Appendix 1(available online only). Measurements of Hearing Outcomes

There are multiple methods to assess hearing and studies report their outcomes in a variety of ways. Pure-tone audiometry and speech discrimination scores provide the most direct, clinically applicable information, and are considered the gold standard for evaluating changes in hearing thresholds. Audiometric measures also include OAE and psychophysical measurements, which are described in more detail in the appendices (Appendix 3, 4).

Self-reported hearing loss is clearly not the audiometric gold standard, but may be the most logistically practical option for initial inquiries in large prospective cohorts followed via questionnaire. Some studies suggest that subjective and objective results may correlate reliably,[77,78] but multiple others do not.[77,79,80] In addition, those who seek medical care more frequently may be more likely to both take ASA and have audiometry, which might bias the results. Findings of studies relying on self-reported hearing loss are ideally corroborated by follow up or concomitant formal audiometric measurements.

Appendix 2 (available online only). Case Reports of Hearing Loss associated with ASA

Author, year	Patient characteristics	ASA regimen evaluated	Follow up Time	Results with NSAID exposure	Time From Exposure to Outcome	Additional Comments
Janssen, 1999 [27]	22 year old female	ASA 10 g at once (overdose suicide attempt)	46 hours	Severe high-frequency HL (50 dB notch at 6k Hz) with tinnitus AU. Slope of the DPOAE I/O functions increased with increasing HL revealing decreased OHC compression	22 hours	Reversible: PT thresholds, DPOAE, and TEOAE returned to normal 46 hours after the salicylate was discontinued
Jordan, 1991 [28]	76 year old male	ASA 6-7 g/ d	1 month	Mild to moderate SNHL AU, that improved to normal at 250-2k Hz, sloping moderate SNHL HL, loud roaring tinnitus AU	NR	Reversible: Hearing thresholds were within normal limits up to 2000 Hz and WRS was 100% bilaterally within 1 months of discontinuing ASA
Koegel, 1985 [29]	52 year old female	ASA 2 g /d for "many" months	24 days	Fluctuating moderate SNHL AU, poor word recognition scores AU, aural fullness, unsteadiness, and tinnitus	Months	Reversible: When drug was discontinued hearing thresholds improved to normal and word recognition was excellent bilaterally -Hearing test revealed a flat, symmetrical SNHL approximately 45 dB
Jarvis, 1966 [30]	19 year old female	ASA 2-3 tablets Q2h x3d (tablet size not reported)	3 days and repeated audiograms thereafter	Vertigo, left-sided tinnitus, and left-sided severe SNHL (80-90dB threshold)	3 days	Reversible: significant improvement since ASA was discontinued
Ramsden, 1985 [31]	29 year old male	100 ASA tablets (tablet size not reported)	4 hours	SNHL (30 dB), bilateral tinnitus, and slight imbalance. ECochG: biphasic recruiting action potentials	4 hours	Reversible: following 24 h of forced alkaline diuresis, SNHL returned to normal, ECochG had a normal configuration, subjective tinnitus improvement
	36 year old female	~20-40 ASA tablets (tablet size not reported)	2 hours	Bilateral symmetric moderate-severe SNHL (50 dB) ECochG: biphasic recruiting action potentials	2 hours	Reversible: hearing returned to normal and tinnitus disappeared 24-48 hours following cessation of ASA.

Naganawa, 2009 [32]	61 year old female	100mg/d ASA	NR	Sudden left-sided SNHL (80 dB) and aural fullness and severe vertigo Normal CT scans of temporal bone. MRI scans negative for vestibular schwannoma and malformation of the inner ear. MRI scans revealed possible hemorrhage in the ampullar endolympth of the semicircular canal	NR	Irreversible: patient reported no improvement in hearing following oral steroid treatment

None of the patients in these case reports were described as having rheumatoid arthritis or connective tissue diseases at baseline.

