INPLASY PROTOCOL

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Protocol for a systematic review assessing the key characteristics of carcinogens for a ubiquitous herbicide and its formulations

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Review question / Objective: **The aim of this systematic review is to use the ten key characteristics of carcinogens (KCCs) to organize and assess the mechanistic evidence for glyphosate and glyphosate-based formulations (GBF) for the purposes of informing cancer hazard identification in risk assessment. To this end, the proposed systematic review will address the following question: Which of the ten KCCs are exhibited in humans and experimental animals that are exposed to glyphosate and GBF through in vivo, ex vivo, and in vitro systems?**
Condition being studied: **Consistent links to NHL among GBF-exposed humans coupled with the ubiquity of the exposure underlines the importance of understanding the mechanisms by which glyphosate and formulations can exert toxicity. Using systematic review to elucidate the glyphosate and GBF associated KCCs will guide our evaluation of the mechanistic data, identify data gaps, and even replace/assist in the development of modes of action (MoA)/adverse outcome pathways (AOPs).**

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 12 August 2021 and was last updated on 12 August 2021 (registration number INPLASY202180045).

INTRODUCTION

Review question / Objective: **The aim of this systematic review is to use the ten key characteristics of carcinogens (KCCs) to organize and assess the mechanistic evidence for glyphosate and glyphosate-based formulations (GBF) for the purposes of informing cancer hazard identification in risk assessment. To this end, the proposed systematic review will address the following question: Which of the ten KCCs are exhibited in humans and experimental animals that are exposed to glyphosate and**

GBF through in vivo, ex vivo, and in vitro systems?

Rationale: Virtually every human on the planet has been exposed to the herbicide glyphosate through its various formulations. Both the extent to which humans are exposed (Gillezeau et al. 2019) and the potential consequent health effects are not well characterized. Indeed, glyphosate's carcinogenic potential remains widely debated across multiple organizations. Although the association of glyphosate/GBF and non-Hodgkin lymphoma (NHL) has been identified in human studies, confirmed by a few meta-analyses (Zhang et al. 2019), and further supported by limited animal data, the key question of how glyphosate promotes carcinogenicity remains unclear. The human epidemiological and animal carcinogenicity data streams can be supported by a comprehensive evaluation of the mechanistic data using the KCC framework proposed by Smith et al. (2016). All human cancer-causing agents reflect one or more of the ten KCCs, which include whether the chemical 1) is electrophilic or can be metabolically activated, 2) is genotoxic, 3) alters DNA repair or causes genome instability, 4) induces epigenetic alterations, 5) promotes oxidative stress, 6) induces chronic inflammation, 7) is immunosuppressive, 8) modulates receptor mediated effects, 9) causes immortalization, and 10) alters cell proliferation, death, or nutrient supply. The KCC framework was adopted by the International Agency for Research on Cancer (IARC) Monographs Program, an intergovernmental agency tasked with identifying human carcinogens. IARC first applied the KCCs in Volume 112, where glyphosate was evaluated. IARC reported that there was strong evidence that glyphosate exhibits genotoxicity and oxidative stress [KCCs 2 and 5, respectively, (International Agency for Research on Cancer 2015)]. Since IARC's preliminary assessment in 2015, both the available new studies on glyphosate/GBF and the KCC landscape have substantially blossomed. Recent advancements in the KCC landscape have mapped out the specific toxicological and biomarker endpoints for each KCC, including example assays that can be used to guide systematic review evaluations (Smith et al. 2020). Similarly, our understanding of various KCCs has deepened through budding efforts to elucidate the properties of chemicals that potentiate non-cancer health endpoints. For example, the recent introduction of the KCs of endocrine disrupting chemicals [KCEDCs, (La Merrill et al. 2020)] and ongoing efforts to delineate KCs of immunotoxicants (KCIs) inherently informs our knowledge of KCs 8, 6, and 7, respectively. These new developments will power our search strategy to capture and systematically review all relevant and applicable studies, furthering our goal to conduct an up-to-date and detailed analysis that both integrates the evidence and addresses the gaps in the current understanding of glyphosate and GBF-related KCCs.

