has had on people's hearing and would like to invite you to take part in a research project called "Follow up audiological assessment of adult head and neck oncology patients in the Christchurch area".

If you would like to take part, you will undergo a complete hearing assessment. This assessment will take place at Christchurch Hospital in the Audiology department. It will consist of a some questions, a full hearing test (pure tone audiometry), a pressure test to assess how well your ear drum is moving (tympanometry), speech audiometry to assess how well you can hear words, and distortion product otoacoustic emissions (DPOAEs), a simple test which assesses the health of the organ of hearing. A summary of these hearing tests is on the next page. This assessment will take approximately 45 minutes to one hour. You will be given breaks in between tests if you feel that you need them.

The results from this follow-up test will be compared to any hearing assessment that you had at the Hospital either before or during your cancer treatment to see whether there has been any change. We are interested in finding out about the number of people who had hearing testing before or during their cancer treatment, and the number of people who have a hearing loss as a result of their cancer treatment. Results from this research may help to improve patient care regarding hearing health.

If this testing shows a hearing impairment, you will be able to discuss the options of rehabilitation (e.g. hearing aids) available to you if you wish.

We will need to collect information such as your name and date of birth. We will ask you to sign a consent form for the collection of such information at the time of testing. The results of the research may be published, but no material which could personally identify you will be used in any reports on this study. All data collected will be treated with complete confidentiality. It is a requirement that all health research data must be stored for 10 years.

Canterbury
District Health Board
Te Poari Hauora ō Waitaha

This study has received ethical approval from the Upper South B Regional Ethics Committee. If you have any queries or concerns regarding your rights as a participant in this study, you may wish to contact a Health and Disability Advocate.
Free phone: 0800 555 050
Free fax: 0800 2 SUPPORT (0800 2787 7678)
Email: advocacy@hdc.org.nz

This assessment is not compulsory. By not taking part, your continuing/future healthcare will not be affected. You may bring a friend, family or whānau support with you to the appointment.

If you have any further questions, please contact Dr David Gibbs at the Oncology Service, Christchurch Hospital. David can be contacted by phone, 0272900968 or by email, david.gibbs@cdhb.govt.nz.

If you would like to have a follow-up hearing assessment and take part in this research, please contact Katrine Alchin to arrange an appointment.
Phone: 027 3285770
Email: kfn11@student.canterbury.ac.nz
Or please return the enclosed response form in the prepaid envelope provided.

Kind regards,

Dr David Gibbs

What's involved in each part of the hearing assessment?

History: The audiologist will ask you a series of questions. These may include your previous ear health, any hearing/communication concerns you may have, any family history of hearing loss, exposure to noise, tinnitus, balance or dizziness, facial numbness and other general health issues.

Otoscopy: The audiologist will have a look in your ears using a special ear-torch called an "otoscope". This will tell us if your ears have any significant wax or debris in the ear canals and if your eardrum looks healthy.

Tympanometry: A small rubber-tipped plug will be placed at the entrance to your ear canal, and you will hear a soft humming sound. The air pressure in the ear canal will then be altered slightly, which is painless (a bit like going up and down a hill in a car, but only for a few seconds). This will tell us how well your eardrum is moving, and whether you have any fluid in your middle ear.

Pure-tone audiometry: You will be played a series of (mostly very quiet) tones (or 'beeps') in each ear, and will be asked to tell the audiologist whenever you have heard a sound. This helps us to find the softest sounds you can hear, and let us know if you have a hearing loss or not.

Speech audiometry: You will be played a recording of some of words (some at quiet levels) which you will be asked to repeat back. If you are unsure, you will be asked to guess. This will tell us how well you hear speech in each ear.

DPOAEs: A small rubber plug (like the one used in the tympanometry test) placed at the entrance of your ear canal will play some moderate volume sounds into your ear. A microphone in the plug will listen for some special sounds that are generated by the ear itself. This will tell us how well your outer hair cells (a set of special sensory cells in the ear required for hearing) are working.

Appendix C

Reminder letter

Canterbury
District Health Board
Te Poari Hauora ō Waitaha

Date

Patient name
Street address
Suburb
Town/City

Dear *(patient name inserted here)*,

In December 2009 we sent you a letter inviting you to take part in a research project called "Follow up audiological assessment of adult head and neck oncology patients in the Christchurch area". You were invited because you have had treatment for head and neck cancer that involved you having radiation treatment and chemotherapy with cisplatin. The aim of this study is to investigate the effects that this treatment has had on people's hearing.

We understand that your time is valuable, and that this may be a busy period for you. However, this research has the potential to improve the standard of hearing care for future patients. We are therefore taking this opportunity to ask you once more if you would like to take part in the study. Your participation would be greatly appreciated.

If you would like to take part, you will undergo a complete hearing assessment. This assessment will take place at Christchurch Hospital in the Audiology department. It will consist of a some questions, a full hearing test (pure tone audiometry), a pressure test to assess how well your ear drum is moving (tympanometry), speech audiometry to assess how well you can hear words, and distortion product otoacoustic emissions (DPOAEs), a simple test which assesses the health of the organ of hearing. A summary of these hearing tests is on the next page. This assessment will take approximately 45 minutes to one hour. You will be given breaks in between tests if you feel that you need them.

The results from this follow-up test will be compared to any hearing assessment that you had at the Hospital either before or during your cancer treatment to see whether there has been any change. We are interested in finding out about the number of people who had hearing testing before or during their cancer treatment, and the number of people who have a hearing loss as a result of their cancer treatment. Results from this research may help to improve patient care regarding hearing health.

If this testing shows a hearing impairment, you will be able to discuss the options of rehabilitation (e.g. hearing aids) available to you if you wish.

We will need to collect information such as your name and date of birth. We will ask you to sign a consent form for the collection of such information at the time of testing. The

Canterbury
District Health Board
Te Poari Hauora ō Waitaha

results of the research may be published, but no material which could personally identify you will be used in any reports on this study. All data collected will be treated with complete confidentiality. It is a requirement that all health research data must be stored for 10 years.

This study has received ethical approval from the Upper South B Regional Ethics Committee. If you have any queries or concerns regarding your rights as a participant in this study, you may wish to contact a Health and Disability Advocate.
Free phone: 0800 555 050
Free fax: 0800 2 SUPPORT (0800 2787 7678)
Email: advocacy@hdc.org.nz

This assessment is not compulsory. By not taking part, your continuing/future healthcare will not be affected. You may bring a friend, family or whānau support with you to the appointment.

If you have any further questions, please contact Dr David Gibbs at the Oncology Service, Christchurch Hospital. David can be contacted by phone, 0272900968 or by email, david.gibbs@cdhb.govt.nz.

If you would like to have a follow-up hearing assessment and take part in this research, please contact Katrine Alchin to arrange an appointment.
Phone: 027 3285770
Email: kfn11@student.canterbury.ac.nz
Or please return the enclosed response form in the prepaid envelope provided.

Kind regards,

Dr David Gibbs

What's involved in each part of the hearing assessment?

History: The audiologist will ask you a series of questions. These may include your previous ear health, any hearing/communication concerns you may have, any family history of hearing loss, exposure to noise, tinnitus, balance or dizziness, facial numbness and other general health issues.

Otoscopy: The audiologist will have a look in your ears using a special ear-torch called an "otoscope". This will tell us if your ears have any significant wax or debris in the ear canals and if your eardrum looks healthy.

Tympanometry: A small rubber-tipped plug will be placed at the entrance to your ear canal, and you will hear a soft humming sound. The air pressure in the ear canal will then be altered slightly, which is painless (a bit like going up and down a hill in a car, but only for a few seconds). This will tell us how well your eardrum is moving, and whether you have any fluid in your middle ear.

Pure-tone audiometry: You will be played a series of (mostly very quiet) tones (or 'beeps') in each ear, and will be asked to tell the audiologist whenever you have heard a sound. This helps us to find the softest sounds you can hear, and let us know if you have a hearing loss or not.

Speech audiometry: You will be played a recording of some of words (some at quiet levels) which you will be asked to repeat back. If you are unsure, you will be asked to guess. This will tell us how well you hear speech in each ear.

DPOAEs: A small rubber plug (like the one used in the tympanometry test) placed at the entrance of your ear canal will play some moderate volume sounds into your ear. A microphone in the plug will listen for some special sounds that are generated by the ear itself. This will tell us how well your outer hair cells (a set of special sensory cells in the ear required for hearing) are working.

Appendix D

Response form

Canterbury
District Health Board
Te Poari Hauora ō Waitaha

Response Form

Follow up audiological assessment of adult head & neck oncology patients in the Christchurch area

Yes, I would like to have a follow-up hearing assessment and take part in this research. Please contact me to arrange a suitable appointment time.

Name:

Address:

Please tick preferred method of communication

Phone (home): ☐

Phone (work): ☐

Cell phone: ☐

Email: ☐

Please send completed form in the prepaid envelope provided. Thank you.

Appendix E

Consent form

Canterbury
District Health Board
Te Poari Hauora ō Waitaha

Consent Form

Follow up audiological assessment of adult head & neck oncology patients in the Christchurch area

English	I wish to have an interpreter	Yes	No
Māori	E hiahia ana ahau ki tetahi kaiwhakamaori/kaiwhaka pakeha korero	Ae	Kao
Cook Islands	Ka inangaro au I tetai tangata uri reo	Ae	Kare
Fijian	Au gadreva me dua e vakadewa vosa vei au	Io	Sega
Niuean	Fia manako au ke fakaaoga e taha tagata fakahokohoko kupu.	E	Nakai
Sāmoan	Ou te manaó ia I ai se faámatala upu	Ioe	Leai
Tokelaun	Ko au e fofou ki he tino ke fakaliliu te gagana Peletania ki na gagana o na motu o te Pahefika	Ioe	Leai
Tongan	Oku ou fiema'u ha fakatonulea	Ioe	Ikai
Mandarin	我需要一个翻译	对	不对
Japanese	通訳の人を希望します。	はい。	いいえ。
Korean	통역이 필요 하세요?	네	아니오

1. I have read and I understand the invitation letter dated 12 October 2009 for volunteers taking part in the above-named study. I have had the opportunity to discuss this study. I am satisfied with the answers I have been given.
2. I have had the opportunity to use whānau support or a friend to help me ask questions and understand the study.
3. I understand that taking part in this study is voluntary (my choice), and that I may withdraw from the study at any time without having to give a reason, including the withdrawal of any information I have provided. This will in no way affect my continuing and/or future health care.
4. I have had this project explained to me in the invitation letter by Dr David Gibbs.
5. I understand that my participation in this study is confidential and that no material which could identify me will be used in any reports on this study.
6. I understand that the audiological assessment will be stopped if it should appear harmful to me.
7. I have had time to consider whether or not to participate in the study.
8. I know who to contact if I have any questions about the study in general.
9. I would like a copy of the summarised results at the completion of the study

   yes/no
10. I agree to my GP or other current provider being informed of my participation in this study/the results of my participation in this study

    yes/no

Canterbury
District Health Board
Te Poari Hauora ō Waitaha

Participant to sign:

I ..... (full name)

hereby consent to take part in this study

Signature.....
Date.....

Researcher to sign:

I..... (full name)

have explained the project to the participant. I believe consent was given freely by the participant and have witnessed the signing of the consent form above

Signature.....
Date.....

Appendix F

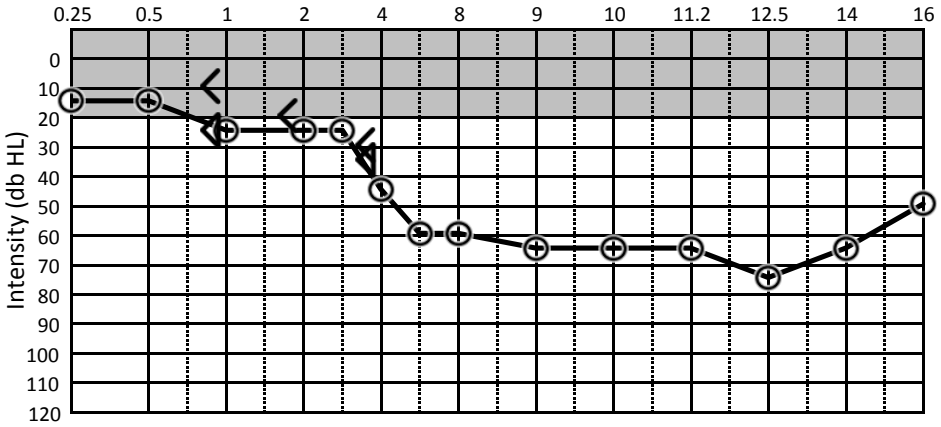
Post-treatment audiological assessment for each of the 23 participants

Participant: Participant # 1 Age: 63 NHI:

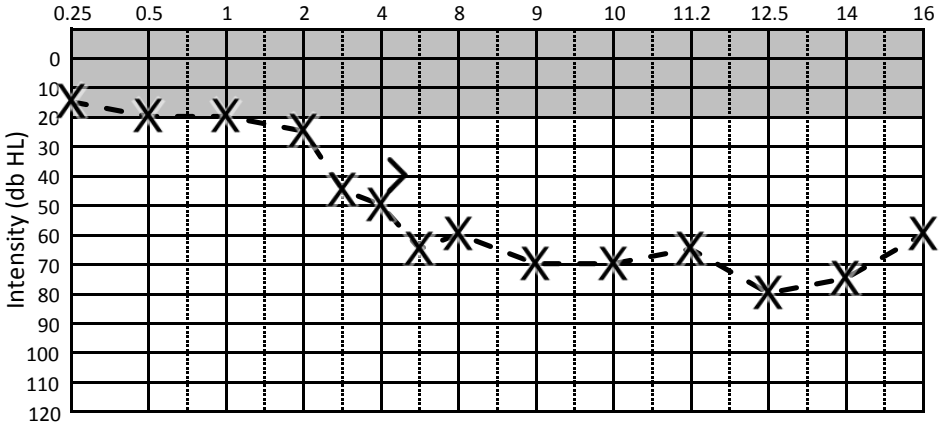
Tested by: Katrine Alchin Date: 29/01/2010

Pure-tone Audiometry

Right



Left



Otoscopy

Right: Clear

Left: Clear

Symbols		
Right		Left
○	Air	X
●	Masked Air	⊠
<	Bone	>
◁	Masked Bone	▷
S	Soundfield	S
U	UCL	U
↓	No Response	↓

Transducer	Reliability
Insert 3A	Good

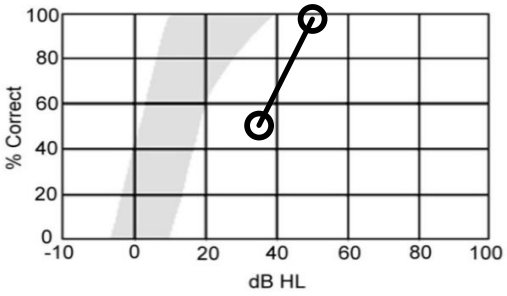
Tympanometry		
	Right	Left
Type	A	A
MEP (daPa)	55	55
Comp. (ml)	0.7	0.5
Vol. (cc)	1.6	1.9

Ipsilateral Reflexes		
Sound Ear	Right	Left
500 Hz	85	85
1 kHz	85	85
2 kHz	95	95
4 kHz	100↓	100↓

Speech Audiometry

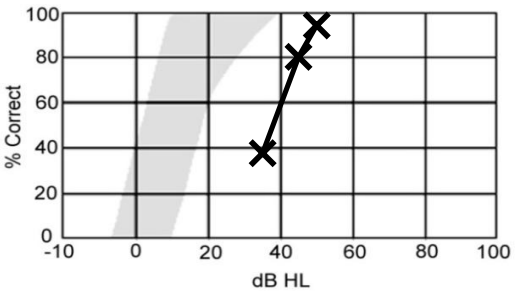
AB word lists

Right



R	50 dB HL	97	%
R	35 dB HL	50	%
R			%

Left



L	50 dB HL	94	%
L	45 dB HL	80	%
L	35 dB HL	37	%

SDT R ____ dB HL

L ____ dB HL

Distortion Product Otoacoustic Emissions (DPOAEs)																
F2(Hz)	2000	2250	2500	2750	3062	3375	3750	4062	4500	5000	5500	6125	6812	7500	8375	9250
Right	✓	✓	✓	✓	×	✓	✓	×	✓	×	×	×	×	×	×	×
Left	✓	✓	✓	×	×	×	×	×	×	×	×	✓	×	✓	×	✓