Appendix 3 (available online only). Studies of the Impact of ASA on Otoacoustic Emissions

Author, year	Study Design (Sample Size)	Patient Description	ASA regimen evaluated	Hearing Evaluation	Follow up Time	NSAID Exposure Results	No NSAID Exposure Results	Time From Exposure to Outcome	Additional Comments
Brown, 1993 [76]	Prospective Placebo-controlled, Double-blind Crossover Study (n=8)	Age 19-34 years with normal hearing at the outset Male healthy volunteers	ASA 3x 320 mg Q6h x24 hrs (a total of 8 doses)	Stimulus frequency emission: level of cubic distortion when the distortion frequency falls a half octave below that of the higher of two stimulus tones	1x/ week over 4 weeks: baseline, ASA, placebo, and post-trial	3 subjects: downward shift of Fc of distortion peak by up to 200 Hz 2 subjects: shift in distortion peak was not associated with a change in psychophysical threshold.	The placebo results were used as the baseline for comparison to the crossover data from the ASA ingestion.	Serial effect measurements at 1-4 weeks	ASA affects the resonance frequency of the bandpass filter revealed by distortion measurement, but not tuning.
Abdala, 2005 [23]	Prospective Cohort (n=41, 10 of which were ASA-exposed, 9 completed the entire study)	Adult ASA recipients: Age 22-37 years (mean 29.1) 4 left ears 6 right ears (n=10) Children with mild SNHL (n=8) Healthy term-born neonates (n=23)	325 mg ASA Q6h for 4 d	DPOAE: suppression growth, threshold, saturation, slope of the I/O function	Baseline, then 72h and 96h after beginning the salicylate regimen	DPOAE mean amplitude reduced by 3.8 dB at 1500 Hz and 7.6 dB at 6000 Hz 96h after ASA. ASA systematically altered DPOAE suppression in adults at 6000 Hz, but not at 1500 Hz. No significant correlation between serum level and DPOAE.	Subjects were compared to their own baseline	72, 96h	Post-ASA DPOAE did not mimic infant findings

Parazzini, 2005 [41]	Prospective Cohort (n=12)	Age 19-38 years healthy males	ASA 975 mg BID x1d, QID x2d, BID x1d in this order	HTL= > 20 dB at 250-8000 Hz and DPOAE	2d before exposure, during exposure, 2d after exposure	7-21.5 dB temporary sensory threshold shift after ASA DPOAE phase gradient was increased with ASA, steeper phase gradients found in higher frequencies with no significant phase gradient effect in lower frequencies.	Subjects were compared to their own baseline	NR	DPOAE phase gradient and amplitude and hearing thresholds were increased by ASA consumption and did not recover after cessation of ASA
McFadden, Plattsmier, 1984[46]	Prospective Cohort (n=5)	Male volunteers with normal hearing and SOAEs	ASA 975 mg QID x4d	Auditory sensitivity evaluated with adaptive, two-interval forced choice at 500 and 3500 Hz SOAE < 6dB above the noise floor	Subjects were seen at least once a day during the exposure and then 2-3 days afterward	4.3-17.5dB worsening in threshold after ASA 60% (3/5) Smaller SOAEs disappeared after 14-20 hours and larger SOAEs disappeared after several days.	Subjects were compared to their own baseline	14-24 hours	Full recovery of SOAEs was seen at 24-48h in some subjects.

Long, 1988[42]	Prospective Cohort (n=4)	1 male, 3 female	ASA 325 mg Q6h x3-4d	Less than the noise floor (-10 dB SPL at 1300 and 1400Hz and -6.5 dB SPL at 1000 and 2000 Hz) Spontaneous, delayed-evoked	1d before exposure, "several" times/d during first days, 2x/d in the middle of ASA, and "several" times/d afterwards	All SOAE (except 1 from GD's ear) were reduced to the noise floor (quantification not reported) within 2 days of ASA -Increased sensitivity of evoked OAEs seen in all 3 subjects	Subjects were compared to their own baseline	2 days	
Rao, 2011 [43]	Prospective Cohort (n=3)	Age 20-30 years	ASA 325mg Q6h x 3 d	DPOAE	24h prior to exposure, then18h, 34h, 40h, 58h, 66h, 114h after first dose of ASA	Reduced responses were seen 18-34h after exposure. The reflective component was more susceptible than the nonlinear.	Subjects were compared to their own baseline	18-34h	Partial results obtained for subject 3 due to fewer measurements
Wier,1989 [44]	Prospective Cohort study (n=4)	All males with one or more reliable SOAEs	ASA 3x 325mg every 6 hours for up to 4 days Daily dose: 3.9g	All subjects had ≥1 reliable SOAE	Every 24 h until the SOAE became unmeasurable or 4 days at the most.	SOAEs greatly reduced or eliminated; EDPs reduced but not eliminated. SOAE threshold shifts ranged from (-1.6) – (+4.8) dB Primaries used to generate EDPs' threshold shifts ranged from (-6.6) – (+9.3) dB	Subjects were compared to their own baseline	Effect present at 24-48h	EDP and SOAE amplitudes returned to within 3 dB of baseline values 48 h after last aspirin dose for 3 subjects. The 4th subject's EDP returned to within 2 dB of baseline 24 h and SOAE returned after 1 week following last aspirin dose