Condition being studied: Consistent links to NHL among GBF-exposed humans coupled with the ubiquity of the exposure underlines the importance of understanding the mechanisms by which glyphosate and formulations can exert toxicity. Using systematic review to elucidate the glyphosate and GBF associated KCCs will guide our evaluation of the mechanistic data, identify data gaps, and even replace/assist in the development of modes of action (MoA)/adverse outcome pathways (AOPs).

METHODS

Search strategy: Preliminary search terms: Glyphosate/GBH: (glyphosate[tw]/"glyphosate-based herb*"[tw]/"glyphosate-based formula*"[tw]/"glyphosate herb*"[tw]/"glyphosate form*"[tw]/"RoundUp"[tw]/"Ranger Pro"[tw]) KCC1: (adduct[tw]/adduct[tiab]/adduct*[tw]/adduct*[tiab]/electrophil*[tw]/electr*[tiab]/DNA Adduc*[tw]/"DNA Adducts"[tiab]/adduct-formation[tw]/"adduct-formation"[tiab]/metabolic activa*[tw]/metabolic activation[tiab]/reactive metabolite[tw]/reactive metabolite[tiab]/glyoxylate[tw]/glyoxylate[tiab]/"pharmacokinetics"[MeSH]

/"pharmacokinetics"[Subheading]/"absorption"[MeSH]/"distribution"[Title]/"excretion"/“hemoglobin adduct*”[tiab]/“DNA adduct*”[tiab]) KCC2: (“dna-alkylating-agent”[tw]/“Comet”[tw]/mutation[MeSH]/Mutagenesis[tw]/“Mutagenicity tests”[MeSH]/“Sister chromatid exchange”[MeSH]/“chromatid”/“SCE”/Mutation[tw]/micronuclei[tiab]/micronucle*/“Cytogenetic Analysis”[MeSH]/“Mutagens”[MeSH]/"DNA fragmentation"/"DNA cleavage"/“DNA strand break*”[tiab]/“DNA cross link*”[tiab]/“DNA oxidation”[tiab]/“unscheduled DNA synthesis”[tiab]/“intercalation”[tiab]/“SOS response”[tiab]/“Chromosomal aberration*”[tiab]/“micronucleus formation”[tiab]/“aneuploidy”[tiab]/“intrachromosomal recombination”[tiab]/“intragenic mitotic recombination”[tiab]/“chromosomal malsegregation”[tiab]) KCC3: (Assay[MeSH]/Clastogen*/"clastogenic" /"clastogenicity"/"clastogen"/"clastogens"/DNA-Repair[MeSH]/“Genetic toxicology”[tw]/genetic-toxicology/chromosome aberrations[MeSH]/chromosom*[MeSH]/“DNA damage”[MeSH]/“DNA protein crosslinks”/DNA-damage[MeSH]/Micron*[MeSH]/Mutagen*[MeSH]/"mutagens"[Pharmacological Action]/"mutagens"/“strand break”/“SOS Response”[tw]/“SOS Response”[tw]/ploidies/ploid/ploidy/Polyploidy[MeSH]/“Genomic Instability”[MeSH]/“DNA Repair”[MeSH]/instability[tw]/instability[tw]/binucle*[tw]/ubiqui*[MeSH]/oncogenes[MeSH]/“Genetic Processes”[tw] /“unscheduled DNA synthesis”/“UDS”/“base-excision repair”[tiab]/“double-strand break repair”[tiab]) KCC4: (“Gene Expression Regulation”[MeSH]/epigen*[MeSH]/“DNA methylation”[MeSH]/“gene silencing”[MeSH]/“histone deacetylases”[MeSH]/“RNA Interference”[MeSH]/microRNA*[MeSH]/RNA[MeSH]/“Small Interfering”[tw]/hypermethyl*[tw]/hypomethyl*[tw]/epimut*[tw]/methylation-associated-silencing/histone-tail/chromatin-organization/“rna"[MeSH]/"epigenesis, genetic"[MeSH]/rna/"rna, messenger"[MeSH]/"rna"/"messenger rna"/mrna/"histones"[MeSH]/histones/epigenetic/miRNA/methylation/“histone methylation”[tiab]/“histone acetylation”[tiab]/“histone phosphorylation”[tiab]) KCC5: (proteasome[MeSH]/“Free Radicals”[MeSH]/"free radicals"/“reactive oxygen species”[MeSH]/"reactive oxygen species"/"oxygen radicals"/“oxidative stress”[MeSH]/ "oxidative stress"/“electron transport”[MeSH]/“oxidative damage”[tw]/“reactive-nitrogen species”[MeSH]/“superoxide-radical”[tw]/“hydroxyl-radical”[tw]/“glutathione-depletion”[tw]/"peroxisome proliferation"[tiab]/ROS[tiab]/“GSH/GSSG ratio”[tiab]/Nrf2[tiab]/catalase[tiab]/superoxide dismutase[tiab]/“glutathione peroxidase”[tiab]/“thioredoxin peroxidase”[tiab]/“nitric oxide synthase”[tiab]/peroxidase[tiab]/myeloperoxidase[tiab]/“TBARS”[tiab]/“4-HNE”[tiab]/“oxidized proteins”[tiab]/JUN[tiab]/“HIF1-A”[tiab]/MMP[tiab]/“heat shock protein*”[tiab]) KCC6: (“C-reactive protein”[MeSH]/“C-reactive protein”/C-reactive-protein*[tw]/eosinophil*[MeSH]/fibrinogene/inflammation[MeSH]/inflammation[tw]/inflammation[tiab]/chronic-inflammation[tw]/inflammatory-leukocyte[tw]/inflammatory-leukocyte*[tw]/pro-inflammatory[tw]/inflammatory[tiab]/systemic inflamm*[tw]/inflammatory condition*[tw]/inflammatory potential[tw]/inflammatory response*[tw]/inflammatory marker*[tw]/inflammatory stat*[tw]/inflammatory index[tw]/inflammatory foci[tw]/markers of inflammation[tw]/(fibrinogen[tw] AND inflammation[tw])/chronic-inflammation[tw]/chronically-inflamed[tw]/(chronic[tw] AND inflammation[tw])/chronic inflamm*[tw]/infiltrating-leukocyt*[tw]/leukocyte-infiltrat*[tw]/pro-inflammatory[tw]/proinflammatory[tw]/tissue inflammation[tw]/pyrogen*[tw]/complement protein*[tw]/inflammatory signal*[tw]/pyroptos*/leukocyt*[tw]/lymphocyt*[tw]/eosinophil*[tw]/CD4[tw]/CD4-Positive T-Lymphocytes[tw]/peripheral-blood[tw]/hematologic*[tw]/T4 Lymphocyte[tw]/T4 Cell*[tw]/granulocyt*[tw]/cytokine*[tw]/CD8-Positive T-Lymphocytes[tw]/erythrocyte sedimentation rate/microbio*[tiab]/microbiome[tiab]/microbiomes[tiab]/chemokine*[tw]/cytokine*[tw]/white blood cell*[tw]/“lymphocyte activation”[tiab]/“myeloperoxidase activity”[tiab]/“MHC Class II”[tiab]/“plasminogen activator”

