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MEMO

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RE: Technical Review – Colloidal Silver and Silver Nanoparticles

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Purpose:

The purpose of this memo is to evaluate the toxicological risk associated with the use of colloidal silver nanoparticles in the Young Dental ClearDefense Silver Fluoride Varnish. This report provides a thorough review of the current scientific understanding of silver toxicity associated with colloidal silver and silver nanoparticles (AgNPs) and provides a comparison to the widely used commercially available 38% Silver Diamine Fluoride (SDF).

Background:

Young Dental's ClearDefense Silver Fluoride Varnish is a formulation of chitosan, colloidal silver/silver cation mixture, sodium fluoride, and acetic acid intended for the treatment of dental hypersensitivity. ClearDefense is provided in an 8mL opaque dropper for a dosage of 0.05mL per drop. ClearDefense is used to treat up to 8 sites per patient by dispensing 1-2 drops of ClearDefense solution into a disposable dappen dish and then transferring the solution directly to the affected tooth surface using a small brush applicator. The solution it then allowed to air dry. If needed, a second application may be administered after 1 week.

ClearDefense is intended to only contact the affected tooth. Instructions are provided within the ClearDefense IFU to isolate the affected area with cotton rolls and protect the gingival tissue of the affected tooth with petroleum jelly (or similar) to avoid contact with surrounding tissues. Thus, the only expected contact is with the dentin of the affected tooth or teeth.

Due to increased regulatory scrutiny on the use of colloidal silver nanoparticles and the potential for increased toxicity, Young Dental has requested a through review of the available toxicological literature on silver toxicity associated with colloidal silver and silver nanoparticles. Further a comparison of the toxicological risk between the ClearDefense and 38% SDF has been requested.

Toxicokinetics (ADME):

Absorption

Repeated-dose oral studies indicate low fractional absorption of AgNPs, with dose-dependent but overall small increases in systemic silver; absorption increases with smaller particles and with higher released-ion fractions. In a 13-week study (Sprague–Dawley rats) with citrate-capped AgNPs (10, 75, 110 nm; 9–36 mg/kg/day) versus silver acetate (100–400 mg/kg/day), tissue silver increased with dose and was higher in females, but overt systemic toxicity was absent in AgNP groups; ion controls accumulated differently (favoring extracellular membranes)[1].

In a 28-day oral study, high-dose AgNPs were recovered widely with liver/spleen predominance[2].

Intact human skin shows minimal penetration; damaged/compromised skin increases entry. Human/porcine *in vitro* models consistently report low but detectable dermal passage under certain conditions; clinical burn-dressing studies confirm measurable serum silver with large wound areas, without clear systemic toxicity[3, 4].

Nano-aerosol deposition occurs throughout the respiratory tract with subsequent mucociliary clearance to GI and some translocation to secondary organs. After short intratracheal/inhalation exposures to radiolabeled or characterized AgNPs, silver is retained in lung with gradual redistribution and biotransformation over weeks[5].

Distribution

Following oral AgNPs (or Ag^+), silver distributes mainly to liver and spleen, with measurable levels in kidney and GI tissues; ultrastructurally, AgNP granules are found intracytoplasmically (macrophages, hepatocytes), whereas ionic silver yields deposits along membranes[1].

Biodistribution studies corroborate liver/spleen predominance and show persistence with slow decline post-exposure[2].

Metabolism

Silver does not undergo enzymatic metabolism; rather, AgNPs undergo oxidative dissolution to Ag^+ which then binds proteins and anions (Cl^-, S/Se donors), forming insoluble, low-solubility species (e.g., Ag_2S/Ag_2Se) that drive long tissue half-lives and the grayscale chromophore of argyria/argyrosis. Human tissue from argyria demonstrates electron-dense silver as selenide/sulfide granules in basal membranes and dermis[6].

In lungs and other tissues, synchrotron and XAS studies show progressive transformation of AgNPs toward sulfide-like phases[7].

Excretion

Elimination is primarily fecal (biliary), with slow urinary clearance; whole-body silver burdens decay over weeks to months, consistent with tissue sequestering as Ag_2S/Ag_2Se. Clinical follow-up of burn patients treated with nanocrystalline dressings shows serum silver peaks around ~1–2 weeks and slow reduction over months[4].

Acute Toxicity:

Acute oral LD_{50} values for Silver salts in mice are reported to be in the range 50-100 mg/kg bw[8, 9]. Acute oral LD_{50} values in the mouse of 100 mg/kg bw for colloidal Silver and 129 mg/kg bw for Silver nitrate; and acute oral LD_{50} values in the rat of 125 mg/kg bw for Silver cyanide and >2820 mg/kg bw for the insoluble Silver oxide are also reported[8, 9]. The US EPA stated that sufficient data are available to conclude that the acute toxicity of Silver is relatively low[10]. A guideline- and GLP-compliant study of acute oral toxicity performed in the rat with nanoSilver reports an LD_{50} value of >2000 mg/kg bw; no mortality or signs of toxicity were observed at the limit dose in this study[8]. The

LD_{50} of silver nitrate in rat is ~1,173 mg/kg, with corrosive GI effects while lower LD_{50} values are reported in small mammals[8, 9].

Short-term nano-aerosol exposures can elicit pulmonary irritation/inflammation at sufficiently high concentrations and acutely lethal concentrations for metallic silver powder are high (4-h LC_{50} > 5 mg/L in rats)[11].

Intravenous bolus AgNPs in rodents can perturb endothelial junctions and provoke multi-organ effects at high doses via ROS-related mechanisms although this route of administration is not typical for medical devices especially the ClearDefense Silver Fluoride[12].

Irritation:

Metallic silver is not classified for skin/eye irritation under EU CLP; by contrast, silver nitrate is corrosive and causes severe eye damage[8]. Occupational hygiene cards similarly flag irritation potential for silver dust (mechanical/particulate) but focus hazard management on soluble Ag compounds[13].