Hall, 2001 [45]	Prospective Cohort (n=9)	Normal hearing	ASA 11.7g over 72h	TEOAEs were measured at 50, 60, 60, and 80 dB SPL. Self-recording audiometry at 3k Hz	7 days	Threshold shift at 3 kHz ranged from 0-14 dB.	Subjects were compared to their own baseline	NR	TEOAE reduction in amplitude at 3k Hz was greatest at 80 dB SPL.

Impact of Aspirin on Otoacoustic Emissions

Eight small studies evaluated the impact of ASA on OAEs: 1 prospective placebo-controlled, double-blinded crossover study[40] and 7 prospective cohort studies.[23,41-46.]

The prospective, placebo-controlled, double-blind crossover study evaluated adult male volunteers (n=8, age 19-34y) with threshold audiogram at 1-8kHz, distortion audiogram ($f2/f1 = 1.225$, $f2$ = 1-8kHz in one-third octave steps, $L1 = 55$/ $L2 = 40$ dB SPL), spontaneous OAEs (1-5 kHz), $f1$ sweep ($f2$ fixed at 40 dB SPL, 4 kHz, while $f1$ 55 dB SPL swept from 2.83 to 3.960 kHz), and a stimulus frequency emission spectrum (single tone at 40 dB SPL swept between 1600-4000Hz). Equivalent rectangular bandwidth (ERB) for each subject was also calculated from the psychophysical data obtained.[40] Adult subjects participated in four conditions: pre-trial screening, ASA, placebo, and post-trial evaluation. Large variation existed among subjects; however, in 38% (3/8) of subjects, ASA created a downward shift of up to 200 Hz in the peak frequency of the bandpass filter. There was no evidence of a downward shift in the frequency of the fine structure that could explain the frequency shift noted in the distortion frequency sweeps, suggesting that the bandpass filter was not affected by the mechanism responsible for the “fine structure” in the SFE spectrum. The

outcomes of this study suggested a link between the tuning of the distortion peak and psychophysically measured equivalent rectangular bandwidth (ERB).

Among the largest of OAE-focused reports was a prospective cohort study (n = 41) conducted at the House Ear Institute.[23] ASA-exposed adults were compared to their own otologically normal baseline. Hearing was assessed with spontaneous otoacoustic emissions (SOAE), distortion product otoacoustic emissions (DPOAE), suppression tuning curves, the DPOAE I/O function at both *f*2 = 1500 Hz and 6000 Hz, air and bone conduction pure-tone thresholds, DP-gram (*f*2 = 1500 – 12,500 Hz), and immittance tympanometry (226 Hz probe tone). An *f*2 / *f*1 ratio of 1.21 with primary tones was presented at 65/55 dB SPL for suppression measurements. ASA exposure (975 mg Q6h x 24h) resulted in a reduction in DPOAE mean amplitude by 3.8 dB at 1500 Hz and 7.6 dB at 6000 Hz 96h post-exposure (p=0.001). ASA suppressed the iso-suppression tuning curves in adults at 6000 Hz (mean *Q*10 shifted from 2.38 during baseline to 1.56 when measured four days after start of ASA, p=0.05), but not at 1500 Hz. Audiometric thresholds were increased by a mean of 12.7 dB at 1500 Hz and by 14.3 dB at 6000 Hz 96h after initial consumption.

