



## Search Hedges for Alternatives to Oral Gavage in Mice and Rats

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### What is a Search Hedge?

A **search hedge** is a prepared search string that can be plugged into a database to find citations on a particular topic or population. Hedges are used frequently in biomedical literature searches to find literature on diseases or populations. They include synonyms or variants of terms. Hedges can save searchers time because the relevant keywords have already been selected for them. Searchers can also combine hedges with the Boolean AND to find a subset of citations on a particular topic: for instance, combining an Environmental Enrichment hedge with a species hedge for Mice. AWIC has been working on developing hedges on Three Rs topics to facilitate searching for literature on animal use alternatives.

While hedges can help retrieve relevant citations on a particular topic, they are never 100% effective. Searchers will need to review results carefully and recognize that there may be other pertinent articles not retrieved by the hedge.

### Introduction:

The National Agricultural Library's [Animal Welfare Information Center](#) (AWIC) conducts annual workshops for scientists, Institutional Animal Care and Use Committee (IACUC) members, students, librarians, veterinarians, animal care personnel, and others constructing a "Three Rs" literature search.

Over the past few decades, members of the research community have made great strides in finding ways to address the Three Rs and have written a great body of literature on the topic. Despite this, scientists and researchers often cite the difficulty of finding Three Rs citations in bibliographic databases. AWIC has seen animal use protocols where researchers said that they did not find any Three Rs literature on their topic, yet their search terms consisted mainly of "refinement," "reduction," "replacement," "Three Rs," and "alternatives." We've found that people who use *only* these terms do not find a lot of relevant results.

One of the reasons why Three Rs articles are hard to locate is that authors may not include words such as "Three Rs," "alternatives," refinement, etc., in abstracts or keywords, even though they may discuss Three Rs concepts or practices in the body of their papers.

Hedges and search filters are constructed search strings used to find citations on a particular populations, diseases, or publication type. We have created search hedges for some of the Three

Rs concepts (such as environmental enrichment, noninvasive blood sampling methods, etc.) to help scientists, researchers, and librarians locate citations on alternatives.

## What is Oral Gavage?

**Oral gavage** is used regularly in biomedical research to administer drugs, compounds, and pathogens orally to laboratory animals by passing a rigid or flexible tube through the animal's mouth and esophagus into the stomach. Due to their small size, mice and rats are particularly susceptible to injury by inexpert execution of oral gavage techniques. Oral gavage can cause discomfort and distress to mice and rats, and if performed incorrectly, may injure or perforate the esophagus or lungs or cause inflammation or aspiration. The stress from the oral gavage procedure can also elevate the animal's cortisol levels and thus threaten the validity of study results.<sup>1</sup>

## Alternatives to Oral Gavage

There are several non-invasive or less invasive methods of feeding an oral compound to mice and rats, including masking the substance in palatable food or liquid or allowing the animal to voluntarily consume it in liquid form from a syringe.

Since AWIC has used this hedge to search specifically for alternatives to oral gavage in laboratory mice and rats, we have included the terms for these animals in the hedge. We have also included terms that have appeared in relevant search results for the vehicles or substances used to noninvasively administer compounds to rodents without gavage (such as juice, jelly, dough, cookies, paste, peanut butter, Nutella, etc.).

Researchers use gavage in other animal species such as dogs and chickens. Searchers may adapt this hedge for different species by replacing the terms for mice, rats, and rodents with terms for other species. However, some of the vehicles used for non-invasively administering compounds orally to mice and rats (juice, peanut butter, cookies) may not be applicable to all other species.

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<sup>1</sup>Gonzales, C., Zaleska, M. M., Riddell, D. R., Atchison, K. P., Robshaw, A., Zhou, H., & Sukoff Rizzo, S. J. (2014). Alternative method of oral administration by peanut butter pellet formulation results in target engagement of BACE1 and attenuation of gavage-induced stress responses in mice. *Pharmacology, biochemistry, and behavior*, 126, 28–35. <https://doi.org/10.1016/j.pbb.2014.08.010>. See also Atcha, Z., Rourke, C., Neo, A. H. P., Goh, C. W. H., Lim, J. S. K., Aw, C.-C., Browne, E. R., & Pemberton, D. J. (2010). Alternative method of oral dosing for rats. *Journal of the American Association for Laboratory Animal Science*, 49(3), 335–343. See also Diogo, L. N., Faustino, I. V., Afonso, R. A., Pereira, S. A., Monteiro, E. C., & Santos, A. I. (2015). Voluntary oral administration of losartan in rats. *Journal of the American Association for Laboratory Animal Science*, 54(5), 549–556.

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## Hedges

Due to the complex syntax and the choice to search certain fields, we have provided the full syntax for this search hedge for PubMed, Web of Science, Scopus, EBSCO, Embase, and for Other Databases.