Sensitization:

Across regulatory reviews, silver metal is not considered a skin sensitizer; the EU RAC concluded no evidence justifying classification, and the SCCS adopted this conclusion in its final opinion on micronized silver in cosmetics[8, 14]. Rare case reports document allergic contact dermatitis to silver nitrate, and patch-testing series in specific patient groups (e.g., venous leg ulcers) show small percentages reacting to $AgNO_3$, likely reflecting the reactivity of the salt rather than Ag[15, 16]

Repeat-dose Toxicity:

Across multiple 28-day oral studies in rats, repeated daily gavage of well-characterized AgNP dispersions produced a clear, dose-related increase in total silver burdens in reticuloendothelial organs, most consistently liver and spleen, without commensurate systemic toxicity. Typical designs used parallel male and female cohorts, daily dosing over 4 weeks, and standard toxicology endpoints (clinical observations, body weight/food use, hematology/clinical chemistry, gross and histopathology), often with terminal tissue silver quantification by ICP-MS and, in some cases, electron microscopy of target organs. While microscopic evaluation sometimes noted pigment-laden Kupffer cells or minimal hepatocellular changes at higher doses, studies generally did not find consistent, adverse shifts in serum chemistries or organ weights at the concentrations tested. When ionic silver comparators (e.g., silver nitrate/acetate) were included, tissue patterns and effect magnitudes reinforced a central role for released Ag^+, that is, particle exposures behaved largely as a delivery system for ionic silver, with the extent of dissolution governing internal dose and response over this time frame[8, 9, 17].

In a pivotal 13-week gavage study, Boudreau and colleagues administered citrate-capped AgNPs of three nominal sizes (10, 75, and 110 nm) at 9, 18, or 36 mg/kg/day to Sprague–Dawley rats, alongside silver acetate controls at 100, 200, or 400 mg/kg/day (vehicle and water controls included). The study incorporated comprehensive clinical observations; body-weight and food-use tracking; hematology and serum chemistry; urinalysis when indicated; and full necropsy with histopathology across a standard organ set. Kinetic/locational data were developed with ICP-MS (tissue silver concentrations) and TEM ultrastructure to distinguish particle-like aggregates from

membrane-associated deposits typical of ionic silver. A bone-marrow micronucleus assay and reproductive-organ evaluations were also included. Results showed no treatment-related changes in clinical pathology, organ weights, or histopathology in any AgNP group, and no elevation in *in vivo* genotoxicity endpoints. Tissue silver increased with dose, with some sex-dependent differences (often higher in females), and TEM distinguished intracellular particulate-like deposits after AgNP dosing from more extracellular/membranous localization after silver acetate. On this basis, a NOAEL ≥ 36 mg/kg/day was supported for the AgNP preparations tested under these conditions, whereas the ionic silver groups primarily informed kinetics and distribution rather than a lower adversity threshold over 13 weeks[1].

A widely cited GLP-like subchronic inhalation study exposed rats to well-characterized AgNP aerosols in whole-body chambers at multiple concentrations for 90 days, with routine clinical checks, body-weight tracking, bronchoalveolar lavage (BAL) markers of irritation/inflammation, organ weights, and full histopathology (lung and liver emphasized). Characterization typically included aerosol mass/number concentrations, mobility diameter, and stability, with periodic chamber verification. The investigators identified a NOAEL of 100 µg/m³, based on the absence of adverse respiratory or systemic findings at this concentration and only minimal, adaptive changes (e.g., limited macrophage responses or subtle liver effects) at higher concentrations; where examined, partial or complete reversibility was noted in post-exposure recovery groups. This study underpins several authoritative occupational evaluations of nanosilver[11, 18].

Consistent with the studies above and subsequent analytical follow-ups, silver burdens in tissues often show sex-related differences (with females sometimes accumulating more in liver or spleen), and deposited silver gradually transforms *in vivo* toward sulfide/selenide species. Spectroscopy and ultrastructural work (e.g., synchrotron XAS and TEM in follow-on publications from ACS venues) support this biotransformation paradigm, which both reduces free Ag^+ activity over time and prolongs residence in the reticuloendothelial system, explaining slow elimination half-times observed after cessation of exposure[1, 7].

Genotoxicity:

Across the available literature, *in vitro* assays frequently report DNA damage from silver nanoparticles (AgNPs), with effects modulated by particle size, surface chemistry, and the extent of Ag^+ release. AshaRani et al. evaluated starch-coated AgNPs in normal human lung fibroblasts (IMR-90) and U251 glioblastoma cells and observed dose-dependent cytotoxicity, reactive oxygen species (ROS) generation, mitochondrial dysfunction, γ-H2AX foci, and chromosomal condensation consistent with clastogenic and aneugenic damage; silver nitrate ($AgNO_3$) produced overlapping patterns at lower mass doses, supporting a prominent role for ionic silver (typical test range: 1–100 µg/mL; exposure 24–72 h). Foldbjerg et al. tested well-characterized PVP-coated AgNPs and Ag^+ in A549 alveolar epithelial cells and reported concentration-related ROS generation, apoptosis/necrosis, and DNA strand breaks (alkaline comet), with partial mitigation by N-acetylcysteine; TEM confirmed cellular uptake of intact particles. These and many similar studies converge on an oxidative-stress-led mode of action with contributions from Ag^+ release and, at higher concentrations, direct microtubule/mitotic interference[19, 20].

Comprehensive reviews reinforce this pattern. A systematic mapping of 43 standard genotoxicity papers (mouse lymphoma assay, *in vitro* micronucleus, comet; plus *in vivo* micronucleus, chromosome aberrations, comet) concluded that positive results are common *in vitro* at cytotoxic or near-cytotoxic ranges, whereas *in vivo* findings are mixed and trend negative when

guideline-compliant designs and appropriate tissue sampling are employed. The authors emphasized incomplete test batteries and limited OECD-compliant studies as key uncertainties[21].