The remainders of the studies were small prospective cohorts, in which ASA was administered in doses ranging from 1.3 – 3.9 g/d and subjects' post-ASA results were compared to their own baseline.[41,42,43,44,45,46] All showed deterioration in OAE measurements after ASA administration.

OAEs describe an objective assessment of cochlear function, specifically the motility of outer hair cells; these measurable sounds are generated and emitted by the ear spontaneously or in response to stimuli. In a normal ear, when sound is presented to the

ear canal via a probe, the organ of Corti vibrates and amplifies the input to the inner hair cells. Spontaneous OAEs (SOAEs) are low-level tones emitted in the absence of any known stimulus that suggest normal cochlear hearing sensitivity at the frequency region of the SOAE. Distortion product OAEs (DPOAEs) are emitted in response to two primary simultaneous pure-tones ($f1$ and $f2$) located at near frequencies and measure the distortion product of non-linear cochlear processing.[81] Generating the intermodulation DPOAE component requires that the ratio of these two primaries ($f2/f1$) has an effect on the amplitudes of the DPOAEs at each frequency tested. The most frequently measured DPOAE is at the $2f1\text{-}f2$ frequency because it is the largest measurable DPOAE in human ears. Transient evoked otoacoustic emissions (TEOAEs) measure the cochlear response to a transient (click or tone burst) signal, which contains a range of frequencies. DPOAEs are the preferred method when determining ototoxicity effects because they can be measured at higher frequencies than TEOAEs. OAEs can be readily added to an ototoxicity monitoring battery because they are measured rapidly and non-invasively from the outer ear canal, and were utilized in several studies within this systematic review.

Appendix 4 (available online only). Studies of the Impact of ASA on Psychophysical methods

Author, year	Study Design (Sample Size)	Patient Description	NSAID evaluated	Hearing Evaluation	Follow up Time	NSAID Exposure Results	No NSAID Exposure Results	Time From Exposure to Outcome	Additional Comments
Beveridge, 1996 [49]	Prospective Placebo-controlled, Double-blind Crossover Study (n=9)	Age 20-32 years Male healthy volunteers	Three ASA 320 mg or Placebo Q6h x3d (3.84 g/day), with a washout period of at least 1 week	Compared differences between variation of signal rather than masker level and broad band versus narrowband maskers	1h, 1 week after final dose	ASA significantly elevated the tips and reduced the slopes of the PTCs, indicating a reduction in frequency selectivity	The placebo results were used as the baseline for comparison to the crossover data from the ASA ingestion.	Effect present at 1h and 1 week	Psychophysical testing showed a reduction in frequency selectivity, which may affect one's ability to understand speech in noise
Carlyon, 1993 [48]	Prospective Placebo-controlled, Double-blind Crossover Study (n=8)	All male Age 19-34 years with normal hearing	Three ASA 320 mg or Placebo Q6h (3.84g/d) x8 doses	Auditory filter shapes in notched-noise forward masking from thresholds that were obtained by adaptively varying the signal level.	1. After subjects had consumed 8x 320 mg ASA Q6h 2. After 8x 320 mg placebo Q6h 3. 1w after initial (1,2) testing was completed	ASA significantly broadened the filter shapes	The placebo results were used as the baseline for comparison to the crossover data from the ASA ingestion.	NR	Psychophysical testing Modest dosage of aspirin can cause a decrease in frequency selectivity, which may affect one's ability to understand speech in noise. Some subject overlap with reference 72.
McFadden, Plattsmier, Pasanen, 1984 [75]	Prospective Crossover Study (n=11)	11 males, 19-23 years old with normal hearing	ASA 3.9g daily x4d All sessions with intensity necessary for 10 minutes 2500 Hz tone to produce ~12 dB of TTS	>5 dB shift in audiometric thresholds, as measured by a two-interval forced choice method	4 days	ASA with exposure to intense noise produced HL ~10-15 dB greater than that produced by exposure to the intense sound alone.	Subjects were compared to their own baseline and to their own performance in other drug regimens	2.8 minutes	Moderate doses of ASA may increase risk of hearing loss.