[tiab]/“COX-1”[tiab]/“COX-2”[tiab]/cyclooxygenase[tiab]/“NF-kB”[tiab]) KCC7: (macrophage[MeSH]/cytotoxicity[tw]/immunolog*[tw]/“B-cell activation factor receptor”[MeSH]/“antigenic modulation”[MeSH]/“immunologic factors”[MeSH]/“Antigenic Modulation”[tw]/autoimmun*[tw]/“B-Cell Activating Factor”[tw]/“B-Cell Activation Factor Receptor”[tw]/b-cell-activation[tw]/"Cytotoxicity, Immunologic"[tw]/cell-mediated immunity[tw]/humoral immunity[tw]/immun*[tw]/"Immunologic Factors"[tw]/“Immunologic Factors”[tw]/"Immunomodulation"[tw]/immune competence[tw]/immune dysregulation[tw]/immune function*[tw]/immune impairment[tw]/immune respons*[tw]/immune stat*[tw]/immune system[tw]/immunosuppress* [tw]/Immunosuppression[tw]/Immunosuppression[tiab]/immunotox*/macrophage[tw]/Killer Cells, Natural[tw]/Natural Killer[tw]/NF-kappaB[tw]/nk[tw]/somatic-hypermutation[tw]/TNF-α[tw]/immune surveillance[tw]/immunostim*[tw]/immune activation[tw]/immunodeficien*[tw]/immunophenotyp* [tw]/“t cell activation”[tw]/“t cell proliferation”[tw]/T-Lymphocytes, Cytotoxic[tw]/“systems immunology”[tw]/chronic-antigenic-stimulation[tw]/leukocyt*[tw]/lymphocyt*[tw]/eosinophil*[tw]/CD4[tw]/CD4-Positive T-Lymphocytes[tw]/peripheral-blood[tw]/hematologic*[tw]/T4 Lymphocyte[tw]/T4 Cell*[tw]/granulocyt*[tw]/cytokine*[tw]/CD8-Positive T-Lymphocytes[tw]/chemokine*[tw]/white blood cell*[tw]/endotoxin[tiab]/“infection”[tiab]/“antibod*”[tiab]/“prostaglandin*”[tiab]/interleukin*[tiab]/“leukotriene*”[tiab]/“thromboxane*”[tiab]/“immunoglobulin*”[tiab]) KCC8: (Receptors*[tw]/Receptor*[tiab]/“Aryl-hydrocarbon-receptor”[tiab]/“xenosensor”[tiab]/“Ah-receptor”[tiab]/“AhR”[tiab]/“Aryl Hydrocarbon”[tw]/“Aryl Hydrocarbon”[tiab]/“Transcriptional Activation”[tiab]/“Transcriptional Activation”[tw]/“Aryl-hydrocarbon-receptor”[tw]/“Aryl-hydrocarbon-receptor”[tiab]/“xenosensor”[tw]/"xenosensor"[tiab]/“Ah-receptor”[tw]/"Ah-receptor"[tiab]/“AhR-receptor”[tw]/"endocrine disruption”[tiab]/"Hormones, Hormone Substitutes, and Hormone Antagonists"[MeSH]/"Endocrine Disruptors"[MeSH]/"Thyroid Hormones"[MeSH]/"Estrogens"[MeSH]/"Progesterone"[MeSH]/"Receptors, Estrogen"[MeSH]/"Receptors, Androgen"[MeSH]/"Receptors, Progesterone"[MeSH]/"Receptors, Thyroid Hormone"[MeSH]/"Receptors, Aryl Hydrocarbon"[MeSH]/"Peroxisome Proliferator-Activated Receptors"[MeSH]/"constitutive androstane receptor"[Supplementary Concept]/"farnesoid X-activated receptor"[Supplementary Concept]/"liver X receptor"[tiab]/"Retinoid X Receptors"[MeSH]/PPAR*[tiab]/EGFR[tiab]/CAR[tiab]/RXR[tiab]/vitamin D[tiab]) KCC9: (telomere/“telomere shorten*”[tiab]/"cellular-Immortalization"/"p53-inactivation"/"pRb-inactivation"/("rb p16ink4a" AND inactivate/inactivated/inactivates/inactivating/inactivation/inactivations/inactivator/inactivators/inactived)/("p16ink4a rb" AND inactivate/inactivated/inactivates/inactivating/inactivation/inactivations/inactivator/inactivators/inactived)/("genes, p16"[MeSH Terms]/(genes AND p16)/"p16 genes”/"p16ink4a") OR ("retinoblastoma protein"[MeSH]/("retinoblastoma" AND "protein")/"retinoblastoma protein")/(aging[MeSH]/aging/senescence/senesce/senesced/senescences/senescent/senescents/senesces/senescing/"Cell Transformation, Neoplastic”[MeSH])) KCC10: (“Angiogenesis Modulating Agents”/Neovascularization/“Cell Hypoxia”/angiogenic/cellular-energetic*/hypoxic-cell/cell-hypoxia/Apoptosis/Cytotoxicity/Caspases/autophagy/necrosis/Autolysis/surviving/Cytotoxin/“Cell Proliferation”/homeostasis/“Cyclin-Dependent Kinases”/mitogens/cell-cycle-control/mitotic-checkpoint/hepatocellular-proliferation/Cytogenesis/hyperplasia/Neoplasia/Comet-assay/Mutagenicity/chromosomal-aberration-test/Sister-chromatid-exchange/SOS-response/Polyploide/Genomic-Instability/DNA-Repair/Aneuploide/gene-silencer/deacetylation/DNA-methylation/histone-deacetylase/ubiquitination/microRNA/non-coding-RNA/SiRNA/electron-transport-