Please note that although we have made our best efforts to create a search hedge that will retrieve citations on non-gavage methods of orally dosing rodents, not every citation in the results will be relevant. We recommend browsing through at least the first 50 results for each hedge, although relevant results may be found further down the results list. Also, we recommend that you set the database's results display order to "Best Match" or "Relevance." (Most databases sort by relevance by default).

## PubMed

(Mice[majr] OR Rats[majr] OR Rodentia[majr] OR "mus musculus"[ti] OR "m musculus"[ti] OR mouse[ti] OR mice[ti] OR murine[ti] OR rat[ti] OR rats[ti] OR rattus[ti] OR "rattus norvegicus"[ti] OR "r norvegicus"[ti] OR "rodent"[ti] OR "rodents"[ti]) AND (voluntary[tiab] OR "self administration"[tiab] OR Self Administration[mh] OR "voluntary ingestion"[tiab:~3] OR "voluntary ingest"[tiab:~3] OR "voluntary ingests"[tiab:~3] OR "voluntarily ingest"[tiab:~3] OR "voluntarily ingests"[tiab:~3] OR "voluntarily ingested"[tiab:~3] OR "voluntary dosing"[tiab:~4] OR "voluntary oral"[tiab:~4] OR "oral dosing"[tiab] OR "voluntary consumption"[tiab:~3] OR "oral infection"[tiab] OR "syringe feeding"[tiab] OR Drinking Water[mh] OR Drug Delivery Systems[mh] OR Food, Formulated[mh] OR Pharmaceutical Preparations/methods[MeSH]) AND (Animal use alternatives[mh] OR Animal Welfare[mh] OR 3rs[tiab] OR "three rs"[tiab] OR welfare[tiab] OR "well being"[tiab] OR wellbeing[tiab] OR gavag\*[tiab] OR mortality[tiab] OR morbidity\*[tiab] OR "adverse effects"[tiab] OR "acute stress"[tiab] OR anxious[tiab] OR "less invasive"[tiab] OR welfare[tiab] OR "less aversive"[tiab] OR "non aversive"[tiab] OR nonaversive[tiab] OR "less aversive"[tiab] OR "less stressful"[tiab] OR "less stressful alternative"[tiab] OR "minimally invasive"[tiab] OR painful[tiab] OR pain[tiab] OR distress[tiab] OR "low stress"[tiab] OR "non invasive"[tiab] OR noninvasive[tiab] OR palatable[tiab] OR "stress-free"[tiab]) AND (Gelatin/administration and dosage[MeSH] OR Drinking Water[mh] OR "drinking water"[tiab] OR lixit[tiab] OR "water bottle"[tiab] OR bread[tiab] OR cookie\*[tiab] OR micropipette[tiab] OR microcapsul\*[tiab] OR gelatin[tiab] OR jelly[tiab] OR jam[tiab] OR dough[tiab] OR paste[tiab] OR wafer\*[tiab] OR "peanut butter"[tiab] OR Nutella[tiab] OR "chocolate milk"[tiab] OR "condensed milk"[tiab] OR juice[tiab] OR jello[tiab] OR syrup[tiab] OR paste[tiab] OR mealworm\*[tiab] OR palatable[tiab] OR refinement[tiab] OR "tablet formulation"[tiab] OR "gel delivery system"[tiab] OR "drinking water"[tiab] OR palatable[tiab] OR treat\*[tiab] OR liquid\*[tiab] OR suspension[tiab] OR sweet[tiab] OR flavored[tiab] OR flavoured[tiab]) NOT (Binge-Eating Disorder[mh] OR Craving[mh] OR Food Addiction[mh] OR Bulimia[mh] OR Alcoholism[mh] OR Behavior, Addictive[mh] OR Addiction Medicine[mh] OR Cocaine[mh] OR addiction[tiab] OR addictive[tiab])

## Scopus

TITLE-ABS((gavage W/5 (alternative\* OR refinement\*)) OR ((voluntary OR voluntarily) W/3 (ingest\* OR oral\* OR intake OR method\* OR technique\* OR administration OR administer\* OR dose OR dosing)) OR {syringe feeding} OR {oral infection}) AND TITLE-ABS({adverse effect} OR {adverse effects} OR {animal welfare} OR anxiety OR anxious OR humane OR {less invasive} OR {less aversive} OR {less stressful} OR alternative\* OR {minimally invasive} OR {minimally-invasive} OR {non invasive} OR {non-invasive} OR noninvasive OR {reduce stress} OR {stress-free} OR {non aversive} OR {non-aversive} OR {less aversive} OR {less stressful} OR voluntary OR 3rs OR {Three Rs} OR {animal use alternatives}) AND TITLE-ABS(bread OR {bread feeding} OR dough OR gelatin OR gel OR jelly OR cookie OR wafer\* OR pellet\* OR {peanut butter} OR Nutella OR {chocolate milk} OR {condensed milk} OR juice OR jello OR syrup OR paste OR jam OR mealworm\* OR micropipette OR refinement\* OR {tablet formulation} OR {gel delivery system} OR {Medicated Dosing System} OR {medicated diet} OR {alternative dosing method} OR {Bio Serv} OR bioserv OR

microcapsul\* OR flavored OR flavoured OR {drinking water} OR palatable OR palatability OR treat OR treats OR liquid) AND TITLE(mice OR rat OR rats OR rodent\* OR murine OR {Mus musculus} OR {M musculus} OR rattus OR {Rattus norvegicus} OR {R norvegicus})