In vivo genotoxicity is better informed by several oral and inhalation studies that collectively temper the *in vitro* signal. In a GLP-like 13-week oral gavage study in rats as discussed above, Boudreau et al. dosed citrate-capped AgNPs (10, 75, 110 nm) at 9, 18, or 36 mg/kg/day and ran a bone-marrow micronucleus (OECD TG 474-like) at termination: no treatment-related increase in micronucleated erythrocytes was detected; target-tissue TEM/ICP-MS confirmed silver burdens and particle-specific ultrastructures, indicating adequate systemic exposure. A silver acetate arm (100–400 mg/kg/day) provided an ionic comparator[1].

In a separate 28-day oral rat study explicitly titled to include genotoxicity, Kim et al. gavaged 60-nm AgNPs (up to 1,000 mg/kg/day) and reported negative bone-marrow micronucleus outcomes alongside size- and sex-dependent tissue burdens; investigators attributed mild histopathology chiefly to accumulated silver and slow transformation to sulfides/selenides, not to primary DNA reactivity[22].

High-dose, short-term studies sometimes do report positives. Patlolla et al. administered 10-nm AgNPs orally to Sprague-Dawley rats for 5 days (5, 25, 50, 100 mg/kg/day), sampling bone marrow 24 h post-last dose. They observed increased ROS, structural chromosomal aberrations, elevated micronucleus frequency, and comet-assay DNA migration, along with a decreased mitotic index, effects concentrated at 50–100 mg/kg/day, and discussed oxidative stress as the proximate driver. Notably, particle characterization was limited and dosing produced supraphysiologic exposures relative to most device scenarios[23].

Adding formal guideline context, Narciso et al. conducted an OECD TG 489 *in vivo* alkaline comet assay in mice after three consecutive days of oral dosing with 20-nm AgNPs at 50, 150, or 300 mg/kg/day, with comet endpoints in blood, liver, spleen, kidney, and duodenum; an ancillary micronucleus assessment in spleen lymphocytes was also performed. No genotoxic effects were found across tissues; TEM and ICP-MS demonstrated biodistribution and intracellular localization (cytoplasmic and organellar) without nuclear localization[24]. A subsequent integrative 28-day study of a silver-kaolin formulation combined TG 474 (bone-marrow micronucleus) and TG 489 (comet) and likewise reported no induction of micronuclei or DNA strand breaks up to 2,000 mg/kg/day, with silver measured in all target organs to confirm exposure[25].

Regulatory assessments reflect these data. EFSA's 2016 re-evaluation of elemental silver (E 174) judged the *in vivo* oral genotoxicity database inconclusive, largely due to limited characterization and deviations from current test guidance[26]; EFSA's 2025 follow-up again concluded that submitted genotoxicity datasets were insufficient for a definitive hazard conclusion and called for nanospecific, guideline-compliant testing with robust particle characterization and Ag^+ release data[27]. NIOSH's 2021 CIB-70 review for occupational nanosilver summarized the mixed genotoxic evidence (positive *in vitro*; limited/mostly negative *in vivo*) and did not identify a consistent *in vivo* mutagenic signal at subchronic exposure levels relevant to workplaces[28].

The preponderance of *in vitro* positives (comet, micronucleus, mouse lymphoma) at concentrations that also elicit oxidative stress, combined with largely negative or equivocal *in vivo* results in guideline-based designs with demonstrated tissue exposure, supports a non-DNA-reactive, threshold-like mode of action dominated by ROS and secondary processes (e.g., inflammation, Ag^+-mediated protein/DNA interactions). Well-designed TG 474/TG 489 studies (including formulations

releasing Ag^{+}) have not shown reproducible *in vivo* genotoxicity at doses that maximize systemic exposure while avoiding frank toxicity[21, 24].

Carcinogenicity:

There are no standard two-year rodent carcinogenicity bioassays for metallic nanosilver, and no epidemiology directly linking silver or AgNP exposure to cancer. The most informative repeated-exposure studies are subchronic inhalation and oral studies designed for systemic toxicity that incidentally note proliferative changes but do not report neoplasia. In the whole-body, 90-day inhalation study in Sprague-Dawley rats exposed to 18–19 nm AgNP aerosols (49, 133, 515 µg/m³; 6 h/day, 5 days/week) discussed above, Sung et al. observed dose-related chronic alveolar inflammation, small granulomatous lesions, and bile-duct hyperplasia without tumors; the authors proposed a NOAEL of ~100 µg/m³ for subchronic effects, pointing to lungs and liver as targets. These lesions are consistent with a non-neoplastic adaptive/proliferative response to persistent particulate burden, not direct carcinogenicity[11].

Regulatory bodies reviewing broader silver datasets (including salts and silver-releasing matrices) have not identified a carcinogenic hazard for metallic silver. The EU SCCS (2023) reviewed silver-zinc zeolite and, citing ECHA CLH (2022) and earlier SCCS opinions, stated that silver is not carcinogenic and that chronic toxicity/carcinogenicity classification was not warranted for the zeolite material; this conclusion is based on long-term toxicology without tumor findings and on weight-of-evidence considerations for metallic silver[8, 14, 29]. EFSA's assessments for E 174 (2016; 2025 follow-up) likewise found no carcinogenic studies suitable for risk assessment and could not conclude on safety due to data gaps, not because of positive carcinogenic findings; they called for nanospecific testing rather than inferring carcinogenicity[26, 27]. NIOSH's CIB-70 (2021) reviewing occupational nanosilver exposure identified subchronic lung and liver effects in rats but did not implicate a carcinogenic hazard in humans[28].