chain/reactive-oxygen-species/Oxidative-stress/free-radical/C-reactive-protein/eosinophile/autoimmunity/Immunomodulation/cellular-homeostasis/Cell-Proliferation/cyclin-dependent-kinase/mitogens/angiogenesis/"DNA Replication"[MeSH]/"Cell Cycle"[MeSH]/brdu/thymidine/angiogenesis/"BrdU labeling"[tiab]/"PCNA labeling"[tiab]/polyamine*[tiab]/"nuclear size"[tiab]/"ornithine decarboxylase induction"[tiab]/hypertrophy[tiab]/fibrosis[tiab]/"steatosis"[tiab]/"hyperplasia"[tiab]/"Alpha2u-globulin"[tiab]/TUNEL[tiab]/"DNA laddering"[tiab]/"DNA fragmentation"[tiab]/"apoptotic nuclei"[tiab]/"Annexin-V"[tiab]/"Bcl-2/Bax ratio"[tiab]/"caspase 9"[tiab]/"mitochondrial membrane"[tiab]/"cell viability"[tiab]/"clonogenic survival"[tiab]/"trypan blue"[tiab]/"LDH"[tiab]/"lactate dehydrogenase"[tiab]/MTT[tiab]/necrosis[tiab]/"colony forming unit*"[tiab]/"signaling pathway*"[tiab]/"MAP kinase activation"[tiab]/"receptor tyrosine kinase"[tiab]/EGF[tiab]/"cyclin-dependent kinase*"[tiab]/"p16"[tiab]/"p21"[tiab]/"p53"[tiab]/"G1 arrest"[tiab]/"G2 arrest"[tiab]/"cell-cell communication"[tiab]/GJIC[tiab]/"cell energetics"[tiab]/VEGF[tiab]/"cell transformation"[tiab]/"anchorage-independent growth"[tiab]/"contact inhibition"[tiab]) Abbreviations: / = or.