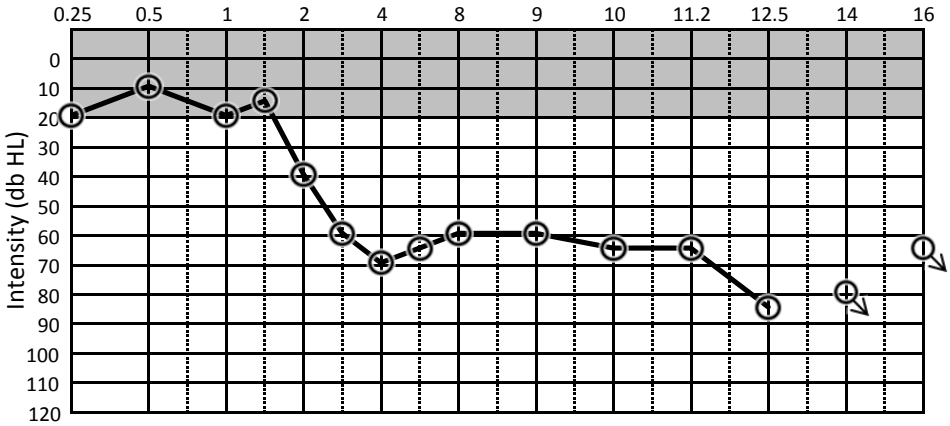
Key: ☑ OAE present (SNR > 5 dB) ☒ OAE absent (≤ -10 dBSPL)

Participant: Participant # 2 Age: 59 NHI:

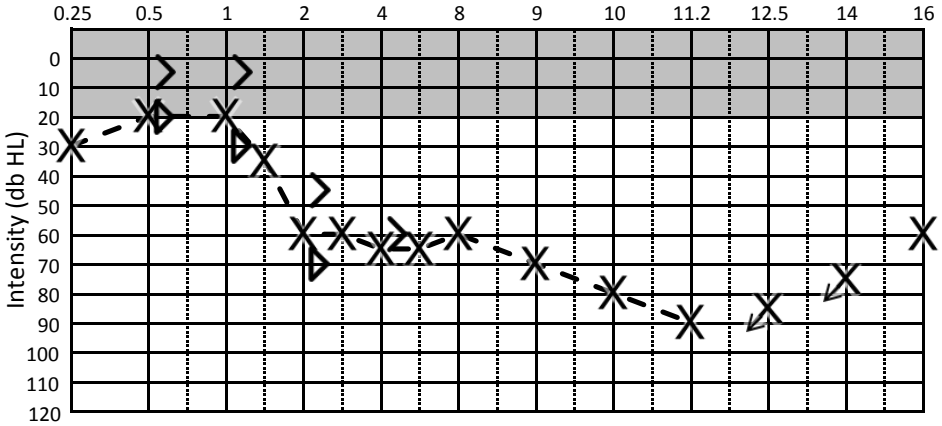
Tested by: Katrine Alchin Date: 19/02/2010

Pure-tone Audiometry

Right



Left



Otoscopy

Right: Clear

Left: Clear

Symbols		
Right		Left
○	Air	X
●	Masked Air	⊠
<	Bone	>
◁	Masked Bone	▷
S	Soundfield	S
U	UCL	U
↓	No Response	↓

Transducer	Reliability
Insert 3A	Good

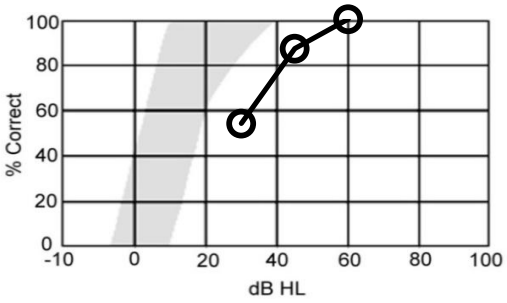
Tympanometry		
	Right	Left
Type	A	A
MEP (daPa)	35	30
Comp. (ml)	0.7	1
Vol. (cc)	1.3	1.9

Ipsilateral Reflexes		
Sound Ear	Right	Left
500 Hz	95	
1 kHz	95	
2 kHz	105↓	CNS
4 kHz	100↓	

Speech Audiometry

AB word lists

Right



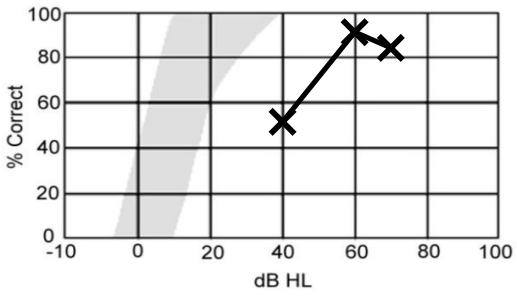
R	60 dB HL	100 %
R	45 dB HL	87 %
R	30 dB HL	54 %

L	70 dB HL	84 %
L	60 dB HL	91 %
L	40 dB HL	51 %

SDT R _____ dB HL

L _____ dB HL

Left



Distortion Product Otoacoustic Emissions (DPOAEs)																
F2(Hz)	2000	2250	2500	2750	3062	3375	3750	4062	4500	5000	5500	6125	6812	7500	8375	9250
Right	×	×	×	×	×	×	×	×	✓	×	×	✓	×	×	×	×
Left	×	×	×	×	×	×	×	×	×	×	×	✓	×	✓	×	✓

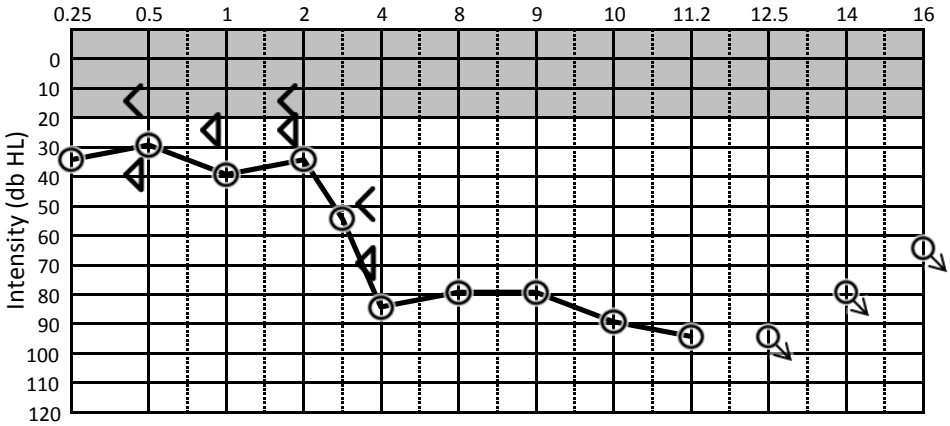
Key: ☑ OAE present (SNR > 5 dB) ☒ OAE absent (≤ -10 dBSPL)

Participant: Participant # 3 Age: 58 NHI:

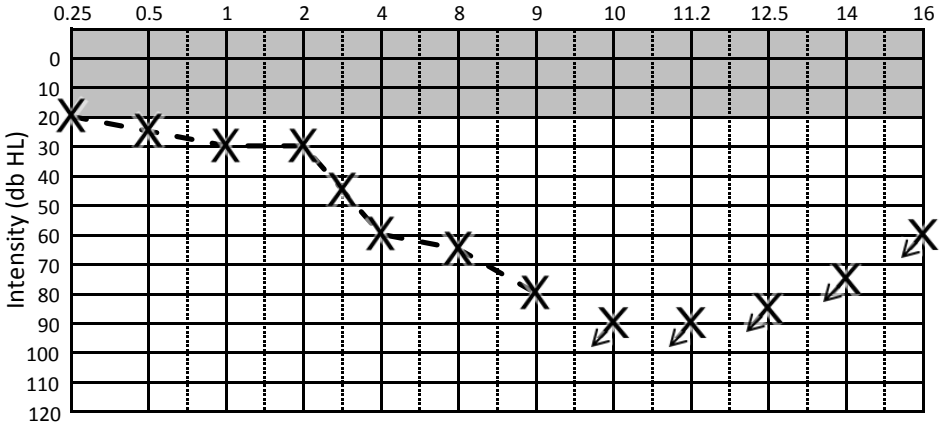
Tested by: Katrine Alchin Date: 21/01/2010

Pure-tone Audiometry

Right



Left



Otoscopy

Right: Clear

Left: Clear

Symbols		
Right		Left
○	Air	X
●	Masked Air	⊠
<	Bone	>
◁	Masked Bone	▷
S	Soundfield	S
U	UCL	U
↓	No Response	↓

Transducer	Reliability
Insert 3A	Good

Tympanometry		
	Right	Left
Type	A	A
MEP (daPa)	0	-5
Comp. (ml)	0.6	0.7
Vol. (cc)	1.1	1

Ipsilateral Reflexes		
Sound Ear	Right	Left
500 Hz	105↓	100
1 kHz	105↓	105↓
2 kHz	105↓	105↓
4 kHz	100↓	100↓

Speech Audiometry

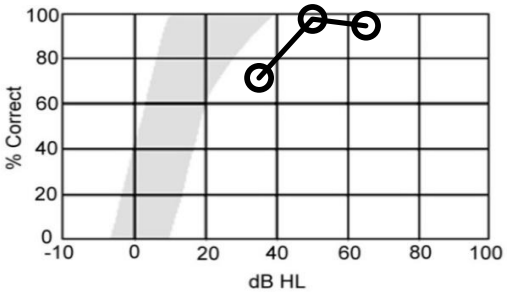
AB word lists

R	65 dB HL	94 %
R	50 dB HL	97 %
R	35 dB HL	71 %
L	60 dB HL	97 %
L	45 dB HL	91 %
L	30 dB HL	64 %

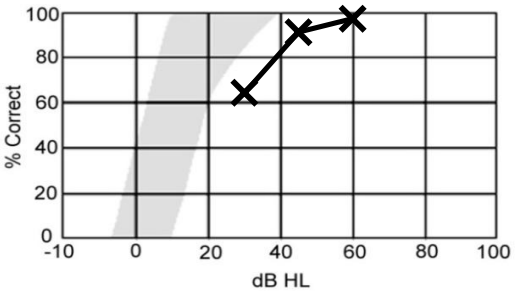
SDT R ____ dB HL

L ____ dB HL

Right



Left



Distortion Product Otoacoustic Emissions (DPOAEs)																
F2(Hz)	2000	2250	2500	2750	3062	3375	3750	4062	4500	5000	5500	6125	6812	7500	8375	9250
Right	✓	✓	✓	×	✓	×	×	×	×	×	×	×	×	×	✓	×
Left	✓	✓	✓	×	×	×	×	×	×	×	×	×	×	×	×	×

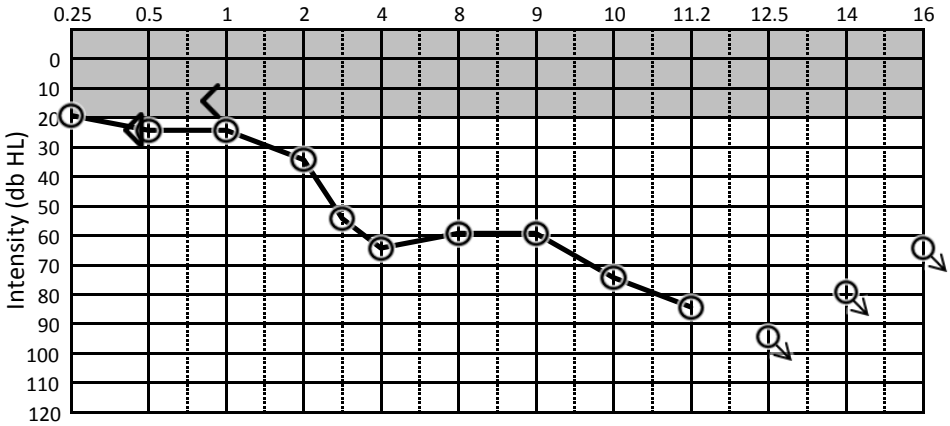
Key: ☑ OAE present (SNR > 5 dB) ☒ OAE absent (≤ -10 dBSPL)

Participant: Participant # 4 Age: 56 NHI:

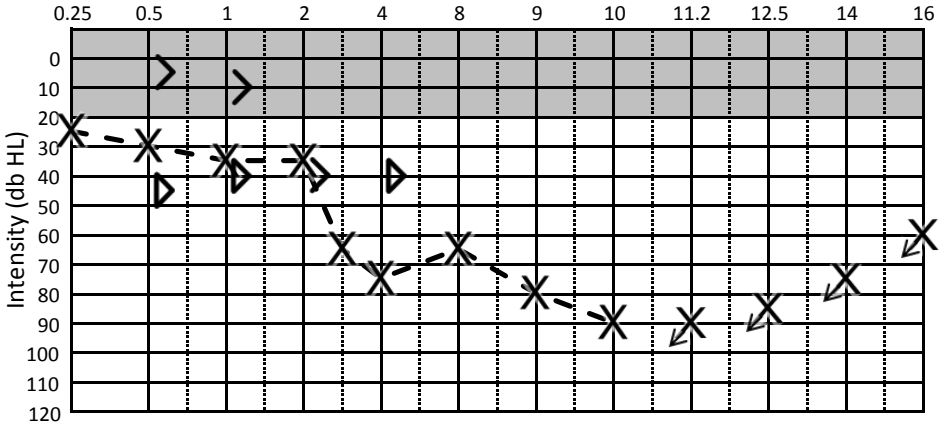
Tested by: Katrine Alchin Date: 29/01/2010

Pure-tone Audiometry

Right



Left



Otoscopy

Right: Clear

Left: Clear

Symbols		
Right		Left
○	Air	X
●	Masked Air	⊠
<	Bone	>
◁	Masked Bone	▷
S	Soundfield	S
U	UCL	U
↓	No Response	↓

Transducer	Reliability
Insert 3A	Fair

Tympanometry		
	Right	Left
Type	A	A
MEP (daPa)	-20	30
Comp. (ml)	0.5	0.3
Vol. (cc)	1.7	2.6

Ipsilateral Reflexes		
Sound Ear	Right	Left
500 Hz	95	
1 kHz	95	
2 kHz	105↓	
4 kHz	100↓	

Speech Audiometry

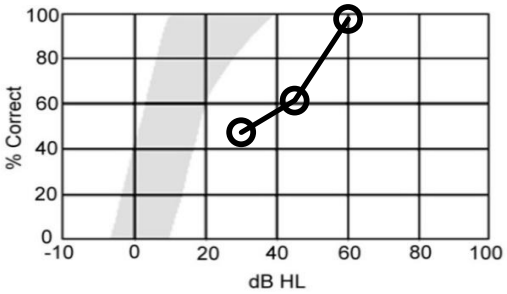
AB word lists

R	60 dB HL	97	%
R	45 dB HL	61	%
R	30 dB HL	47	%
L	75 dB HL	91	%
L	65 dB HL	88	%
L	50 dB HL	61	%

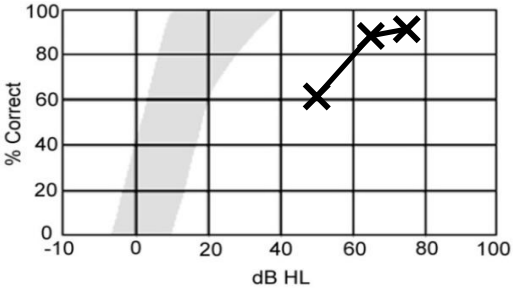
SDT R ____ dB HL

L ____ dB HL

Right



Left



Distortion Product Otoacoustic Emissions (DPOAEs)																
F2(Hz)	2000	2250	2500	2750	3062	3375	3750	4062	4500	5000	5500	6125	6812	7500	8375	9250
Right	✓	×	×	×	×	×	×	×	×	×	×	✓	×	✓	×	✓
Left	×	✓	×	×	×	×	×	×	×	×	×	×	×	✓	×	×