The absence of tumor data from chronic bioassays for AgNPs, combined with lack of a consistent *in vivo* genotoxic signal and regulatory reviews that do not classify metallic silver as carcinogenic, supports a conclusion that carcinogenic potential of AgNPs remains unsubstantiated at present. Proliferative changes reported in subchronic studies (e.g., bile-duct hyperplasia) are interpreted as adaptive/secondary to persistent particulate or ionic burdens and chronic low-grade inflammation, not as neoplastic precursors in the absence of tumor progression in longer studies. Data gaps remain (notably: a definitive two-year bioassay with well-characterized AgNPs and dissolution), but current evidence does not demonstrate carcinogenicity for nanosilver[11, 21].

Reproductive Toxicity:

In the 13-week oral study discussed above, Boudreau et al. dosed Sprague–Dawley rats with citrate-capped AgNPs (10, 75, 110 nm; 9, 18, 36 mg/kg/day) or silver acetate (100, 200, 400 mg/kg/day). The design incorporated standard systemic toxicology plus reproductive organ histology, estrous cyclicity, and bone-marrow micronucleus. AgNP groups showed no adverse, treatment-related changes in reproductive endpoints at any size/dose; tissue silver burdens (ICP-MS) and ultrastructural findings (TEM) confirmed exposure[1].

Several rodent studies report testicular changes and sperm parameter decrements after relatively high AgNP exposures (often parenteral or high-dose oral), with oxidative stress and endocrine perturbations as plausible mediators. Representative findings include reduced testes/epididymis weights, decreased testosterone/estradiol, increased lipid peroxidation, and

abnormal sperm morphology, typically at mg/kg-level doses that exceed subchronic oral NOAELs[30-32]. Reviews of male reproductive endpoints concur that testes can accumulate silver and that effects concentrate at high or non-oral dosing with limited characterization, warranting careful weight-of-evidence interpretation for human relevance[33].

NIOSH's occupational review (CIB-70) summarized the available reproductive data as limited and did not identify a consistent fertility hazard at subchronic exposure levels relevant to workplaces[28]; EFSA's E 174 opinions (2016; 2025 follow-up) judged the reproductive data insufficient for definitive conclusions, citing limits in characterization and nanospecific test designs[26, 27].

Developmental Toxicity:

A frequently cited gestational oral study concluded that AgNPs up to ~20 mg/kg/day did not produce classical embryo-fetal toxicity in rats, while ionic silver produced greater toxicity and higher fetal silver levels for comparable total-Ag dosing; again implicating Ag^+ as the active moiety with AgNPs functioning as a source/sink that modulates delivery[34]. Other oral studies at higher doses report minimal maternal effects (e.g., hepatic oxidative stress) with no fetal structural malformations up to ~1000 mg/kg/day, though maternal NOAELs can be lower (< 100 mg/kg/day) based on liver endpoints; findings that hinge on study design and route[35].

Several mouse/rat studies using intraperitoneal or inhalation exposure report placental/fetal silver and, at sufficient exposure, increased resorptions, reduced placental size, or fetal growth effects. For example, gestational AgNP exposure in mice has been linked to reduced maternal and placental weights with higher resorption counts, and to offspring pulmonary developmental changes after maternal inhalation; however, these studies often lack full OECD guideline structure, use very high or bolus doses, or show limited particle characterization[36, 37]. A 2019–2020 line of mouse work similarly reported adverse fetal outcomes at ~1 mg/kg/day via injection, with histomorphologic changes and apoptotic markers in fetal tissues; translation to human risk is constrained by route and exposure intensity differences[38].

Robust evidence shows maternal-to-fetal transfer of silver during gestation. In rats, oral or injected AgNPs led to detectable silver in fetuses (kidney, liver, lung, brain) by ICP-MS and TEM, consistent with placental crossing[39]. Importantly, an *ex vivo* human placenta perfusion study using well-characterized AgNPs (PEG- and carboxylate-modified) demonstrated low but measurable Ag translocation to the fetal side. The authors carefully dissected ionic vs particulate contributions using spICP-MS and $AgNO_3$ controls and concluded that both translocation of particles and dissolution/re-precipitation pathways must be considered; overall Ag transfer fractions were low (≈0.015–0.062%), albeit with substantial placental tissue accumulation relative to translocated amounts[40].

Ema et al. (2017) summarized mammalian studies as showing developmental effects mainly under conditions of high exposure or non-oral routes, with ionic silver generally more potent; the review called for guideline-conformant prenatal studies with rigorous particle/Ag^+ characterization. More recent narrative/systematic reviews echo species/route sensitivity, document fetal/placental silver, and emphasize the centrality of Ag^+-driven oxidative stress as the plausible mode of action[41, 42].

Silver Nanoparticles and the Blood Brain Barrier:

Across *in vitro*, *ex vivo*, and *in vivo* studies, AgNPs can interact with, and under some conditions traverse, the blood brain barrier (BBB) via two principal routes: (i) hematogenous access across brain microvascular endothelium and (ii) nose-to-brain transport along olfactory/trigeminal pathways after inhalation or intranasal exposure. In brain endothelial models, AgNPs disrupt tight-junction integrity and increase paracellular permeability through pro-inflammatory signaling (e.g., cytokine/NO induction, MAPK activation), with permeability and cytotoxicity scaling with particle size, coating, and Ag^+ release; co-culture Transwell systems and proteomic studies report barrier weakening, altered transporter expression, and oxidative stress, consistent with a non–DNA-reactive, ROS-dominated mechanism [43-45].

In *in vivo* rodent studies, intranasal or inhalation exposures produce olfactory bulb deposition and microglial activation, supporting a direct nose-to-brain pathway. For example, size-dependent deposition and microglial responses have been documented in the nasal epithelium/olfactory bulb, and intranasal dosing has yielded brain silver with associated oxidative-stress gene responses and hippocampal markers at high bolus doses (tens–hundreds of mg/kg)[46-48]. By contrast, some carefully controlled studies indicate limited overall brain biodistribution after intranasal AgNPs, highlighting that quantitative brain burdens depend strongly on dose, particle chemistry, and exposure regimen[49].