Participant or population: To capture the full scope of toxicological studies of glyphosate and/or GBF and to develop a comprehensive understanding of their capacities to induce any of the ten KCCs, we will examine all in vivo and ex vivo studies of human and experimental animals (mammal), and in vitro studies of human and mammalian cells.

Intervention: Exposure to glyphosate and GBF in vivo, ex vivo, or in vitro.

Comparator: No/low exposure counterpart.

Study designs to be included: Eligible human in vivo study designs will include case-control, cohort, and cross-sectional studies, as well as descriptive studies (i.e. outcome studies). Experimental studies of glyphosate/GBF exposure in animal models (in vivo), tissues extracted from humans or animals (ex vivo), or in human or mammalian cells (in vitro) will also be included.

Eligibility criteria: All in vivo or ex vivo human and experimental animal (mammal) studies, or in vitro mechanistic studies of human and mammalian cells exposed to glyphosate and/or GBF reporting any KCC-related outcome will be eligible for inclusion. Only studies published in peer-reviewed journals or edited books will be included. We will exclude commentaries, method papers, reviews, retracted papers, studies with endpoints unrelated to KCCs, and studies with model organisms other than humans or mammals.

Information sources: We will query the PubMed and Embase databases. Additionally, bibliographies from reports and previous evaluations from national and international agencies will be hand-screened to supplement the primary literature search.

Main outcome(s): Only studies that report results related to the ten KCCs will be included; a complete list of KCC outcomes and endpoints is described in Smith et al. (2020).

Additional outcome(s): The additional outcomes of interest include perturbations of the gut microbiome, which have recently been linked to KCC6 (chronic inflammation).

Data management: Electronic literature searches will be conducted using SysRev, a systematic review search database tool (Bozada et al. 2021). Each study will be screened for inclusion by title and abstract a minimum of two times by two blinded reviewers. Conflicts among labels, defined as discordance among inclusion labels, will be resolved by a third reviewer (LZ or MTS). All in vivo, ex vivo, and in vitro studies marked for inclusion will be sorted by KCC classification and assay type. Study details will be extracted by two independent reviewers into a Microsoft Excel spreadsheet; conflicts will be resolved by a

senior investigator (LZ or MTS). Summary statistics will be generated using R Statistical Software Package.