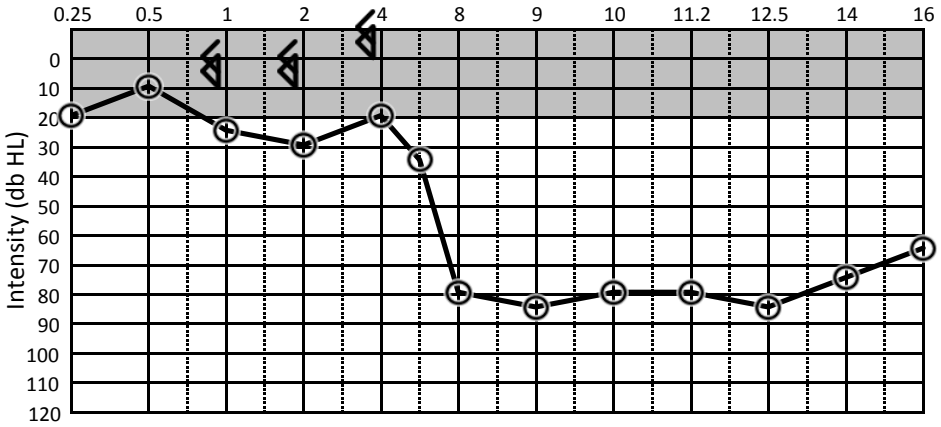
Key: ☑ OAE present (SNR > 5 dB) ☒ OAE absent (≤ -10 dBSPL)

Participant: Participant # 5 Age: 61 NHI:

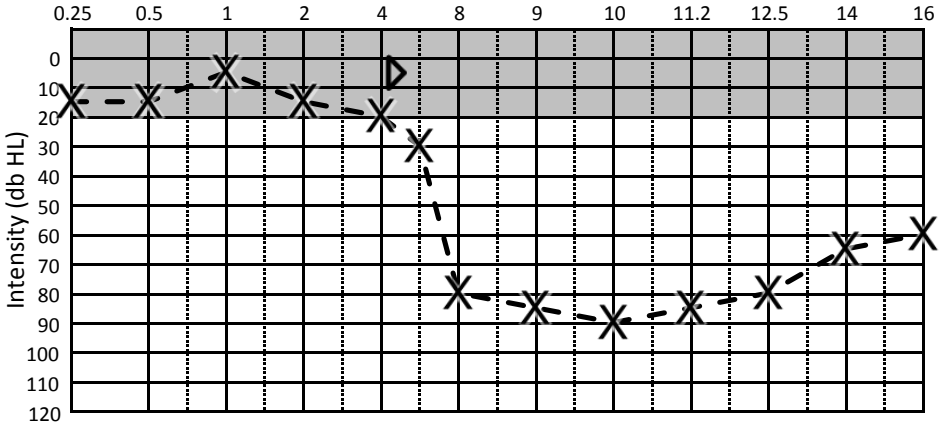
Tested by: Katrine Alchin Date: 21/01/2010

Pure-tone Audiometry

Right



Left



Otoscopy

Right: Significant wax

Left: Clear

Symbols		
Right		Left
○	Air	X
●	Masked Air	⊠
<	Bone	>
◁	Masked Bone	▷
S	Soundfield	S
U	UCL	U
↓	No Response	↓

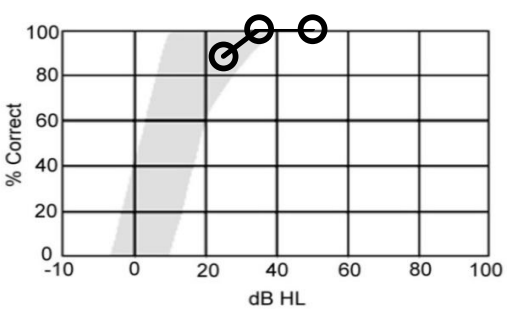
Transducer	Reliability
Insert 3A	Good

Tympanometry		
	Right	Left
Type	A	A
MEP (daPa)	-40	-15
Comp. (ml)	1	1.4.
Vol. (cc)	1.8	1.7

Ipsilateral Reflexes		
Sound Ear	Right	Left
500 Hz		
1 kHz		
2 kHz		
4 kHz		

Speech Audiometry

Right



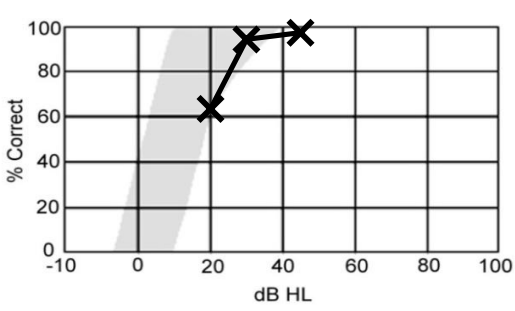
AB word lists

R	50 dB HL	100	%
R	35 dB HL	100	%
R	25 dB HL	88	%
L	45 dB HL	97	%
L	30 dB HL	94	%
L	20 dB HL	63	%

SDT R _____ dB HL

L _____ dB HL

Left



Distortion Product Otoacoustic Emissions (DPOAEs)																
F2(Hz)	2000	2250	2500	2750	3062	3375	3750	4062	4500	5000	5500	6125	6812	7500	8375	9250
Right	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	×	×	×	×
Left	✓	✓	✓	×	×	×	×	×	✓	×	×	×	×	×	×	✓

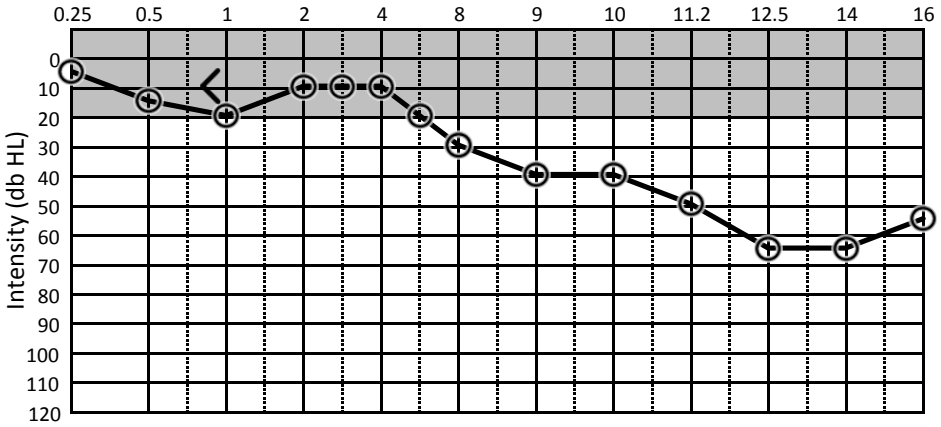
Key: ☑ OAE present (SNR > 5 dB) ☒ OAE absent (≤ -10 dBSPL)

Participant: Participant # 6 Age: 53 NHI:

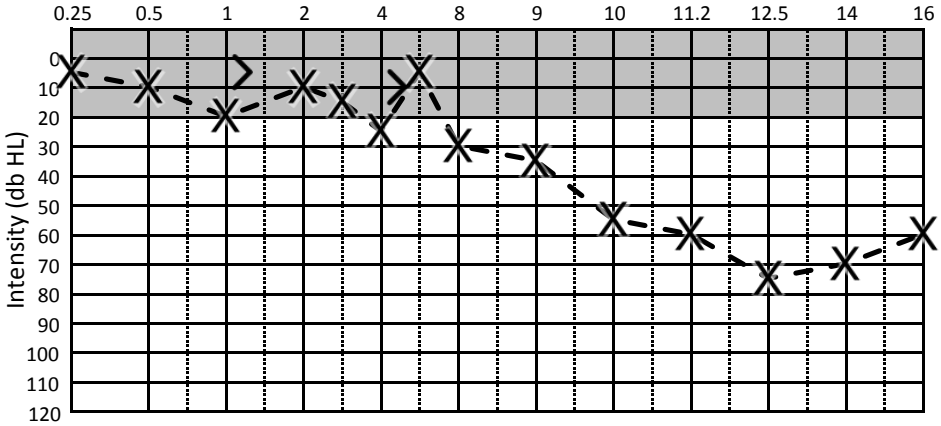
Tested by: Katrine Alchin Date: 10/02/2010

Pure-tone Audiometry

Right



Left



Otoscopy

Right: Clear

Left: Clear

Symbols		
Right		Left
○	Air	X
●	Masked Air	⊠
<	Bone	>
◁	Masked Bone	▷
S	Soundfield	S
U	UCL	U
↓	No Response	↓

Transducer	Reliability
Insert 3A	Good

Tympanometry		
	Right	Left
Type		
MEP (daPa)		
Comp. (ml)		
Vol. (cc)		

Ipsilateral Reflexes		
Sound Ear	Right	Left
500 Hz		
1 kHz		
2 kHz		
4 kHz		

Speech Audiometry

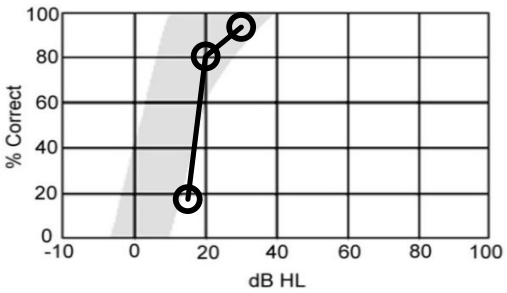
AB word lists

R	30 dB HL	93	%
R	20 dB HL	80	%
R	15 dB HL	17	%
L	40 dB HL	91	%
L	30 dB HL	94	%
L	20 dB HL	64	%

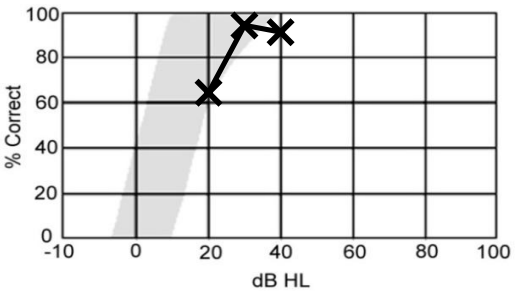
SDT R _____ dB HL

L _____ dB HL

Right



Left



Distortion Product Otoacoustic Emissions (DPOAEs)																
F2(Hz)	2000	2250	2500	2750	3062	3375	3750	4062	4500	5000	5500	6125	6812	7500	8375	9250
Right	×	✓	×	×	✓	×	×	×	×	×	×	✓	×	×	×	×
Left	✓	✓	×	✓	×	×	✓	×	×	×	×	✓	×	✓	×	×

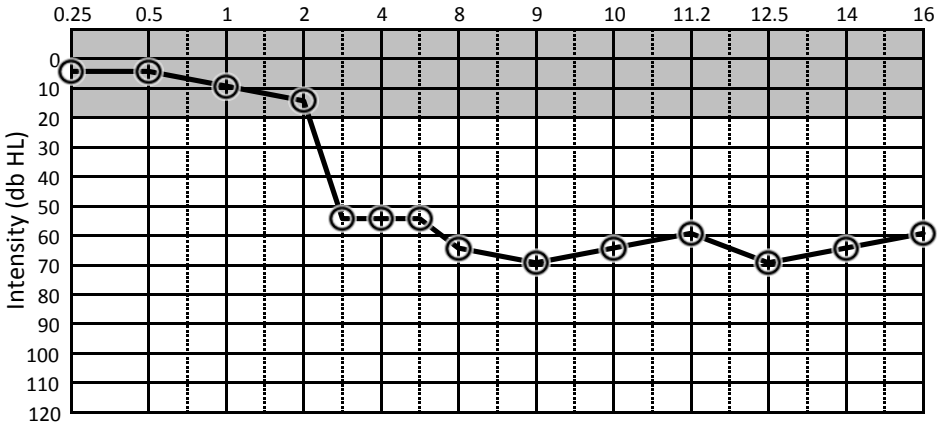
Key: ☑ OAE present (SNR > 5 dB) ☒ OAE absent (≤ -10 dBSPL)

Participant: Participant # 7 Age: 55 NHI:

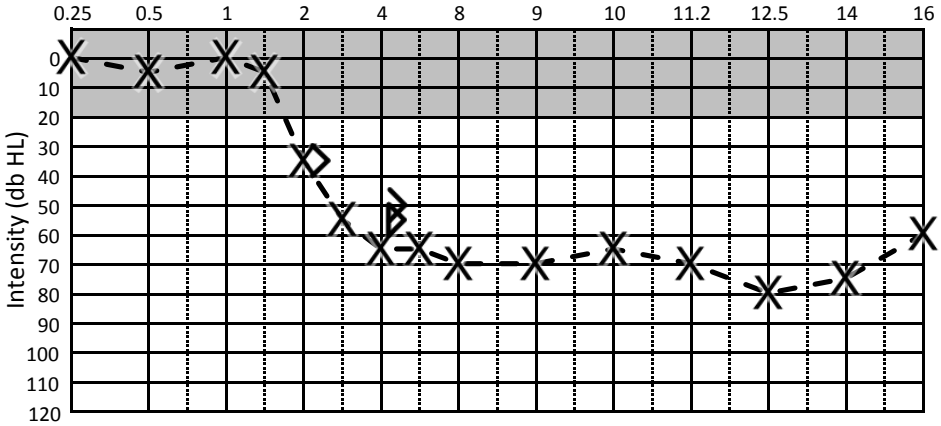
Tested by: Katrine Alchin Date: 18/02/2010

Pure-tone Audiometry

Right



Left



Otoscopy

Right: Significant wax

Left: Clear

Symbols

Right		Left
○	Air	X
●	Masked Air	⊠
<	Bone	>
◁	Masked Bone	▷
S	Soundfield	S
U	UCL	U
↓	No Response	↓

Transducer	Reliability
TDH	Good

Tympanometry

	Right	Left
Type	A	A
MEP (daPa)	-5	-35
Comp. (ml)	0.7	0.9
Vol. (cc)	2.2	1.8

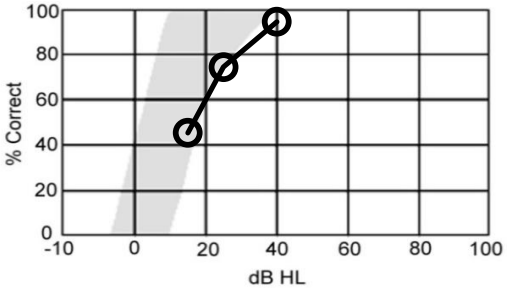
Ipsilateral Reflexes

Sound Ear	Right	Left
500 Hz	95	80
1 kHz	85	80
2 kHz	90	80
4 kHz	100↓	95

Speech Audiometry

AB word lists

Right



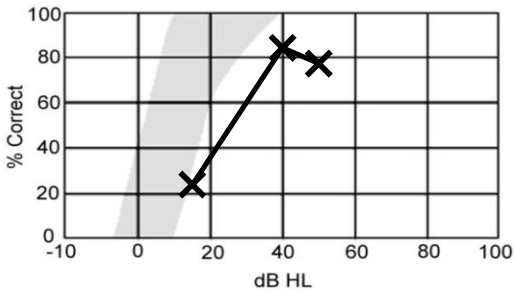
R	15 dB HL	45	%
R	25 dB HL	74	%
R	40 dB HL	94	%

L	15 dB HL	23	%
L	40 dB HL	84	%
L	50 dB HL	77	%

SDT **R** _____ dB HL

L _____ dB HL

Left



Distortion Product Otoacoustic Emissions (DPOAEs)

F2(Hz)	2000	2250	2500	2750	3062	3375	3750	4062	4500	5000	5500	6125	6812	7500	8375	9250
Right																
Left																

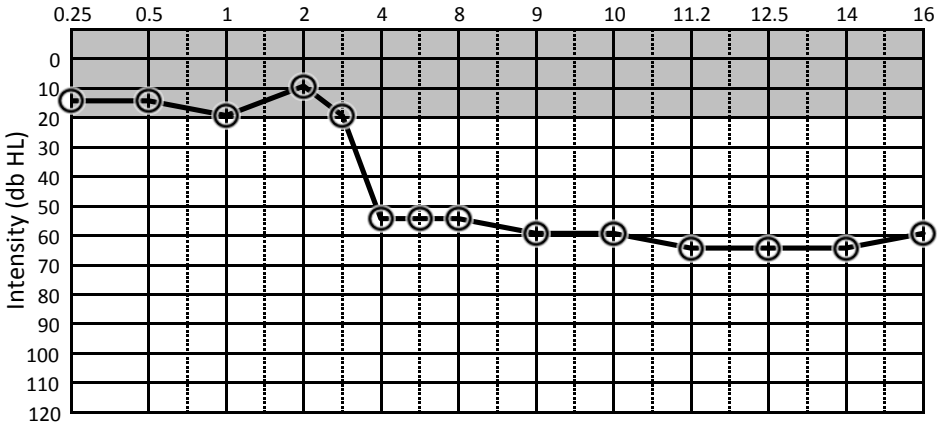
Key: ☑ OAE present (SNR > 5 dB) ☒ OAE absent (≤ -10 dBSPL)