Hematogenous BBB passage appears possible but constrained: advanced *in vitro*/organ-on-chip and perfusion approaches show low fractional translocation of metallic nanoparticles, and recent work implicates biotransformation (e.g., sulfidation/oxidation) in reducing BBB penetration over time, again pointing to the central role of Ag^+ availability and nanoparticle transformation state in determining brain access[50, 51].

Newer inhalation studies with silver-silicate nanostructures similarly report olfactory bulb microglial activation and support nose-to-brain transport, while calling for longer-term, dose-realistic experiments to define persistence and health relevance. Overall, the weight of evidence is that AgNPs can reach brain tissues under high-intensity or direct-nasal exposures, with effects mediated largely by barrier perturbation and oxidative stress, whereas routine/low-level exposures yield low translocation fractions and uncertain clinical significance[52].

Silver, Colloidal Silver, and Silver Nanoparticles in Dental Applications:

In contemporary dentistry, silver is used most robustly as silver diamine fluoride (SDF, 38%) to arrest active caries, leveraging silver's antibacterial activity and fluoride-driven remineralization, with accumulating clinical evidence across children and school-based programs[53, 54]. A large network meta-analysis of nonrestorative treatments ranks SDF among the most effective options for arresting dentin lesions, and recent randomized trials in public health settings show SDF-based protocols performing on par with (or complementing) conventional sealant/varnish strategies for caries control. Professional guidance reflects this: the ADA notes SDF's off-label use for caries arrest (approved in the U.S. for hypersensitivity) and its chief trade-off, permanent black staining of treated lesions, while the AAPD provides chairside guidance for pediatric care[55, 56]. Pharmacokinetic data in healthy adults indicate very low systemic silver after topical SDF, with no SDF-attributed adverse events in that study, supporting a wide therapeutic window when used as directed[57].

Beyond SDF, silver nanoparticles (AgNPs) are under active study as antimicrobial modifiers in dental materials (e.g., resins, adhesives, glass-ionomers, liners, provisional cements), as endodontic irrigants or sealers, and as surface coatings for orthodontic appliances and implants to

suppress biofilms[58, 59]. *In vitro* and *ex vivo* work consistently shows broad antibacterial effects against cariogenic and endodontic pathogens; early translational studies suggest AgNP-containing irrigants can reduce microbial counts, though performance depends on particle size, coating, concentration, and contact time, and materials trade-offs (e.g., dentin microhardness) are possible[60-62].

Silver Nanoparticles in the Context of Young Dental's ClearDefense:

ClearDefense is formulated as a chitosan-based colloidal silver/silver-cation mixture with sodium fluoride and acetic acid, delivered topically to isolated dentin using cotton-roll isolation and gingival protection; a typical application uses 1–2 drops (0.05 mL/drop) into a dappen dish to treat up to eight discrete sites, then air-dries on the tooth surface. The Instructions for Use (IFU) are designed to avoid gingival or mucosal contact and to minimize ingestion, with an optional second application no sooner than one week later. This route of exposure (localized dentin contact; minimal oral ingestion; no inhalation or parenteral exposure) is fundamentally different from the high-burden experimental scenarios that dominate the hazard literature (e.g., whole-body inhalation, intranasal bolus, or high-dose oral gavage) and should frame the risk associated with the use of the product.

Human and animal kinetics indicate that fractional absorption of AgNPs by the oral route is low, with tissue silver primarily sequestering in liver/spleen and then slowly transforming to sulfide/selenide complexes that reduce ionic activity over time (i.e., a persistence phenomenon, not an escalating internal dose)[2, 6]. In a pivotal 13-week oral study, citrate-capped AgNPs at 9–36 mg/kg/day produced no adverse clinical pathology or histopathology and a NOAEL ≥ 36 mg/kg/day, despite confirmed deposition[1]. By comparison, clinical pharmacokinetics for 38% silver diamine fluoride (SDF), a higher-silver, widely used dental agent, show very low systemic silver after topical application (adult Cmax ≈ 0.67 ng/mL, t½ ≈ 46 h) with no SDF-attributed adverse events[57]. These data situate the order of magnitude of systemic silver expected from appropriately used dental topicals, i.e., ng/mL-range, if detectable at all, far below doses that have produced organ toxicity in animals or clinical sequelae in burn patients with massive wound areas[4]. Collectively, the route, dose, and kinetics relevant to ClearDefense point to minimal systemic exposure and large margins to subchronic NOAELs[1, 26, 28].

Subacute/subchronic oral studies with AgNPs consistently show silver accumulation without adverse systemic toxicity at doses multiple orders above realistic dental exposures[1, 2]. While *in vitro* genotoxicity assays often return positives at cytotoxic concentrations driven by oxidative stress and Ag^+ [19, 20], *in vivo* guideline tests (TG 474/TG 489) are largely negative when adequate tissue exposure is demonstrated[22, 24, 25]. No two-year bioassay demonstrates carcinogenicity for metallic/nano-silver, and major authorities do not classify metallic silver as carcinogenic; subchronic inhalation findings (e.g., minimal lung/liver changes at ≥133 µg/m³) are route-specific and not probative for topical dental use[8, 11, 26, 27]. These strands collectively support low systemic hazard at the very low exposures relevant to ClearDefense.