Quality assessment / Risk of bias analysis: Studies marked for inclusion will be reviewed and assigned quality scores using an adapted form of the Grading of Recommendations Assessment, Development and Evaluation (GRADE) method (Atkins et al. 2004) and on criteria delineated in the IARC preamble [i.e. assay type, exposure variation, species, dose groups and level, presence of dose-response relationship, statistical significance, etc. (International Agency for Research on Cancer (2019)]. Risk of bias will be assessed at the individual study level and if suspected, will be outlined in the final narrative. We will characterize the strength of the evidence for each KCC using IARC's evaluations of strong, limited, or insufficient.

Strategy of data synthesis: The findings of this systematic review will be presented in a qualitative format. Data in relevant studies will be summarized individually by study in a summary table and findings will be presented in narrative form.

Subgroup analysis: Multiple subgroups will be analyzed after stratifying studies by various exposure and outcome metrics. For example, while humans are exposed to GBF only, mechanistic studies may use glyphosate alone as the exposure—these groups will be assessed individually and collectively. Similar subgroup analyses will be conducted for each KCC, and shared endpoints within a given KCC.

Sensitivity analysis: We will conduct various sensitivity analyses to assess the impact of excluded studies. Only studies of glyphosate and GBF and a KCC outcome are eligible for inclusion in our systematic review. Although excluded from our main analysis, studies with related exposures (i.e. aminomethylphosphonic acid, AMPA, a primary degradation product of glyphosate) or related outcomes (i.e. KCC endpoints in a study designed to measure reproductive toxicity) will be analyzed in sensitivity analyses.

Language: No language restrictions will be applied, though foreign language articles need to be obtained in full and translated completely to be eligible for inclusion.

Country(ies) involved: United States.

Other relevant information: References - 1. Atkins D, Best D, Briss PA, Eccles M, Falck-Ytter Y, Flottorp S, et al. 2004. Grading quality of evidence and strength of recommendations. Bmj 328:1490. 2. Bozada T, Borden J, Del Cid M, Malinowski J, Luechtefeld T. 2021. Sysrev: A fair platform for data curation and systematic evidence review. bioRxiv. 3. Gillezeau C, van Gerwen M, Shaffer RM, Rana I, Zhang L, Sheppard L, et al. 2019. The evidence of human exposure to glyphosate: A review. Environmental health : a global access science source 18:2. 4. International Agency for Research on Cancer. 2015. Glyphosate. In: Some organophosphate insecticides and herbicides: Diazinon, glyphosate, malathion, parathion, and tetrachlorvinphos, Vol. 112. Lyon, France: IARC, 1-92. 5. International Agency for Research on Cancer. 2019. Preamble to the iarc monographs (amended january 2019). Available: https://monographs.iarc.who.int/wp-content/uploads/2019/07/Preamble-2019.pdf. 6. La Merrill MA, Vandenberg LN, Smith MT, Goodson W, Browne P, Patisaul HB, et al. 2020. Consensus on the key characteristics of endocrine-disrupting chemicals as a basis for hazard identification. Nat Rev Endocrinol 16:45-57. 7. Smith MT, Guyton KZ, Gibbons CF, Fritz JM, Portier CJ, Rusyn I, et al. 2016. Key characteristics of carcinogens as a basis for organizing data on mechanisms of carcinogenesis. Environmental health perspectives 124:713-721. 8. Smith MT, Guyton KZ, Kleinstreuer N, Borrel A, Cardenas A, Chiu WA, et al. 2020. The key characteristics of carcinogens: Relationship to the hallmarks of cancer, relevant biomarkers, and assays to measure them. Cancer epidemiology, biomarkers & prevention : a publication of the American Association for Cancer

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Keywords: Roundup; key characteristics; human exposures; glyphosate; herbicide; carcinogenesis; mechanistic.

Dissemination plans: The findings of this systematic review will be submitted to a peer-reviewed scientific journal for publication.

Contributions of each author:

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Conflicts of interest: M.T.S. and L.Z. have received consulting fees from attorneys in cases involving chemical agents, including the subject of this protocol. The other authors declare they have no actual or potential competing financial interests.