Participant: Participant # 8 Age: 52 NHI:

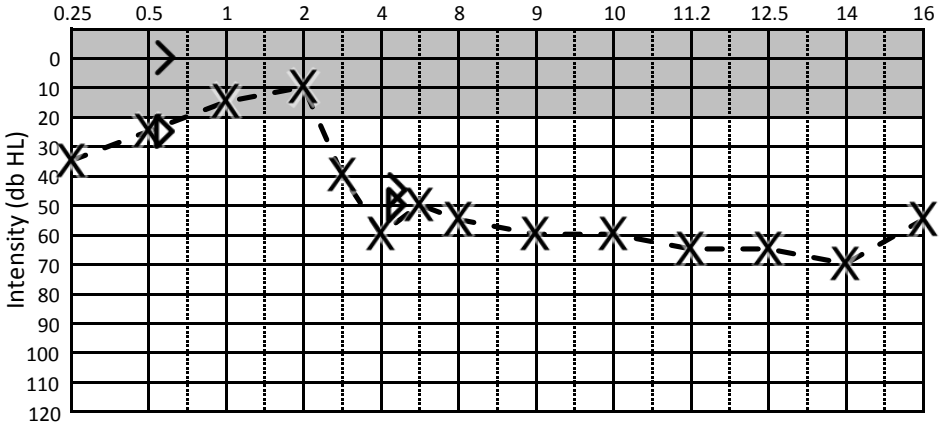
Tested by: Katrine Alchin Date: 5/02/2010

Pure-tone Audiometry

Right



Left



Otoscopy

Right: Clear

Left: Clear

Symbols		
Right		Left
○	Air	X
●	Masked Air	⊠
<	Bone	>
◁	Masked Bone	▷
S	Soundfield	S
U	UCL	U
↓	No Response	↓

Transducer	Reliability
Insert 3A	Good

Tympanometry		
	Right	Left
Type	A	A
MEP (daPa)	20	15
Comp. (ml)	1.3	0.9
Vol. (cc)	1.1	1.1

Ipsilateral Reflexes		
Sound Ear	Right	Left
500 Hz	90	90
1 kHz	85	90
2 kHz	90	95
4 kHz	100↓	100↓

Speech Audiometry

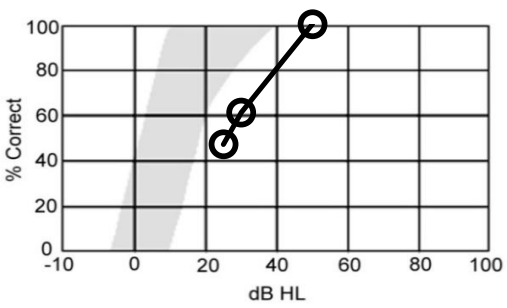
AB word lists

R	50 dB HL	100 %
R	30 dB HL	61 %
R	25 dB HL	47 %
L	50 dB HL	87 %
L	35 dB HL	67 %
L	25 dB HL	47 %

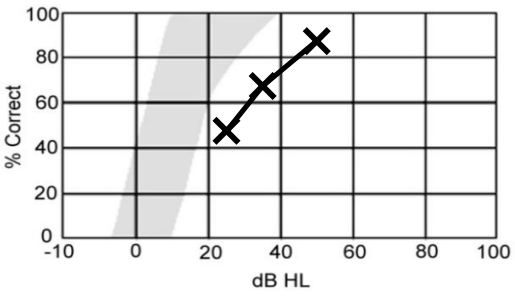
SDT R ____ dB HL

L ____ dB HL

Right



Left



Distortion Product Otoacoustic Emissions (DPOAEs)																
F2(Hz)	2000	2250	2500	2750	3062	3375	3750	4062	4500	5000	5500	6125	6812	7500	8375	9250
Right	✓	✓	✓	✓	✓	✓	×	×	✓	×	×	×	×	×	×	×
Left	✓	✓	✓	×	×	×	×	×	×	×	×	×	×	×	×	✓

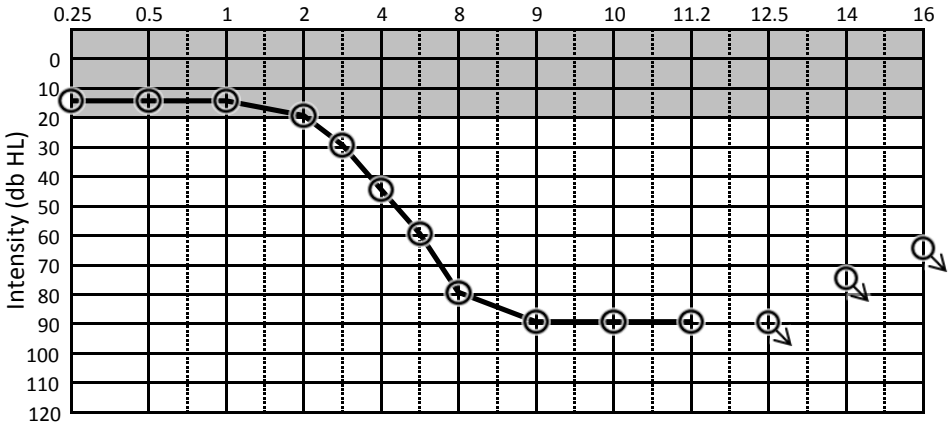
Key: ☑ OAE present (SNR > 5 dB) ☒ OAE absent (≤ -10 dBSPL)

Participant: Participant # 9 Age: 69 NHI:

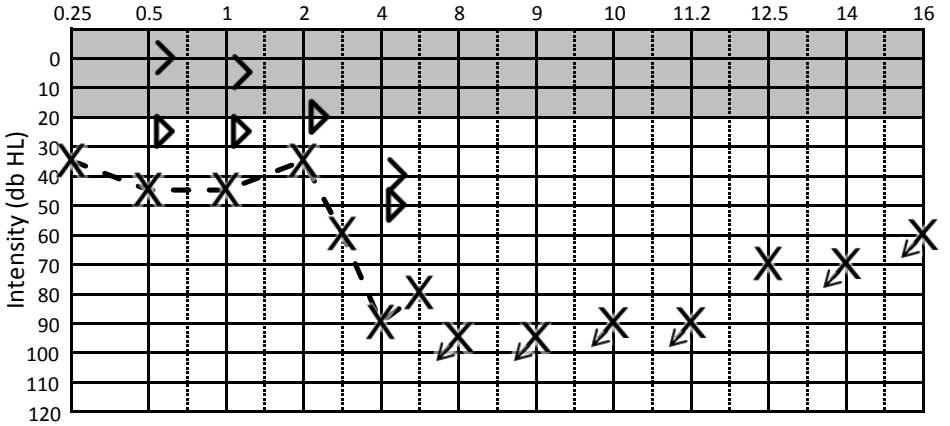
Tested by: Katrine Alchin Date: 17/03/2010

Pure-tone Audiometry

Right



Left



Otoscopy

Right: Clear

Left: Clear

Symbols		
Right		Left
○	Air	X
●	Masked Air	⊠
<	Bone	>
◁	Masked Bone	▷
S	Soundfield	S
U	UCL	U
↓	No Response	↓

Transducer	Reliability
Insert 3A	Good

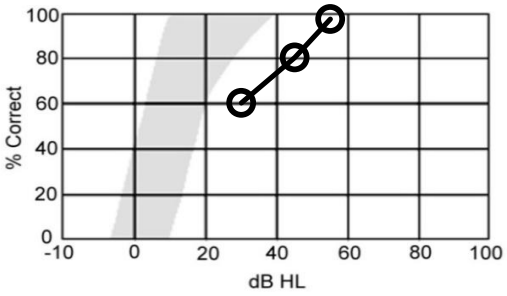
Tympanometry		
	Right	Left
Type	Ad	Ad
MEP (daPa)	25	-10
Comp. (ml)	2.4	4
Vol. (cc)	3	2.6

Ipsilateral Reflexes		
Sound Ear	Right	Left
500 Hz	105↓	110↓
1 kHz	105↓	110↓
2 kHz	105↓	105↓
4 kHz	100↓	100↓

Speech Audiometry

AB word lists

Right



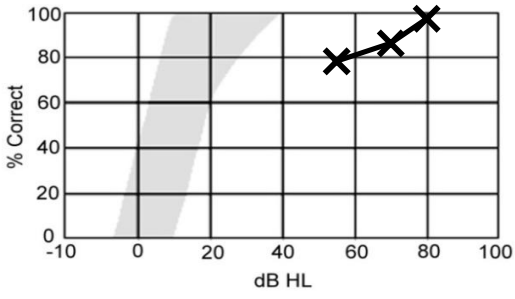
R	55 dB HL	97 %
R	45 dB HL	80 %
R	30 dB HL	60 %

L	80 dB HL	97 %
L	70 dB HL	86 %
L	55 dB HL	78 %

SDT R _____ dB HL

L _____ dB HL

Left



Distortion Product Otoacoustic Emissions (DPOAEs)																
F2(Hz)	2000	2250	2500	2750	3062	3375	3750	4062	4500	5000	5500	6125	6812	7500	8375	9250
Right	✓	×	✓	×	✓	×	×	×	×	×	×	×	×		×	✓
Left	×	×	×	×	×	×	×	×	×	×	×	×	×	×	×	

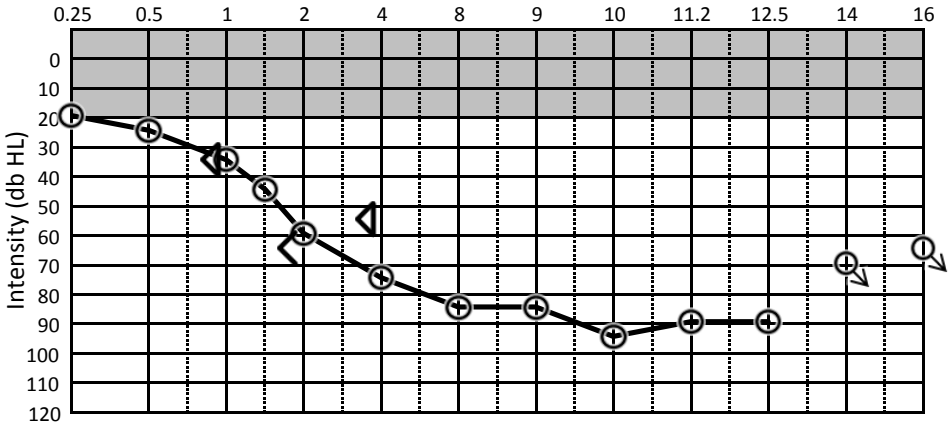
Key: ☑ OAE present (SNR > 5 dB) ☒ OAE absent (≤ -10 dBSPL)

Participant: Participant # 10 Age: 67 NHI:

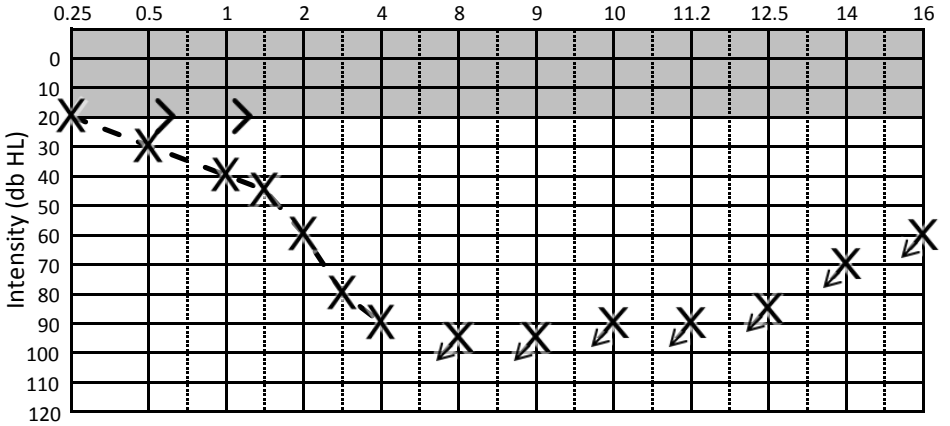
Tested by: Katrine Alchin Date: 28/01/2010

Pure-tone Audiometry

Right



Left



Otoscopy

Right: Clear

Left: Clear

Symbols		
Right		Left
○	Air	X
●	Masked Air	⊠
<	Bone	>
◁	Masked Bone	▷
S	Soundfield	S
U	UCL	U
↓	No Response	↓

Transducer	Reliability
Insert 3A	Good

Tympanometry		
	Right	Left
Type	A	A
MEP (daPa)	30	-5
Comp. (ml)	1.4	1.2
Vol. (cc)	2	1.6

Ipsilateral Reflexes		
Sound Ear	Right	Left
500 Hz	90	85
1 kHz	90	85
2 kHz	100	105↓
4 kHz	100↓	100↓

Speech Audiometry

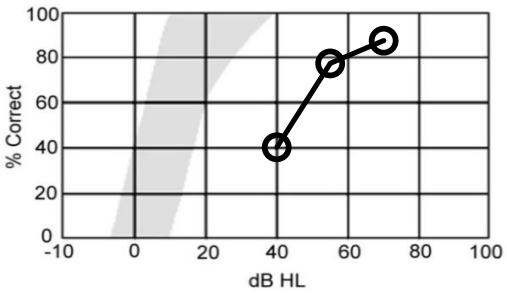
AB word lists

R	70 dB HL	87	%
R	55 dB HL	77	%
R	40 dB HL	40	%
L	70 dB HL	80	%
L	55 dB HL	67	%
L	40 dB HL	20	%

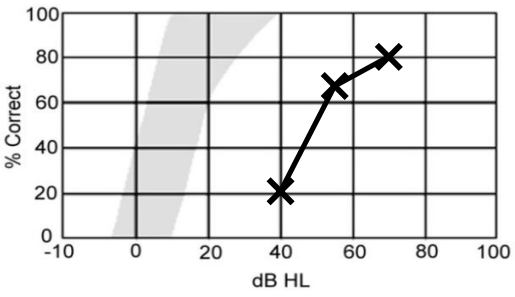
SDT R _____ dB HL

L _____ dB HL

Right



Left



Distortion Product Otoacoustic Emissions (DPOAEs)																
F2(Hz)	2000	2250	2500	2750	3062	3375	3750	4062	4500	5000	5500	6125	6812	7500	8375	9250
Right																
Left																

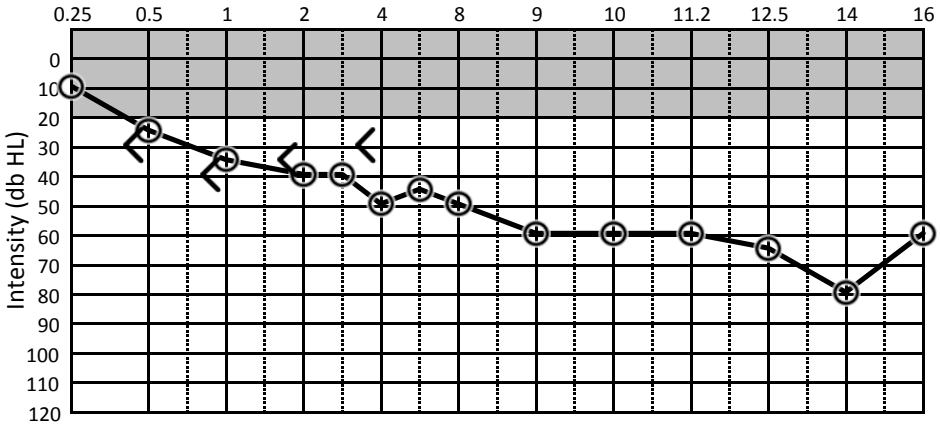
Key: ☑ OAE present (SNR > 5 dB) ☒ OAE absent (≤ -10 dBSPL)

Participant: Participant # 11 Age: 51 NHI:

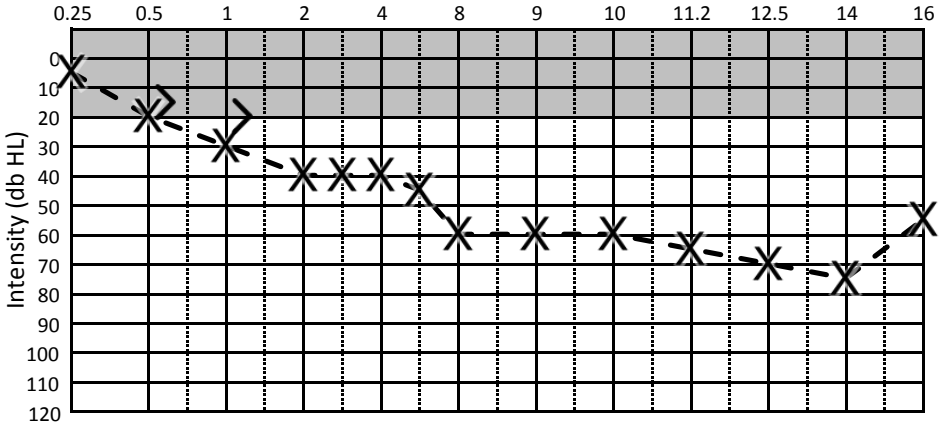
Tested by: Katrine Alchin Date: 4/02/2010

Pure-tone Audiometry

Right



Left



Otoscopy

Right: Clear

Left: Significant wax

Symbols		
Right		Left
○	Air	X
●	Masked Air	⊠
<	Bone	>
◁	Masked Bone	▷
S	Soundfield	S
U	UCL	U
↓	No Response	↓

Transducer	Reliability
Insert 3A	Good

Tympanometry		
	Right	Left
Type	A	A
MEP (daPa)	0	5
Comp. (ml)	0.3	0.5
Vol. (cc)	1	1.2

Ipsilateral Reflexes		
Sound Ear	Right	Left
500 Hz	80	80
1 kHz	80	80
2 kHz	80	80
4 kHz	80	80

Speech Audiometry

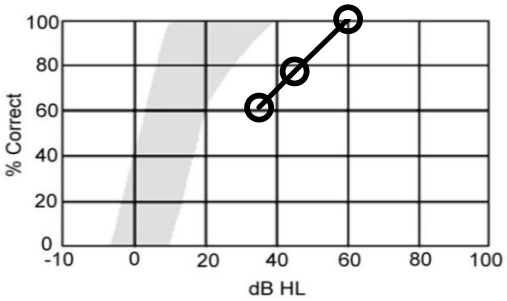
AB word lists

R	60 dB HL	100	%
R	45 dB HL	77	%
R	35 dB HL	61	%
L	60 dB HL	94	%
L	45 dB HL	81	%
L	35 dB HL	66	%

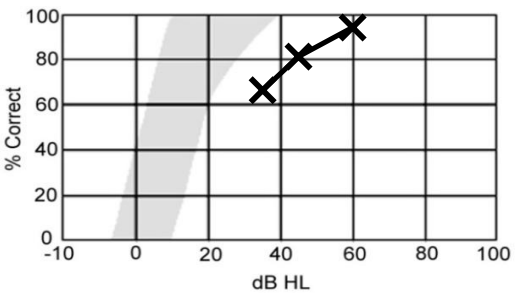
SDT R _____ dB HL

L _____ dB HL

Right



Left



Distortion Product Otoacoustic Emissions (DPOAEs)																
F2(Hz)	2000	2250	2500	2750	3062	3375	3750	4062	4500	5000	5500	6125	6812	7500	8375	9250
Right	×	×	×	✓	×	×	×	✓	×	×	×	✓	×	×	×	✓
Left	×	✓	×	×	✓	✓	✓	×	✓	×	×	×	×	×	×	✓

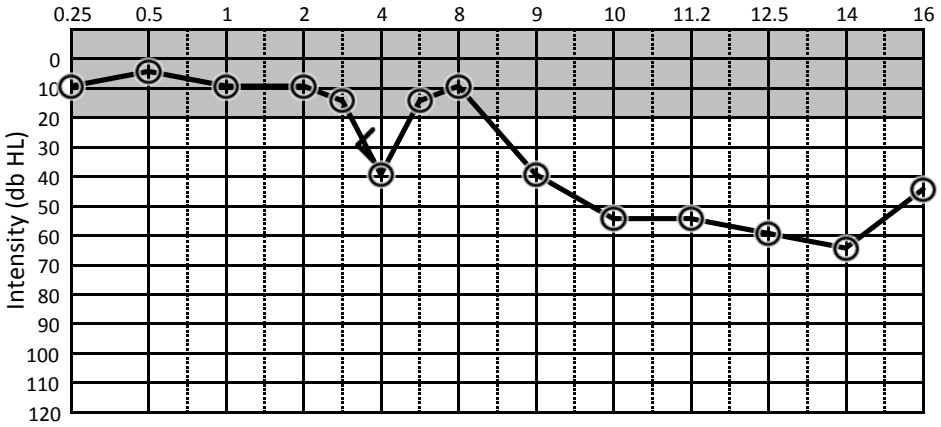
Key: ☑ OAE present (SNR > 5 dB) ☒ OAE absent (≤ -10 dBSPL)

Participant: Participant # 12 Age: 56 NHI:

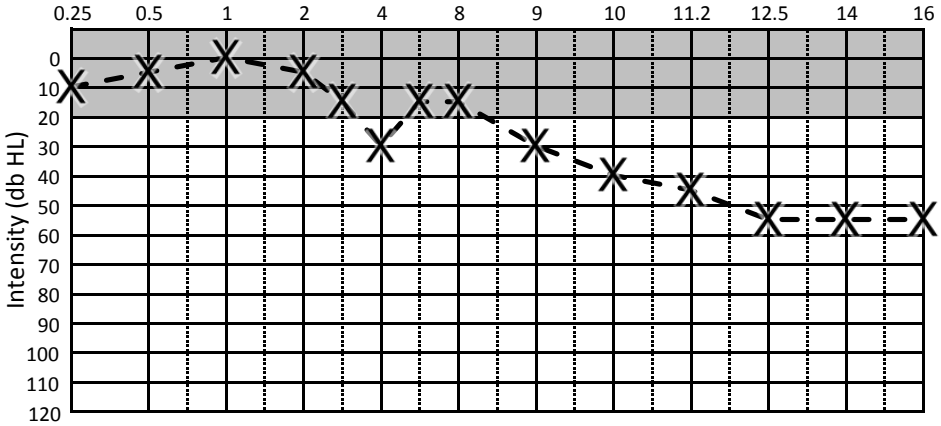
Tested by: Katrine Alchin Date: 22/02/2010

Pure-tone Audiometry

Right



Left



Otoscopy

Right: Clear

Left: Significant wax

Symbols		
Right		Left
○	Air	X
●	Masked Air	⊠
<	Bone	>
◁	Masked Bone	▷
S	Soundfield	S
U	UCL	U
↓	No Response	↓

Transducer	Reliability
TDH	Good

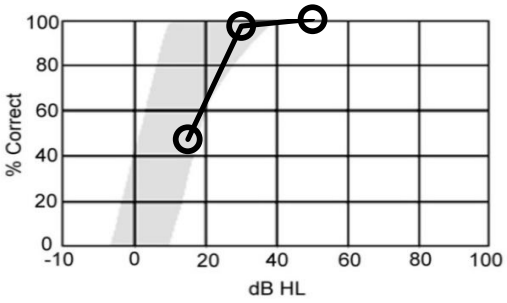
Tympanometry		
	Right	Left
Type	A	A
MEP (daPa)	20	20
Comp. (ml)	0.7	0.8
Vol. (cc)	1.4	1.3

Ipsilateral Reflexes		
Sound Ear	Right	Left
500 Hz	100	90
1 kHz	95	85
2 kHz	105	95
4 kHz	100↓	95

Speech Audiometry

AB word lists

Right

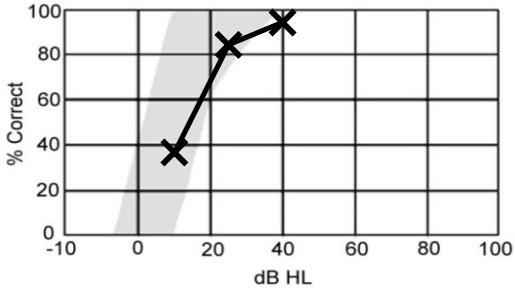


R	50 dB HL	100 %
R	30 dB HL	97 %
R	15 dB HL	47 %
L	40 dB HL	94 %
L	25 dB HL	84 %
L	10 dB HL	36 %

SDT R _____ dB HL

L _____ dB HL

Left



Distortion Product Otoacoustic Emissions (DPOAEs)																
F2(Hz)	2000	2250	2500	2750	3062	3375	3750	4062	4500	5000	5500	6125	6812	7500	8375	9250
Right	✓	✓	✓	✓	✓	×	×	×	×	×	×	✓	✓	×	✓	×
Left	✓	✓	✓	✓	✓	✓	×	×	×	✓	✓	✓	×	×	×	✓

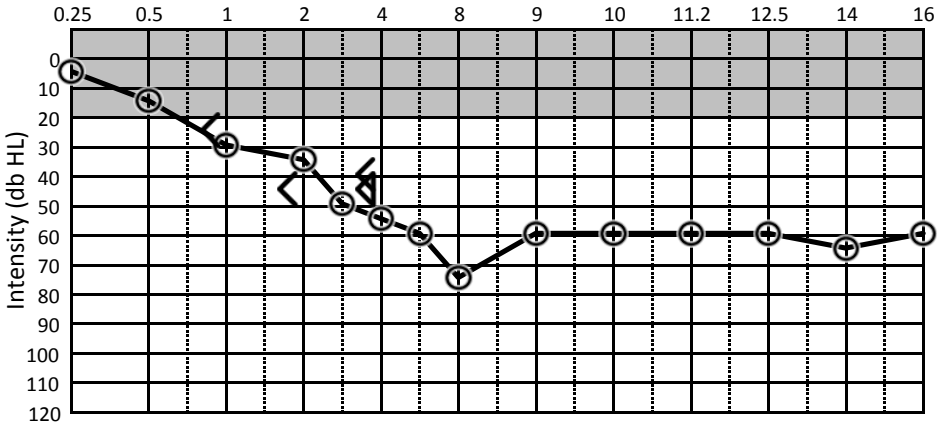
Key: ☑ OAE present (SNR > 5 dB) ☒ OAE absent (≤ -10 dBSPL)

Participant: Participant # 13 Age: 67 NHI:

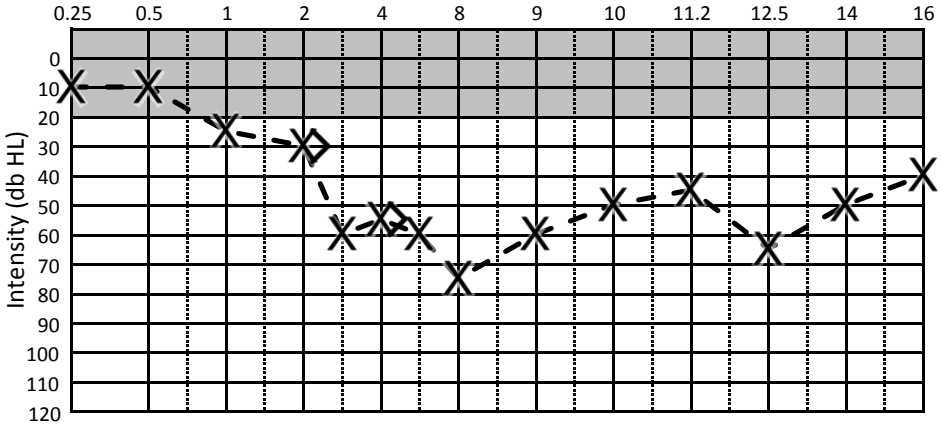
Tested by: Katrine Alchin Date: 22/02/2010

Pure-tone Audiometry

Right



Left



Otoscopy

Right: Significant wax

Left: Clear

Symbols

Right		Left
○	Air	X
●	Masked Air	⊠
<	Bone	>
◁	Masked Bone	▷
S	Soundfield	S
U	UCL	U
↓	No Response	↓

Transducer	Reliability
TDH	Good

Tympanometry

	Right	Left
Type	A	
MEP (daPa)	25	
Comp. (ml)	0.4	
Vol. (cc)	1.2	

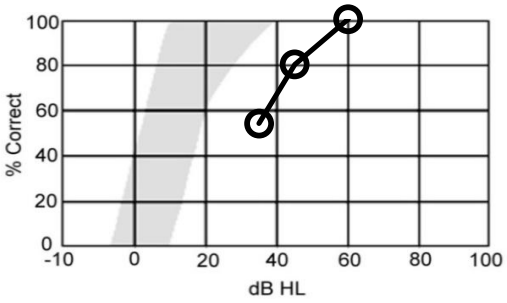
Ipsilateral Reflexes

Sound Ear	Right	Left
500 Hz		
1 kHz		
2 kHz		CNS
4 kHz		CNS

Speech Audiometry

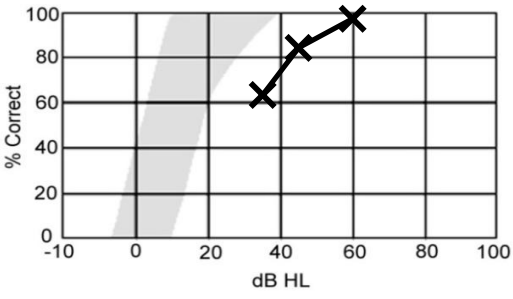
AB word lists

Right



R	60 dB HL	100	%
R	45 dB HL	80	%
R	35 dB HL	54	%

Left



L	60 dB HL	97	%
L	45 dB HL	84	%
L	35 dB HL	63	%

SDT **R** _____ dB HL

L _____ dB HL

Distortion Product Otoacoustic Emissions (DPOAEs)

F2(Hz)	2000	2250	2500	2750	3062	3375	3750	4062	4500	5000	5500	6125	6812	7500	8375	9250
Right	✓	✓	×	×	×	×	×	×	×	×	×	×	×	✓	×	×
Left	✓	✓	×	×	×	×	×	×	×	×	×	×	×	×	×	×

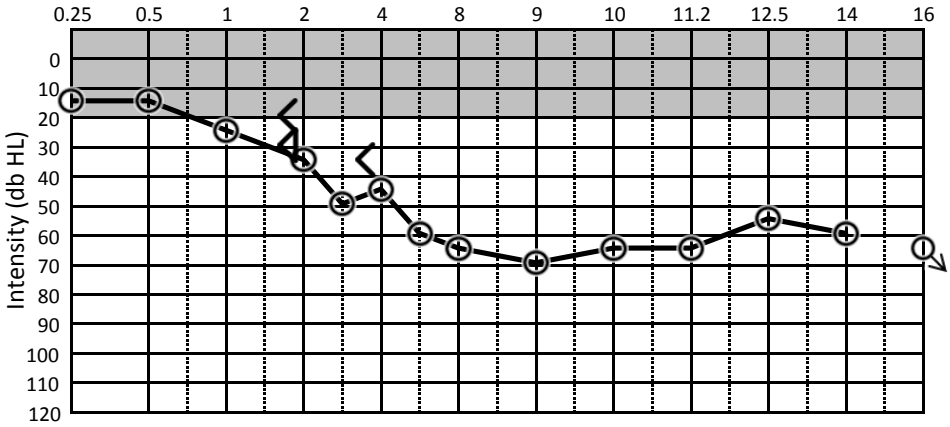
Key: ☑ OAE present (SNR > 5 dB) ☒ OAE absent (≤ -10 dBSPL)

Participant: Participant # 14 Age: 55 NHI:

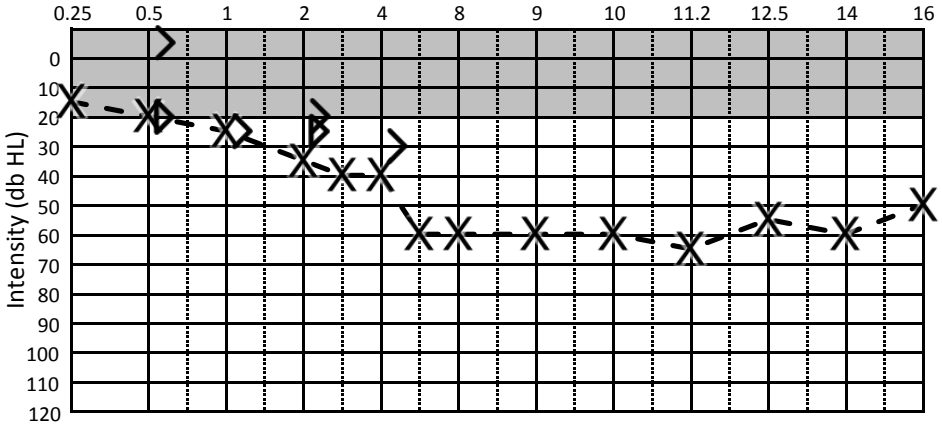
Tested by: Katrine Alchin Date: 18/03/2010