The BBB literature shows that AgNPs can perturb barrier integrity *in vitro* at high concentrations and can reach the olfactory bulb after intranasal/inhalation exposures in rodents; i.e., nose-to-brain transport under direct nasal delivery or aerosol conditions[44, 46, 48]. Several sophisticated models also suggest low fractional translocation across hematogenous BBB pathways, further decreasing as particles biotransform (e.g., sulfidation)[49-51]. None of these scenarios is representative of ClearDefense's intended use, which does not involve inhalation or intranasal deposition, and where any swallowed fraction is transient and tiny relative to experimental boluses. In humans, even intensive dental silver use (SDF) yields ng/mL serum levels[57]; orders of magnitude below the µg/mL-equivalent cellular exposures used to elicit BBB perturbation *in vitro* or the mg/kg intranasal doses

used to drive nose-to-brain transport *in vivo*[44, 46]. Accordingly, the plausible systemic silver concentrations from ClearDefense are far too low to produce BBB opening or meaningful brain deposition, and the risk of AgNP crossing the BBB from product use is not appreciable on route, dose, and kinetics grounds[49-51].

Metallic silver is not classified for skin/eye irritation, while silver nitrate is corrosive[8]. Regulatory committees conclude no evidence to classify metallic silver as a skin sensitizer, with rare allergic contact dermatitis tied to silver salts rather than Ag^0 [8, 14, 15]. The ClearDefense IFU further mitigates local exposure (gingival protection, site isolation), aligning practice with the low irritancy/sensitization profile expected for metallic/colloidal silver at dental doses, resulting in a negligible risk associated with local exposure.

Considering (i) the localized dental route with minimal ingestion, (ii) very low systemic silver observed clinically for more silver-rich dental agents (SDF), (iii) high oral NOAELs and largely negative *in vivo* genotoxicity, (iv) no demonstrated carcinogenicity for metallic/nano-silver, and (v) the route-mismatch and high-dose dependence of BBB findings, the weight of evidence supports a minimal toxicological risk associated with ClearDefense when used as directed[1, 26-28, 50, 51, 57].

Silver Ion Release of ClearDefense vs 38% SDF:

To further support the conclusions that the risk associated with the clinical use of ClearDefense is negligible, Young Dental performed an *in vitro* comparison of ion release from three dental varnishes over seven days: (i) Advantage Arrest® 38% silver diamine fluoride (25% silver wt/wt), (ii) Silver Fluoride Hypersensitivity Varnish with 1,000 ppm Ag, and (iii) Silver Fluoride Hypersensitivity Varnish with 2,000 ppm Ag (representing ClearDefense with 0.2% silver wt/wt)[63].

Acrylic rods (n=6 per group) were randomized to products, each coated with 0.0075 g varnish and cured overnight at room temperature, then sequentially immersed in fresh 2 mL aliquots of deionized water at predefined intervals up to 7 days; aliquots were refrigerated until analysis. Samples were prepared for ion-selective electrode (ISE) measurements and quantified after direct calibration with appropriate standards. Silver mV readings were converted to ppm and subjected to statistical evaluation using a general linear model ANOVA with Tukey's post-hoc tests at each time point[63].

Fluoride release was rapid for all products, with most F^- liberated within the first 15 minutes. At 15 minutes, mean free fluoride was 41,722 ppm for SDF vs 11,771 and 12,311 ppm for the 1,000-ppm-Ag and 2,000-ppm-Ag varnishes, respectively; SDF was significantly higher than both comparators at this time point. At 30 minutes, the same rank order persisted (411 vs 231 vs 265 ppm; SDF significantly higher). By 1 hour, releases were 11 (SDF) vs 51 (1,000-ppm-Ag) vs 126 ppm (2,000-ppm-Ag), and the two test varnishes significantly exceeded SDF at that later time point. These trends reflect an early burst from SDF followed by relatively greater sustained F^- from the test varnishes[63].

Silver release showed an even more pronounced early burst from SDF. At 15 minutes, mean free Ag^+ was ~152,535 ppm for SDF versus ~10,909 ppm (2,000-ppm-Ag) and ~333 ppm (1,000-ppm-Ag), corresponding to cumulative fractions of ~61% (SDF) and ~17% (2,000-ppm-Ag varnish) of the total formulation Ag^+ content; SDF again released significantly more Ag^+ than either subject varnish at early time points (e.g., 30 min: 2,458 vs 295 vs 173 ppm; 1 h: 1,066 vs 295 vs 135 ppm;

2 h: 607 vs 132 vs 127 ppm; 4 h: 453 vs 32 vs 44 ppm). Across 0.5–24 hours, statistics consistently favored higher Ag^+ release from SDF relative to both test varnishes[63].

Taken together, the GLP-like bench study indicates that all three varnishes release fluoride rapidly, with early maxima at 15–30 minutes, and that SDF releases substantially more silver at all early time points, consistent with its far greater Ag^+ content. The subject Silver Fluoride Hypersensitivity Varnish (2,000 ppm Ag) delivered lower absolute silver and fluoride to the medium but achieved high fractional release of fluoride and comparatively modest fractional release of silver; the SDF comparator showed the opposite pattern for Ag^+.

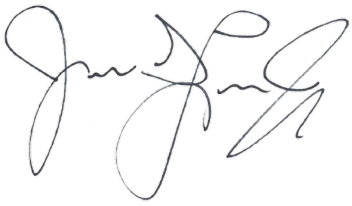
In practical patient terms, these bench data indicate very low silver exposure from Young's Silver Fluoride Hypersensitivity Varnish relative to 38% SDF. Across the early, clinically relevant window, the predicate SDF released orders of magnitude more free Ag^+ than Young Dental's Silver Fluoride Hypersensitivity Varnish, with statistical tests consistently favoring higher Ag^+ release from SDF at each time point examined. Thus, with the product's tooth-surface–only use instructions (isolation, gingival protection, tiny drop volumes), which are designed to minimize ingestion and mucosal contact, the markedly lower Ag^+ release supports a minimal toxicological risk to patients relative to SDF and a negligible likelihood of any systemic effect (including CNS-related concerns), given the small applied mass and absence of inhalation or intranasal exposure pathways.