Bonding, 1979 [24]	Prospective Cohort (n=21)	4 males, 12 females Age 16-29 years with normal hearing Control: 5 normal hearing subjects	ASA 4g every 24 h	Control Audiometry and CB estimations using loudness summation	Audiometric testing was performed 2-3 weeks after HL developed	15-40 dB HL at 1k Hz 56% (9/16) had a wider CB with temporary ASA induced HL	Subjects compared to their own baseline	Effect present after 2-3 d of treatment	Reversible
McFadden, Plattsmier, Pasanen, 1984 [46]	Prospective Cohort (n=5)	5 males, college age, hearing thresholds were within 15 dB HL from 250-8000 Hz at the outset	ASA 3.9 g/d, mg q6h for 5 days	Forward masking and gap detection were compared to individual "baseline" findings	~21 hrs, ~45 hrs, ~69 hrs, ~93 hrs, and ~117 hrs after the first dose	In 3 psychophysical tasks, subjects taking a moderate dose of ASA perform differently from their own normal performance, similarly to the ways normal and SNHL listeners differ on these tasks.	Subjects were compared to their own baseline	1-3 days	Psychophysical: Performance in forward-masking, temporal-integration, and gap-detection tasks

Impact of ASA on Psychophysical Measurements

Five prospective studies assessed the impact of ASA on psychophysical measurements, all of which suggested an adverse effect on hearing. A prospective, double-blind crossover study evaluated healthy adult male volunteers (n=9) after either 3.84g/d ASA or placebo for 3 days (washout 1 week).[49] The impact of ASA on psychophysical tuning curves (PTC) was assessed by comparing differences in variation of the signal level rather than the masker level and broadband versus narrowband maskers, using a forced-choice adaptive procedure with a 2 dB step size. ASA elevated the peaks and significantly reduced the slopes of PTCs ($p<0.01$), thus

indicating an ASA-induced reduction in frequency selectivity. A second small placebo-controlled double-blinded crossover study evaluated the impact of the same dose of ASA on otologically normal male adults' (n=8) auditory filter shapes in notched-noise forward masking (obtained by adaptively varying the signal level).[48] ASA resulted in a broadened auditory filter shape. Both of these studies suggest that 3.84g/d of ASA may cause a decrease in frequency selectivity, which may impair the perception of speech against background noise. Additionally, 3 small, prospective studies without placebo controls also demonstrated an adverse effect of ASA on psychophysical results when administered at a dose of 3.9-6.8g/d.[24,47,36]

Psychophysical or psychoacoustic testing is a subjective measurement of how a person perceives differences in a physical sound stimulus. For example, insufficiencies in auditory processing may be due problems with the natural compression found in the cochlea. The normal auditory system is compressive; while an impaired auditory system is non-compressive.[82] Psychophysical testing may not be as reliable as standard audiometry due to its intrinsic subjectivity; this testing also relies on the subject's ability to provide full attention to the task given and subjectively judge the correct forced-choice response.

Table Abbreviations
ASA: acetylsalicylic acid (aspirin)
BCDSP: Boston Collaborative Drug Surveillance Program
BMI: body mass index
BPD: bronchopulmonary dysplasia
BSL: blood serum level
CAPD: continuous ambulatory peritoneal dialysis
CB: critical band
Cf: center frequency
CI: cochlear implant
CVD: cardiovascular disease
D: days
DFMO: difluoromethylornithine
DPOAE: distortion product otoacoustic emissions
EDP: evoked distortion product
ESRD: end stage renal disease
GI: gastrointestinal
H: hours
HL: hearing loss
HR: Hazard ratios using Cox proportional hazards regression models
HTL: hearing threshold levels
HTN: hypertension
Hx: history
IV: intravenously
NICU: neonatal intensive care unit
NR: not recorded
PAN: Polyarteritis Nodosa
Pt: patient
PT: pure tone
PTA: pure-tone average
RA: rheumatoid arthritis
ROP: retinopathy
RR: relative risk
SDS: speech discrimination scores
SNR: signal to noise ratio
SOAE: spontaneous otoacoustic emission
SRT: speech reception threshold
TEOAE: Transient evoked otoacoustic emissions
W: weeks
Y= years

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