Pure-tone Audiometry

Right



Left



Otoscopy

Right: Significant wax

Left: Significant wax

Symbols		
Right		Left
○	Air	X
●	Masked Air	⊠
<	Bone	>
◁	Masked Bone	▷
S	Soundfield	S
U	UCL	U
↓	No Response	↓

Transducer	Reliability
TDH	Good

Tympanometry		
	Right	Left
Type	A	A
MEP (daPa)	25	15
Comp. (ml)	0.8	0.7
Vol. (cc)	2	1.9

Ipsilateral Reflexes		
Sound Ear	Right	Left
500 Hz	85	95
1 kHz	90	95
2 kHz	85	95
4 kHz	100↓	100↓

Speech Audiometry

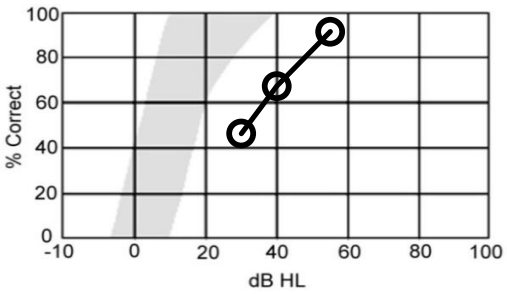
AB word lists

R	55 dB HL	91	%
R	40 dB HL	67	%
R	30 dB HL	46	%
L	60 dB HL	100	%
L	45 dB HL	88	%
L	30 dB HL	57	%

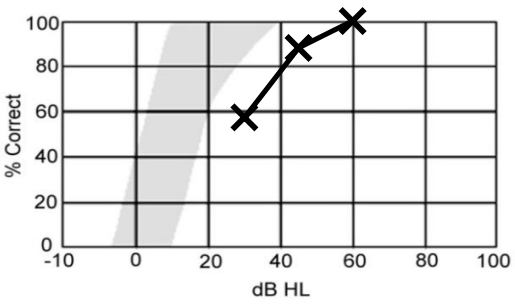
SDT R _____ dB HL

L _____ dB HL

Right



Left



Distortion Product Otoacoustic Emissions (DPOAEs)																
F2(Hz)	2000	2250	2500	2750	3062	3375	3750	4062	4500	5000	5500	6125	6812	7500	8375	9250
Right	✓	✓	✓	×	×	×	×	×	×	×	×	✓	×		×	×
Left	✓	✓	✓	×	×	×	×	×	×	×		×	×	×	×	

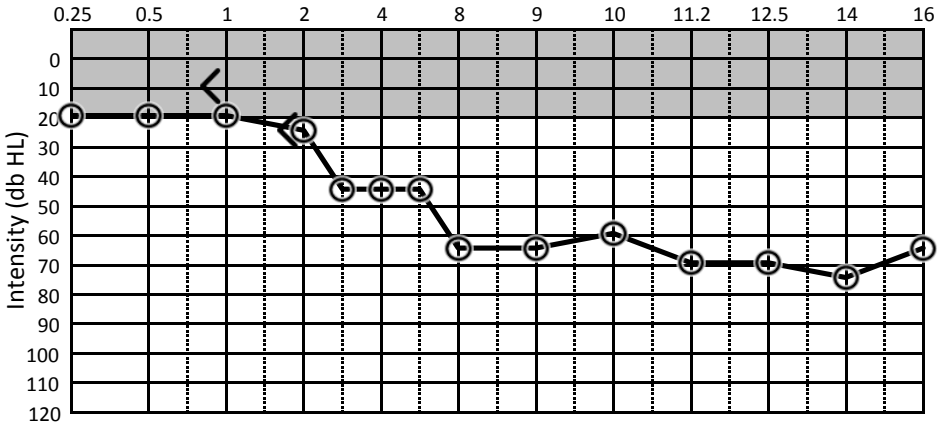
Key: ☑ OAE present (SNR > 5 dB) ☒ OAE absent (≤ -10 dBSPL)

Participant: Participant # 15 Age: 57 NHI:

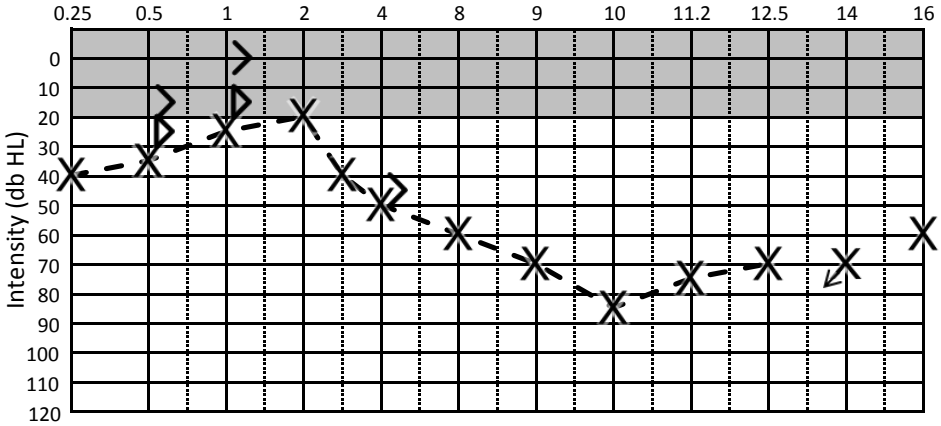
Tested by: Katrine Alchin Date: 20/01/2010

Pure-tone Audiometry

Right



Left



Otoscopy

Right: Clear

Left: Clear

Symbols		
Right		Left
○	Air	X
●	Masked Air	⊠
<	Bone	>
◁	Masked Bone	▷
S	Soundfield	S
U	UCL	U
↓	No Response	↓

Transducer	Reliability
Insert 3A	Good

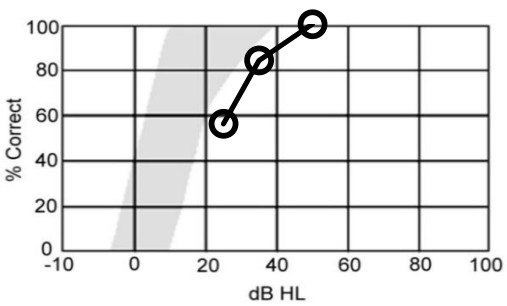
Tympanometry		
	Right	Left
Type		Ad
MEP (daPa)		-70
Comp. (ml)		1.9
Vol. (cc)		1.3

Ipsilateral Reflexes		
Sound Ear	Right	Left
500 Hz		
1 kHz		
2 kHz		
4 kHz		

Speech Audiometry

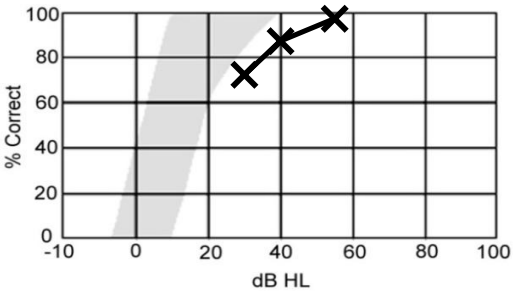
AB word lists

Right



R	50 dB HL	100	%
R	35 dB HL	84	%
R	25 dB HL	56	%

Left



L	55 dB HL	97	%
L	40 dB HL	87	%
L	30 dB HL	72	%

SDT R _____ dB HL

L _____ dB HL

Distortion Product Otoacoustic Emissions (DPOAEs)																
F2(Hz)	2000	2250	2500	2750	3062	3375	3750	4062	4500	5000	5500	6125	6812	7500	8375	9250
Right																
Left																

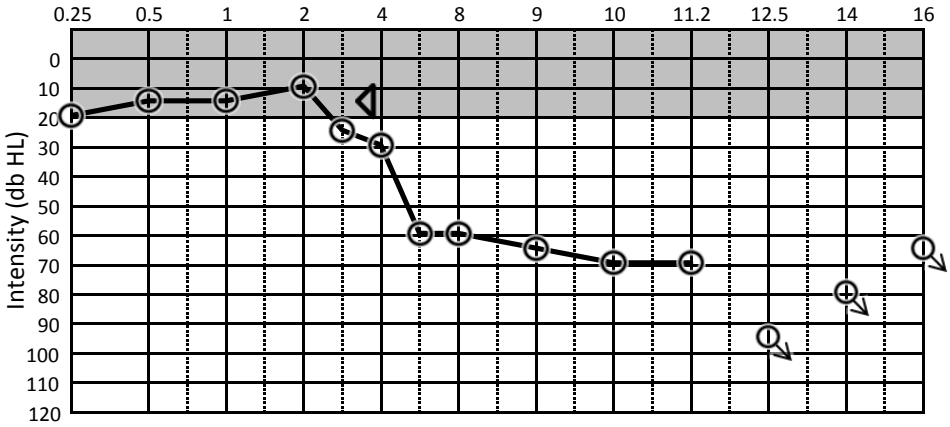
Key: ☑ OAE present (SNR > 5 dB) ☒ OAE absent (≤ -10 dBSPL)

Participant: Participant # 16 Age: 63 NHI:

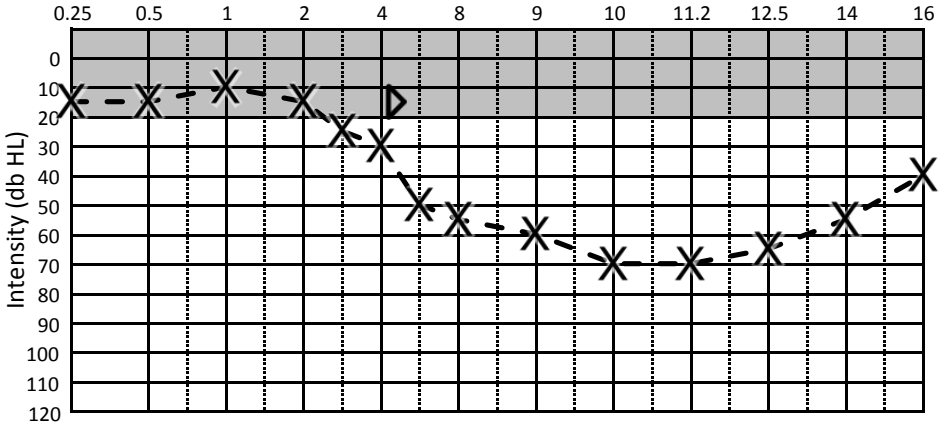
Tested by: Katrine Alchin Date: 3/02/2010

Pure-tone Audiometry

Right



Left



Otoscopy

Right: Clear

Left: Clear

Symbols		
Right		Left
○	Air	X
●	Masked Air	⊠
<	Bone	>
◁	Masked Bone	▷
S	Soundfield	S
U	UCL	U
↓	No Response	↓

Transducer	Reliability
Insert 3A	Good

Tympanometry		
	Right	Left
Type	A	A
MEP (daPa)	25	15
Comp. (ml)	1.1	0.9
Vol. (cc)	3.4	2.9

Ipsilateral Reflexes		
Sound Ear	Right	Left
500 Hz		
1 kHz		
2 kHz		
4 kHz		

Speech Audiometry

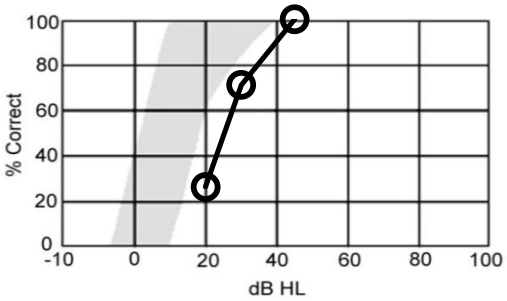
AB word lists

R	45 dB HL	100	%
R	30 dB HL	71	%
R	20 dB HL	26	%
L	45 dB HL	97	%
L	30 dB HL	57	%
L	20 dB HL	47	%

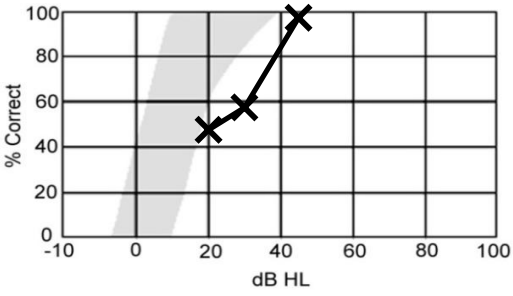
SDT R _____ dB HL

L _____ dB HL

Right



Left



Distortion Product Otoacoustic Emissions (DPOAEs)																
F2(Hz)	2000	2250	2500	2750	3062	3375	3750	4062	4500	5000	5500	6125	6812	7500	8375	9250
Right	✓	✓	✓	×	✓	×	×	×	×	×	×	✓	×	×	×	✓
Left	✓	✓	✓	×	×	×	×	×	×	×	×	×	×	×	×	×

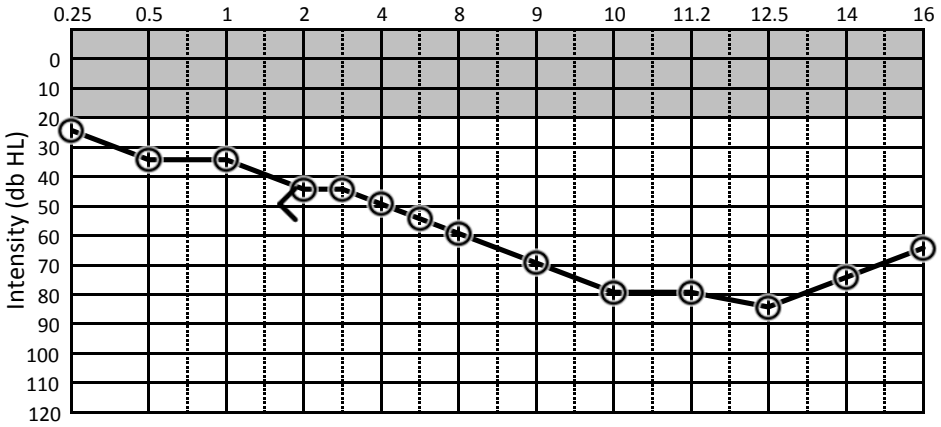
Key: ☑ OAE present (SNR > 5 dB) ☒ OAE absent (≤ -10 dBSPL)

Participant: Participant # 17 Age: 71 NHI:

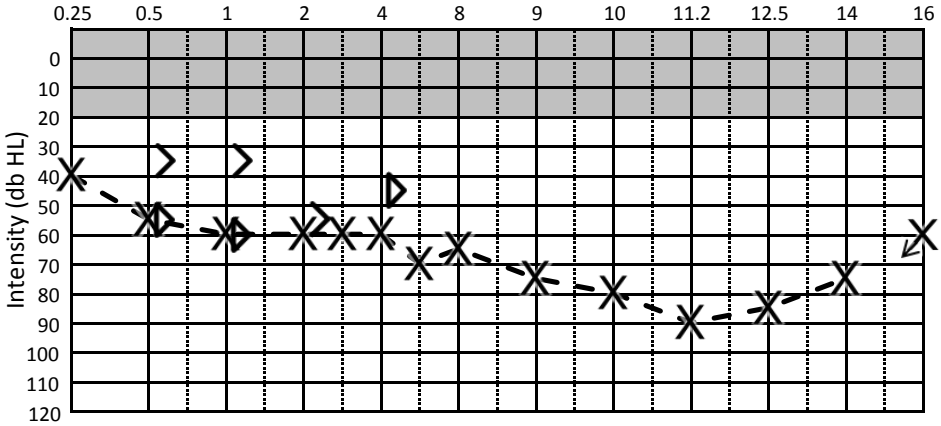
Tested by: Katrine Alchin Date: 3/02/2010

Pure-tone Audiometry

Right



Left



Otoscopy

Right: Clear

Left: Clear

Symbols		
Right		Left
○	Air	X
●	Masked Air	⊠
<	Bone	>
◁	Masked Bone	▷
S	Soundfield	S
U	UCL	U
↓	No Response	↓

Transducer	Reliability
Insert 3A	Good

Tympanometry		
	Right	Left
Type	A	A
MEP (daPa)	15	20
Comp. (ml)	0.4	0.4
Vol. (cc)	0.7	0.8