Conclusion:

In conclusion, the weight of evidence supports a negligible toxicological risk for patients when Young Dental's ClearDefense Silver Fluoride Varnish is used as directed. The clinical route (localized application to isolated dentin with minimal ingestion and no inhalation) yields very low systemic silver exposure, and the broader toxicology literature shows high oral NOAELs for AgNPs, largely negative *in vivo* genotoxicity at relevant doses, and no demonstrated carcinogenicity for metallic/nano-silver. Human pharmacokinetics for higher-silver dental comparators (e.g., 38% SDF) show ng/mL-range systemic silver after topical use, underscoring the substantial margin between real-world dental exposures and doses associated with adverse effects in animals or rare clinical case reports. Critically, BBB concerns are not applicable to ClearDefense's exposure paradigm (no intranasal/aerosol route; transient, tiny swallowed fraction), and BBB perturbation reported in experimental systems occurs at orders-of-magnitude higher concentrations or by nose-to-brain pathways not engaged by varnish use. Overall, the integrated ADME, repeat-dose, genotoxicity, carcinogenicity, and human experience datasets converge on minimal systemic hazard for ClearDefense.

Relative to 38% SDF, ClearDefense presents a reduced toxicological risk. Bench testing demonstrates markedly lower silver-ion release from ClearDefense than from SDF across clinically relevant time points, consistent with ClearDefense's substantially lower silver content and tooth-surface-only use instructions that further limit patient exposure. At the same time, the formulation meets the fluoride-release expectations of relevant standards, supporting therapeutic intent without unnecessary silver load[64]. In aggregate, these performance and exposure characteristics, coupled with the conservative interpretation of contemporary silver toxicology, indicate that ClearDefense achieves its clinical purpose while minimizing patient silver exposure and maintaining a wider safety margin compared with 38% SDF.

Author:



James Lyons, PhD, MBA, DABT
Principal Consultant

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James S. Lyons, PhD, MBA, DABT

Professional Summary:

Board certified toxicologist and biocompatibility subject matter expert specializing in medical devices, with 10+ years of biomedical research/testing and medical device industry experience. Up-to-date knowledge of global medical device industry standards and regulations including FDA, EU MDR, Japanese PMDA and Korean MFDS. Professional, creative, and flexible with a proven history of leadership. Active member of multiple AAMI BE - Biological Evaluation Committee (U.S. TAG to ISO/TC 194) working groups and other professional organizations.

Relevant Professional Experience:

May 2021 – Current – **JL Tox Consulting, LLC, York, PA**

JL Tox Consulting, LLC is a provider of toxicology and medical device biocompatibility consulting services. We support all biocompatibility, toxicology, and chemistry projects, questions, or concerns. Provide industry leading experience in new product development, MDR and CAPA remediation, and lifecycle management including biocompatibility test plans, impact assessments, gap assessments, toxicological risk assessments, and biocompatibility evaluations.

Founder and Principal Consultant

Responsibilities

- Act as a technical expert in toxicology and biocompatibility
- Provide consulting to clients, including risk assessments, biological evaluation test plans (including chemical characterization), biological evaluation test summaries, and other expert opinion papers
- Maintain up-to-date understanding of medical device industry standards and regulations, including USP, AAMI/ANSI/ISO, BPOG, BPSA, ICH, PQRI, OECD Standards/Guidelines and global regulatory expectations

Achievements

- Guided numerous sponsors to successful regulatory submissions related to Biocompatibility and successful product launches with no delays or issues from Biocompatibility

September 2023 – May 2024 – **Abbott Medical Devices, Remote**

Abbott Laboratories is an American multinational medical devices and health care company with headquarters in Abbott Park, Illinois, United States. Abbott's core businesses focus on diagnostics, medical devices, branded generic medicines and nutritional products, which have been supplemented through acquisitions.

Global Director, Biocompatibility

Responsibilities

- Act as DRI of all global biocompatibility projects and regulatory submissions for Abbott Structural Heart, Abbott Neuromodulation, and Abbott Cardiac Rhythm Management business units.
- Act as a technical expert in toxicology and biocompatibility for medical device products across all Abbott medical device franchises
- Provide technical strategy and direction on risk assessments, biological evaluation test plans (including chemical characterization), biological evaluation test summaries, and other expert opinion papers
- Develop and deliver technical presentations for internal and external company seminars and training, webinars, etc.
- Maintain up-to-date understanding of medical device industry standards and regulations, including USP, AAMI/ANSI/ISO, BPOG, BPSA, ICH, PQRI, OECD Standards/Guidelines

Achievements

- Built a track record of successful regulatory submissions with minimal to no deficiencies and zero additional testing needed to address regulatory questions.
- Maintained no disruption to Abbott business as a result of Biocompatibility issues

- Successfully implemented cost savings efforts across Abbott franchises by means of reduced testing and reduced project delays due to Biocompatibility issues amounting to $4M+ annually

February 2021 – September 2023 – **Abbott Medical Devices, Remote**

Abbott Laboratories is an American multinational medical devices and health care company with headquarters in Abbott Park, Illinois, United States. Abbott's core businesses focus on diagnostics, medical devices, branded generic medicines and nutritional products, which have been supplemented through acquisitions.

Manager, Biocompatibility

Responsibilities

- Manage operation of biocompatibility and toxicological risk assessment teams
- Act as a technical expert in toxicology and biocompatibility for medical device products across medical device franchises
- Provide technical guidance on risk assessments, biological evaluation test plans (including chemical characterization), biological evaluation test summaries, and other expert opinion papers
- Develop and deliver technical presentations for internal and external company seminars and training, webinars, etc.
- Maintain up-to-date understanding of medical device industry standards and regulations, including USP, AAMI/ANSI/ISO, BPOG, BPSA, ICH, PQRI, OECD Standards/Guidelines

Achievements

- Successfully implemented internal toxicological risk assessment support
- Oversaw toxicology and biocompatibility section in several successful regulatory submissions globally

January 2019 – February 2021 – **Depuy Synthes, West Chester, PA**

Johnson & Johnson is an American multinational medical devices, pharmaceutical and consumer packaged goods manufacturing company founded in 1886. Its common stock is a component of the Dow Jones Industrial Average and the company is ranked No. 37 on the 2018 Fortune 500 list of the largest United States corporations by total revenue.

Contract Toxicologist, Toxicology and Biocompatibility

Responsibilities

- Acted as a technical expert in toxicology and biocompatibility for medical device products across medical device franchises
- Provided risk assessments, biological evaluation test plans (including chemical characterization), biological evaluation test summaries, and other expert opinion papers
- Developed and deliver technical presentations for internal and external company seminars and training, webinars, etc.
- Maintained up-to-date understanding of medical device industry standards and regulations, including USP, AAMI/ANSI/ISO, BPOG, BPSA, ICH, PQRI, OECD Standards/Guidelines

Achievements

- Provided toxicology and biocompatibility section in several successful regulatory submissions in the US and EU
- Successfully implemented harmonization of toxicology and biocompatibility procedures across DPS medical device franchises
- Successfully implemented remediation plan for new medical device regulations in the EU

May 2018 – December 2018 – **WuXi Apptec, WuXi Advanced Therapies, Philadelphia, PA**

WuXi Apptec is a leading global pharmaceutical and medical device open-access capability and technology platform with global operations. As an innovation-driven and customer-focused company, WuXi Apptec provides a broad and integrated portfolio of services throughout the drug R&D process.

Senior Toxicologist, Consulting Services

Responsibilities

- Acted as a technical expert in toxicology and biocompatibility for medical device, biologics,

and biopharma services
- Provided consulting to clients, including risk assessments, biological evaluation test plans (including chemical characterization), biological evaluation test summaries, and other expert opinion papers
- Developed and deliver technical presentations for internal and external company seminars and training, webinars, etc.
- Maintained up-to-date understanding of medical device industry standards and regulations, including USP, AAMI/ANSI/ISO, BPOG, BPSA, ICH, PQRI, OECD Standards/Guidelines

Achievements

- Grew toxicology service offerings for WuXi Apptec's Advanced Therapies Unit
- Successfully implemented a new marketing strategy for toxicology services that has led to securing multiple new projects and contracts

February 2017 – May 2018 – **Eurofins Medical Device Testing, Lancaster PA**

Eurofins is an analytical testing company which provides a full range testing services to the medical device and biopharmaceutical industries. Eurofins is made up of 16 laboratories across North America, Europe, and Asia-Pacific with over 18,000 employees worldwide.

Toxicologist, Biocompatibility SME

Responsibilities

- Performed toxicological risk assessments of medical devices
- Advised clients on chemical characterization and biocompatibility testing needs, including cytotox., sensitization, irritation, acute/sub-chronic tox, hemocompatibility, genotox, etc.
- Developed and established new biocompatibility testing according to emerging standards
- Maintained up-to-date understanding of medical device industry standards and regulations, including AAMI/ANSI/ISO, ICH, PQRI, OECD Standards/Guidelines
- Advised clients on 510(k) and PMA submissions including interacting directly with the FDA for pre submission meetings and Day-100 meetings
- Wrote and published articles and presented at local and international conferences

Achievements

- Established and grew Eurofins toxicology and biocompatibility presence in North America by establishing internal toxicological risk assessment procedures and policies, presenting and promoting company brand and services, working directly with clients and regulatory bodies to build and establish a presence within the industry in North America.
- Advised and guided multiple clients towards successful regulatory submissions by recommending the appropriate biological evaluation plan for their specific situation, advising them on the best path for their regulatory submission, completing toxicological risk assessments on their products, and working directly with the FDA when questions arise
- Lead the successful implementation of biocompatibility of breathing gas pathway testing services

July 2014 – September 2017 – **University of Maryland School of Medicine, Baltimore MD**

Graduate Research Assistant

Responsibilities

- Designed, planned, and executed scientific experiments related to skeletal physiology utilizing *in vitro* techniques and *in vivo* models to evaluate the skeletal response to mechanical forces.
- Analyzed scientific data and performed statistical analyses
- Assisted in management of grant budgets
- Presented work at local and international scientific conferences
- Wrote and published peer reviewed manuscripts

Achievements

- Assisted in securing ~$1.3 mil in grant funding from different government and private agencies including the NIH
- Secured an international patent on a device used for research purposes
- Secured an international patent on therapeutic intervention to treat osteoporosis
- Received several research awards

- Completed Good Laboratory Practice (GLP) certification
- Completed Responsible Conduct of Research certification

June 2016 – December 2016 – **Aptagen LLC, York PA**

Aptagen, LLC is a biotechnology company offering aptamer (synthetic antibody) products and services as research reagents, diagnostic and biomarker discovery tools, as well as for use in drug discovery and targeted delivery for therapeutics, and bioindustrial applications. Aptagen has 25 years of experience in developing aptamers (synthetic antibodies) for all types of downstream applications.

Operations and Lab Manager

Responsibilities

- Managed day to day operation of 7 employee Contract Service Organization
- Managed over 40 laboratory projects for a variety industry and private sector clients including big pharma, academic institutions, mid-level biotech companies, and start-ups
- Managed service subcontracts on outsourced lab work
- Managed project budgets
- Lead internal product design and development
- Wrote and submitted grant applications and other funding opportunities including NIH grants, DoD grants, and industry partnership/collaboration proposals.

Achievements

- Partnered in acquiring new projects amounting to ~$250,000 in revenue
- Lead the process to acquire ~$1.75mil Department of Defense grant
- Lead the successful completion of ~$150,000 in projects

Education:

MBA, University of North Carolina Kenan-Flagler School of Business, 2019
PhD, Molecular Physiology – University of Maryland School of Medicine, 2017
BS, Biotechnology – Harrisburg University of Science and Technology, 2013

Certifications:

Diplomat of the American Board of Toxicology, 2024