Ipsilateral Reflexes		
Sound Ear	Right	Left
500 Hz		
1 kHz		
2 kHz		
4 kHz		

Speech Audiometry

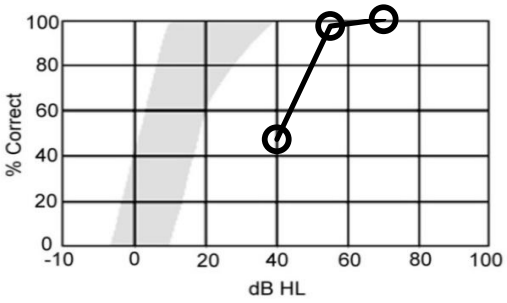
AB word lists

R	70 dB HL	100	%
R	55 dB HL	97	%
R	40 dB HL	47	%
L	90 dB HL	81	%
L	75 dB HL	60	%
L			%

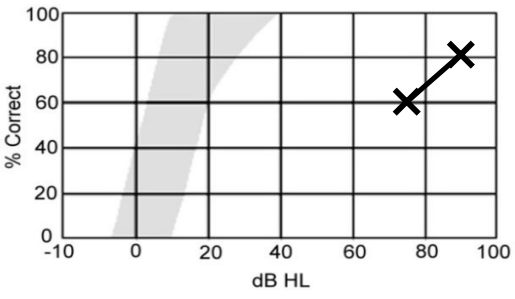
SDT R ____ dB HL

L ____ dB HL

Right



Left



Distortion Product Otoacoustic Emissions (DPOAEs)																
F2(Hz)	2000	2250	2500	2750	3062	3375	3750	4062	4500	5000	5500	6125	6812	7500	8375	9250
Right	×	×	×	×	×	×	×	×	×	×	×	×	×	✓	×	×
Left	×	×	×	×	×	✓	×	✓	×	×	×	×	×	×	×	×

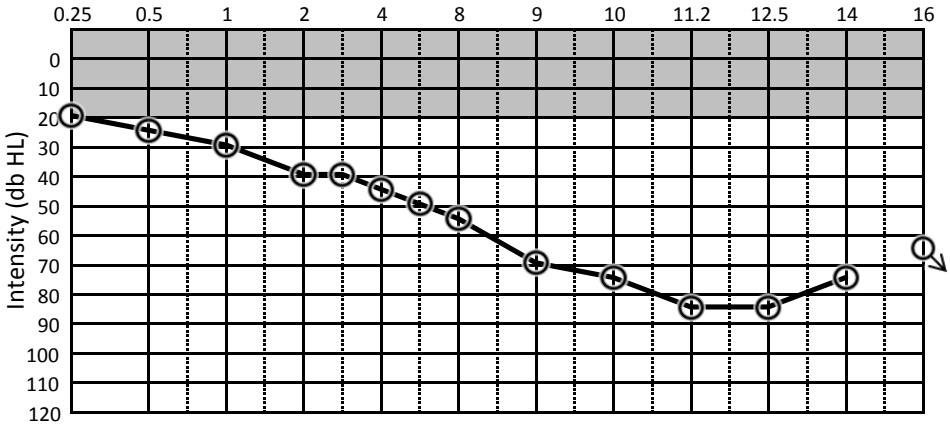
Key: ☑ OAE present (SNR > 5 dB) ☒ OAE absent (≤ -10 dBSPL)

Participant: Participant # 18 Age: 81 NHI:

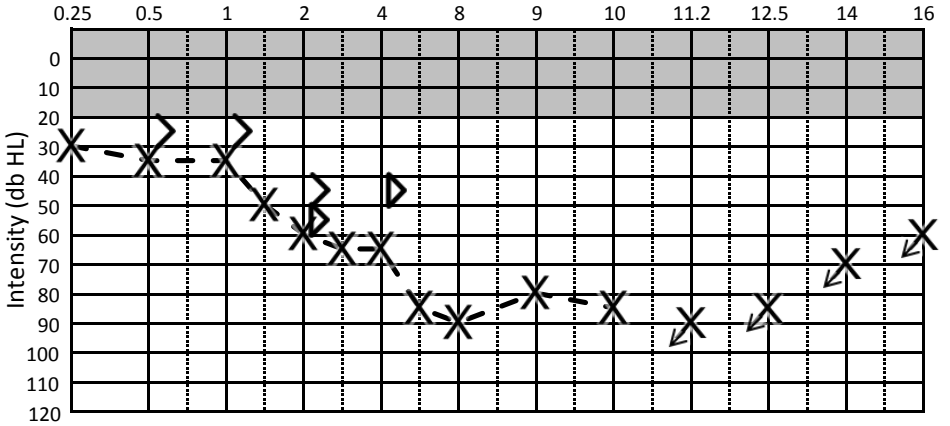
Tested by: Katrine Alchin Date: 5/02/2010

Pure-tone Audiometry

Right



Left



Otoscopy

Right: Clear

Left: Clear

Symbols

Right		Left
○	Air	X
●	Masked Air	⊠
<	Bone	>
◁	Masked Bone	▷
S	Soundfield	S
U	UCL	U
↓	No Response	↓

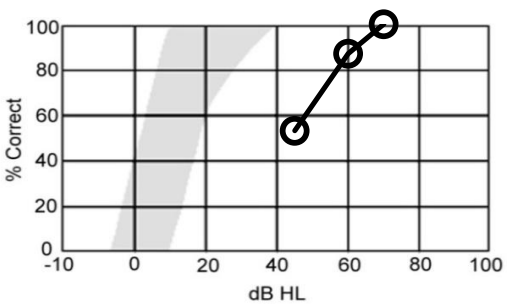
Transducer	Reliability
TDH	Good

Tympanometry		
	Right	Left
Type	As	A
MEP (daPa)	5	10
Comp. (ml)	0.1	0.3
Vol. (cc)	1.3	0.9

Ipsilateral Reflexes		
Sound Ear	Right	Left
500 Hz		
1 kHz		
2 kHz		
4 kHz		

Speech Audiometry

Right



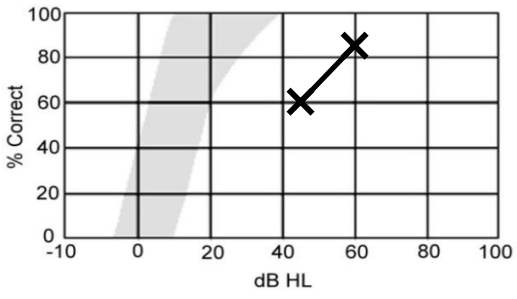
AB word lists

R	70 dB HL	100	%
R	60 dB HL	87	%
R	45 dB HL	53	%
L	60 dB HL	85	%
L	45 dB HL	60	%
L			%

SDT R _____ dB HL

L _____ dB HL

Left



Distortion Product Otoacoustic Emissions (DPOAEs)																
F2(Hz)	2000	2250	2500	2750	3062	3375	3750	4062	4500	5000	5500	6125	6812	7500	8375	9250
Right																
Left																

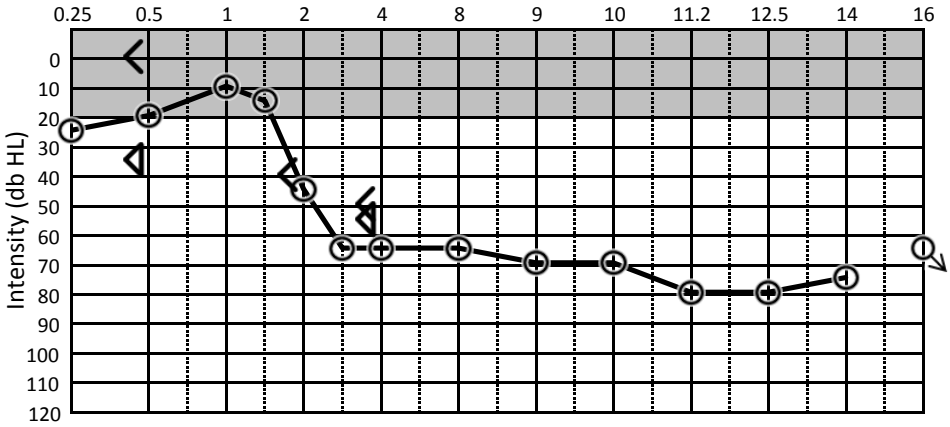
Key: ☑ OAE present (SNR > 5 dB) ☒ OAE absent (≤ -10 dBSPL)

Participant: Participant # 19 Age: 68 NHI:

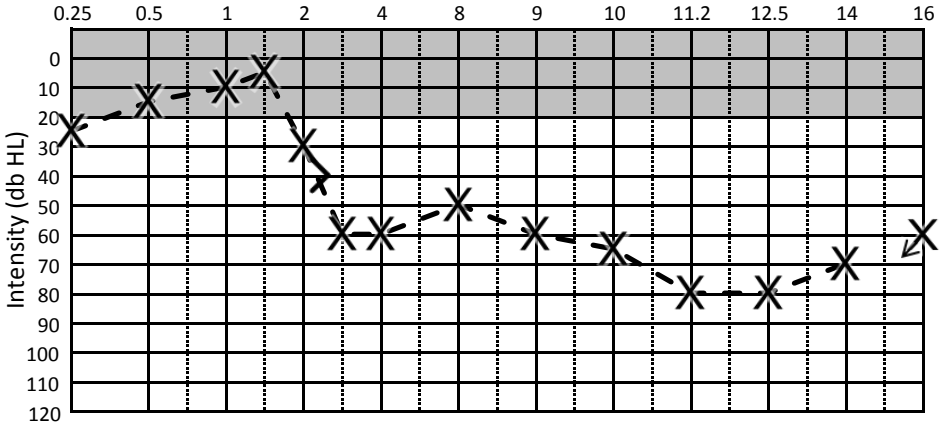
Tested by: Katrine Alchin Date: 7/01/2010

Pure-tone Audiometry

Right



Left



Otoscopy

Right: Clear

Left: Clear

Symbols		
Right		Left
○	Air	X
●	Masked Air	⊠
<	Bone	>
◁	Masked Bone	▷
S	Soundfield	S
U	UCL	U
↓	No Response	↓

Transducer	Reliability
Insert 3A	Good

Tympanometry		
	Right	Left
Type	A	A
MEP (daPa)	-5	5
Comp. (ml)	0.4	0.4
Vol. (cc)	1.4	1.2

Ipsilateral Reflexes		
Sound Ear	Right	Left
500 Hz		
1 kHz		
2 kHz		
4 kHz		

Speech Audiometry

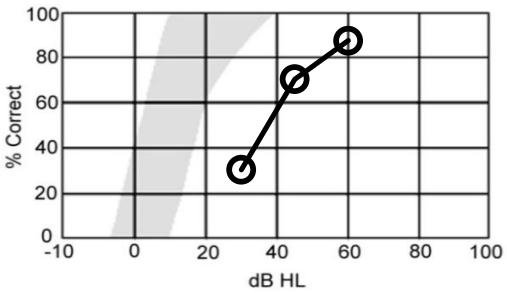
AB word lists

R	60 dB HL	87	%
R	45 dB HL	70	%
R	30 dB HL	30	%
L	40 dB HL	94	%
L	25 dB HL	50	%
L			%

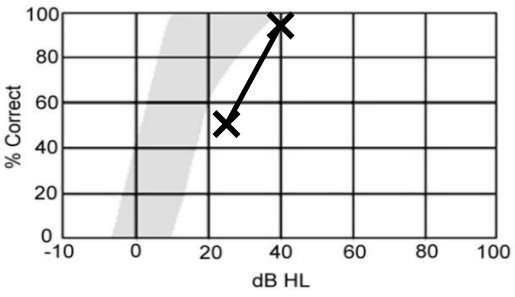
SDT R _____ dB HL

L _____ dB HL

Right



Left



Distortion Product Otoacoustic Emissions (DPOAEs)																
F2(Hz)	2000	2250	2500	2750	3062	3375	3750	4062	4500	5000	5500	6125	6812	7500	8375	9250
Right																
Left																

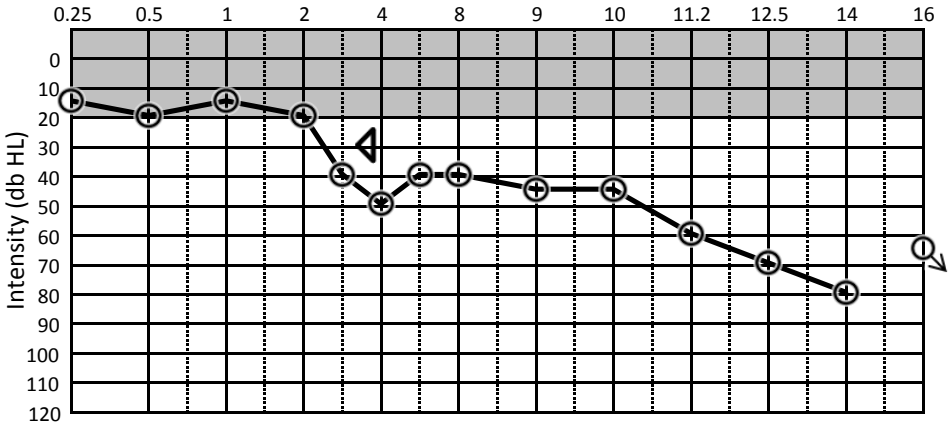
Key: ☑ OAE present (SNR > 5 dB) ☒ OAE absent (≤ -10 dBSPL)

Participant: Participant # 20 Age: 58 NHI:

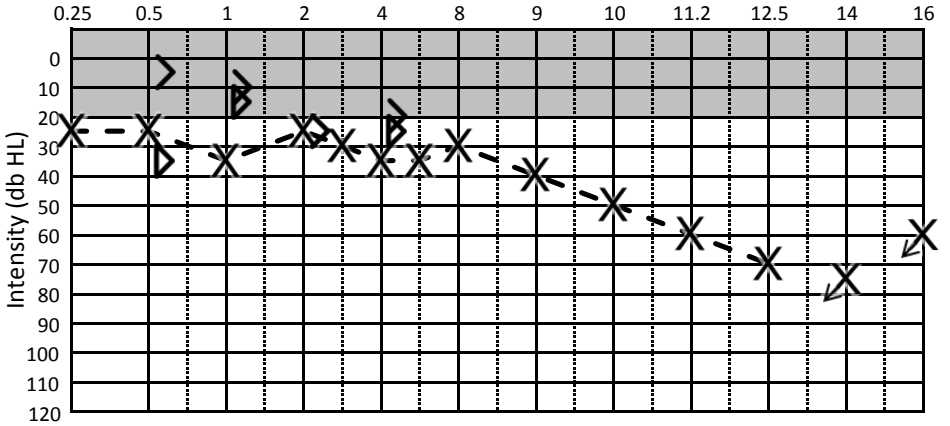
Tested by: Katrine Alchin Date: 4/02/2010

Pure-tone Audiometry

Right



Left



Otoscopy

Right: Clear

Left: Clear

Symbols		
Right		Left
○	Air	X
●	Masked Air	⊠
<	Bone	>
◁	Masked Bone	▷
S	Soundfield	S
U	UCL	U
↓	No Response	↓

Transducer	Reliability
Insert 3A	Good

Tympanometry		
	Right	Left
Type	A	A
MEP (daPa)	10	50
Comp. (ml)	1.2	1
Vol. (cc)	1.6	1.4

Ipsilateral Reflexes		
Sound Ear	Right	Left
500 Hz	110	110↓
1 kHz	105	110↓
2 kHz	105↓	105↓
4 kHz	100↓	100↓

Speech Audiometry

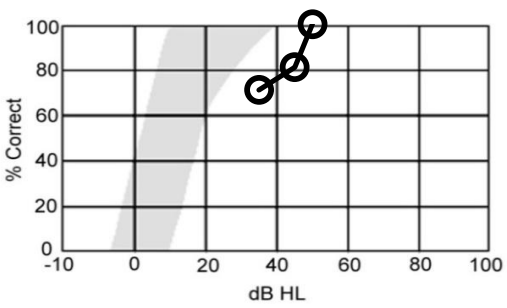
AB word lists

R	50 dB HL	100 %
R	45 dB HL	81 %
R	35 dB HL	71 %
L	60 dB HL	100 %
L	45 dB HL	80 %
L	35 dB HL	81 %

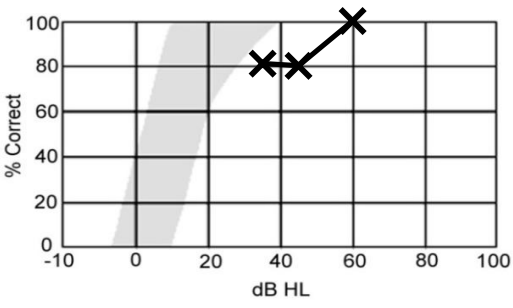
SDT R ____ dB HL

L ____ dB HL

Right



Left



Distortion Product Otoacoustic Emissions (DPOAEs)																
F2(Hz)	2000	2250	2500	2750	3062	3375	3750	4062	4500	5000	5500	6125	6812	7500	8375	9250
Right	✓	✓	✓	✓	×	✓	×	×	×	×	×	✓	×	✓	×	✓
Left	×	✓	✓	✓	×	✓	✓	×	×	×	×	×	×	×	✓	×

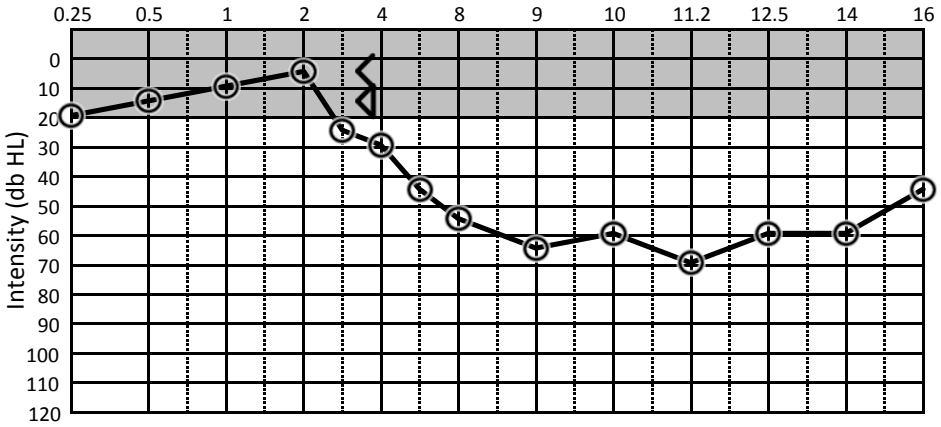
Key: ☑ OAE present (SNR > 5 dB) ☒ OAE absent (≤ -10 dBSPL)

Participant: Participant # 21 Age: 58 NHI:

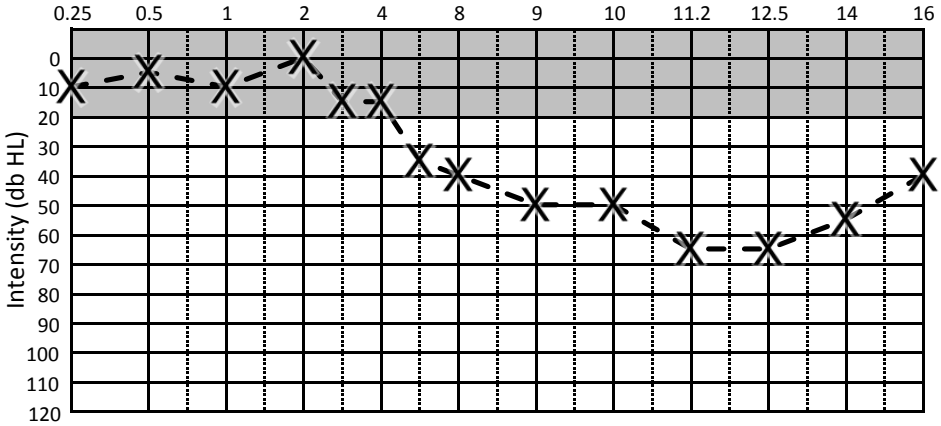
Tested by: Katrine Alchin Date: 17/03/2010

Pure-tone Audiometry

Right



Left



Otoscopy

Right: Clear

Left: Clear

Symbols		
Right		Left
○	Air	X
●	Masked Air	⊠
<	Bone	>
◁	Masked Bone	▷
S	Soundfield	S
U	UCL	U
↓	No Response	↓

Transducer	Reliability
Insert 3A	Good

Tympanometry		
	Right	Left
Type	C	A
MEP (daPa)	-110	-5
Comp. (ml)	0.5	0.5
Vol. (cc)	1.3	1.3

Ipsilateral Reflexes		
Sound Ear	Right	Left
500 Hz	90	90
1 kHz	85	85
2 kHz	85	85
4 kHz	100↓	100↓

Speech Audiometry

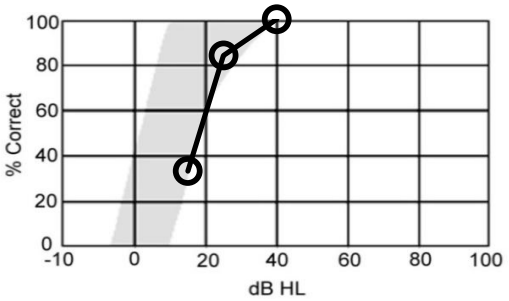
AB word lists

R	40 dB HL	100	%
R	25 dB HL	84	%
R	15 dB HL	33	%
L	35 dB HL	94	%
L	20 dB HL	80	%
L	10 dB HL	13	%

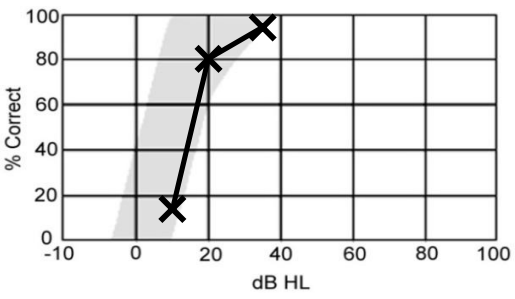
SDT R _____ dB HL

L _____ dB HL

Right



Left



Distortion Product Otoacoustic Emissions (DPOAEs)																
F2(Hz)	2000	2250	2500	2750	3062	3375	3750	4062	4500	5000	5500	6125	6812	7500	8375	9250
Right	✓	✓	✓	✓	✓	✓	✓	✓	×	×	×	×	×	✓	×	✓
Left	✓	✓	✓	✓	✓	✓	✓	✓	✓	×	×	✓	×	×	×	✓

Key: ☑ OAE present (SNR > 5 dB) ☒ OAE absent (≤ -10 dBSPL)

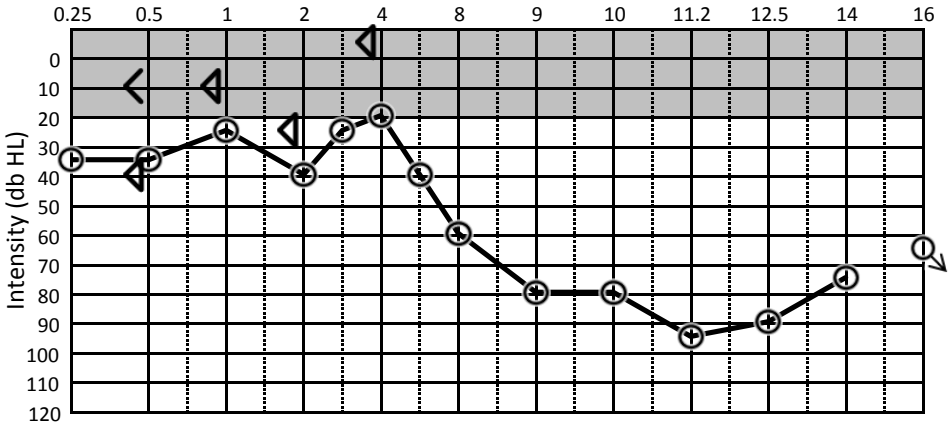
Participant: Participant # 22 Age: 52 NHI:

Tested by: Katrine Alchin Date: 13/01/2010

Pure-tone Audiometry

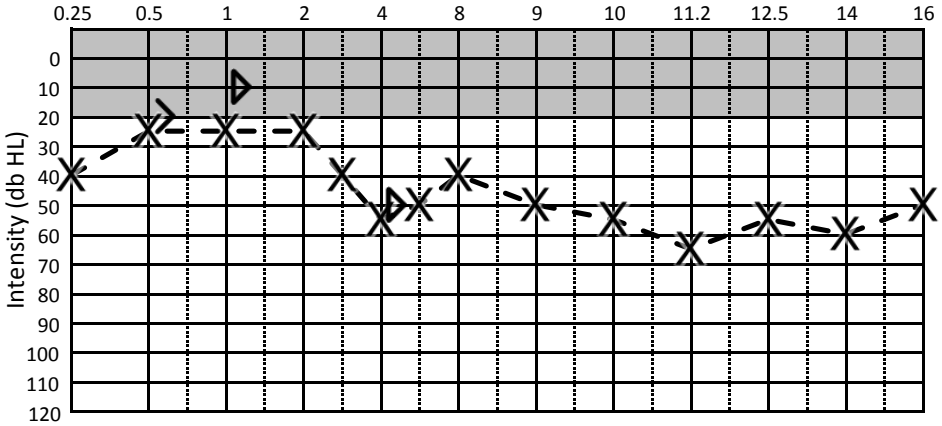
Right

Frequency (kHz)



Left

Frequency (kHz)



Otoscopy

Right: Clear

Left: Clear

Symbols		
Right		Left
○	Air	X
●	Masked Air	⊗
<	Bone	>
◁	Masked Bone	▷
S	Soundfield	S
U	UCL	U
↓	No Response	↓

Transducer	Reliability
Insert 3A	Good

Tympanometry		
	Right	Left
Type	Ad	A
MEP (daPa)	20	10
Comp. (ml)	4.1	0.8
Vol. (cc)	1.4	1.7

Ipsilateral Reflexes		
Sound Ear	Right	Left
500 Hz	105↓	95
1 kHz	105↓	90
2 kHz	105↓	90
4 kHz	100↓	100↓

Speech Audiometry

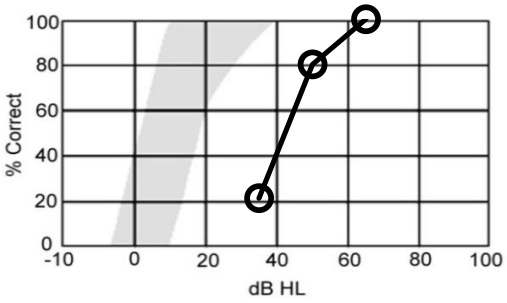
AB word lists

R	65 dB HL	100	%
R	50 dB HL	80	%
R	35 dB HL	21	%
L	65 dB HL	94	%
L	55 dB HL	74	%
L	40 dB HL	54	%

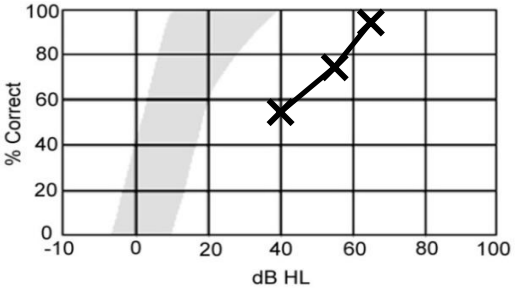
SDT R _____ dB HL

L _____ dB HL

Right



Left



Distortion Product Otoacoustic Emissions (DPOAEs)																
F2(Hz)	2000	2250	2500	2750	3062	3375	3750	4062	4500	5000	5500	6125	6812	7500	8375	9250
Right	✓	×	✓	×	✓	×	×	✓	✓	✓	✓	×	×	×		
Left	✓	✓	✓	×	×	×	×	×	✓	×	×	✓	×	×		

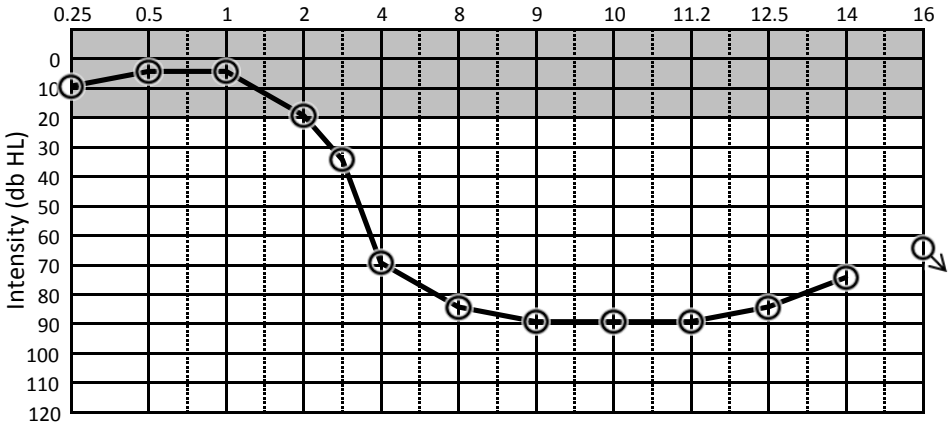
Key: ☑ OAE present (SNR > 5 dB) ☒ OAE absent (≤ -10 dBSPL)

Participant: Participant # 23 Age: 55 NHI:

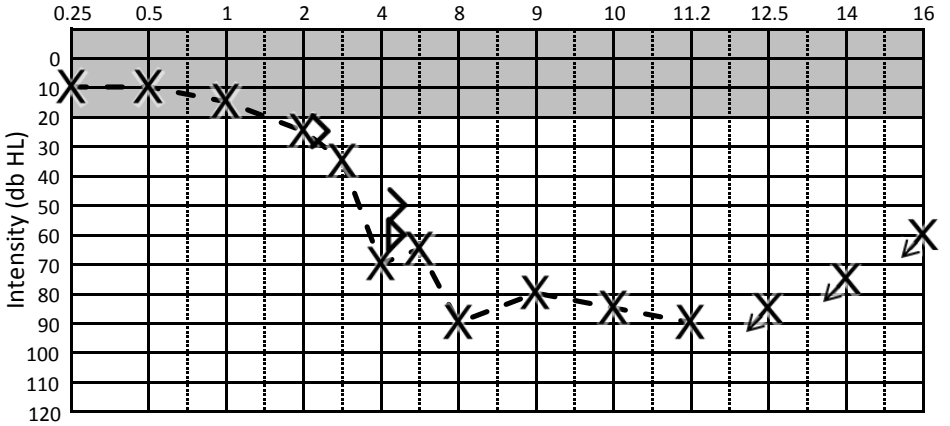
Tested by: Katrine Alchin Date: 29/01/2010

Pure-tone Audiometry

Right



Left



Otoscopy

Right: Significant wax

Left: Debris

Symbols		
Right		Left
○	Air	X
●	Masked Air	⊠
<	Bone	>
◁	Masked Bone	▷
S	Soundfield	S
U	UCL	U
↓	No Response	↓

Transducer	Reliability
TDH	Good

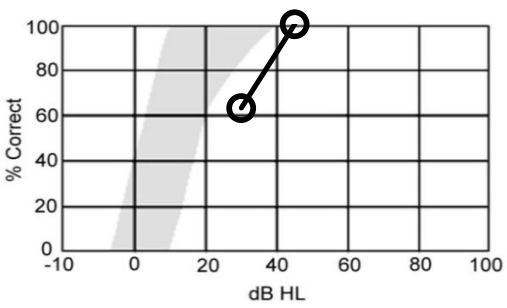
Tympanometry		
	Right	Left
Type		
MEP (daPa)		
Comp. (ml)		
Vol. (cc)		

Ipsilateral Reflexes		
Sound Ear	Right	Left
500 Hz		
1 kHz		
2 kHz		
4 kHz		

Speech Audiometry

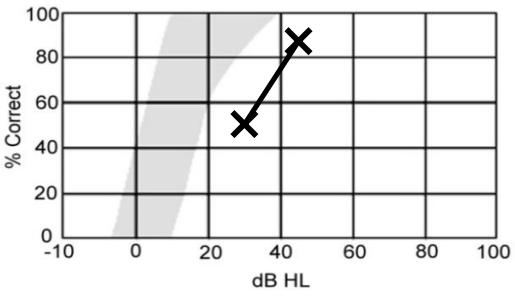
AB word lists

Right



R	45 dB HL	100	%
R	30 dB HL	63	%
R			%

Left



L	45 dB HL	87	%
L	30 dB HL	50	%
L			%

SDT R _____ dB HL

L _____ dB HL

Distortion Product Otoacoustic Emissions (DPOAEs)																
F2(Hz)	2000	2250	2500	2750	3062	3375	3750	4062	4500	5000	5500	6125	6812	7500	8375	9250
Right																
Left																

Key: ☑ OAE present (SNR > 5 dB) ☒ OAE absent (≤ -10 dBSPL)