## Web of Science

((TS=((Gavage NEAR/5 (alternative\* OR refinement)) OR ((voluntary OR voluntarily) NEAR/3 (ingest\* OR oral\* OR intake OR method\* OR technique\* OR administration OR administer\* OR dose OR dosing)) OR "syringe feeding" OR "oral infection"))) AND TS=("adverse effect\*" OR "animal welfare" OR anxiety OR anxious OR humane OR "less invasive" OR "less aversive" OR "non invasive" OR noninvasive OR "reduce stress" OR "stress-free" OR "non aversive" OR "less aversive" OR "less stressful" OR voluntary OR 3Rs OR "Three Rs" OR "animal use alternatives")) AND TI=(mice OR rat OR rats OR rodent\* OR murine OR "Mus musculus" OR "M musculus" OR rattus OR "Rattus norvegicus" OR "R norvegicus")) AND TS=(bread OR "bread feeding" OR dough OR gelatin OR gel OR jelly OR cookie OR wafer\* OR pellet\* OR "peanut butter" OR Nutella OR "chocolate milk" OR "condensed milk" OR juice OR jello OR syrup OR paste OR jam OR mealworm\* OR micropipette OR refinement\* OR "tablet formulation" OR "Medicated Dosing System" OR "medicated diet" OR "alternative dosing method" OR "Bio Serv" OR bioserv OR microcapsul\* OR flavo\$red OR "drinking water" OR palatable OR palatability OR treat OR treats OR liquid)

## EBSCO

TX ( ((Gavage N5 (alternative\* OR refinement)) OR ((voluntary OR voluntarily) N3(ingest\* OR oral\* OR intake OR method\* OR technique\* OR administration OR administer\* OR dose OR dosing)) OR "syringe feeding" OR "oral infection")) ) AND TX ( "adverse effect\*" OR "animal welfare" OR anxiety OR anxious OR humane OR "less invasive" OR "less aversive" OR "non invasive" OR noninvasive OR "reduce stress" OR "stress-free" OR "non aversive" OR "less aversive" OR "less stressful" OR voluntary OR 3Rs OR "Three Rs" OR "animal use alternatives" ) AND TI ( mice OR rat OR rats OR rodent\* OR murine OR "Mus musculus" OR "M musculus" OR rattus OR "Rattus norvegicus" OR "R norvegicus" ) AND TX ( bread OR "bread feeding" OR dough OR gelatin OR gel OR jelly OR cookie OR wafer\* OR pellet\* OR "peanut butter" OR Nutella OR "chocolate milk" OR "condensed milk" OR juice OR jello OR syrup OR paste OR jam OR mealworm\* OR micropipette OR refinement\* OR "tablet formulation" OR "Medicated Dosing System" OR "medicated diet" OR "alternative dosing method" OR "Bio Serv" OR bioserv OR microcapsul\* OR flavo#red OR "drinking water" OR palatable OR palatability OR treat OR treats OR liquid )

## Embase

(gavage OR 'oral gavage' OR 'voluntary ingestion' OR 'oral drug administration' OR 'voluntary oral administration' OR 'syringe feeding' OR 'alternative oral dosing' OR 'voluntary intake' OR 'oral dosing method' OR 'alternative oral administration' OR 'oral treatment\*' OR 'Micropipette' OR 'oral infection' OR 'ingest voluntarily' OR 'ingests voluntarily' OR 'ingested voluntarily') NEAR/15 ('adverse event' OR 'adverse effect\*' OR 'animal welfare' OR 'anxiety' OR anxious OR

humane OR 'less invasive' OR 'less aversive' OR 'less stressful' OR alternative\* OR 'non invasive procedure' OR noninvasive OR 'reduce stress' OR voluntary) NEAR/15 ('Rat' OR rats OR rattus OR 'R norvegicus' OR 'rodent' OR rodent\* OR 'mouse' OR mice OR murine OR mus OR 'Mus musculus' OR 'M musculus') NEAR/15 ('bread' OR 'bread feeding' OR 'dough' OR 'gelatin' OR gel OR jelly OR jellies OR jam OR cookie OR wafer\* OR 'drug pellet' OR pellet\* OR 'peanut butter' OR Nutella OR mealworm\* OR 'chocolate milk' OR 'condensed milk' OR juice OR jello OR 'syrup' OR 'paste' OR 'micropipette' OR 'animal testing refinement' OR 'tablet formulation' OR 'gel delivery system' OR 'Medicated Dosing System' OR 'medicated diet' OR 'alternative dosing method' OR BioServ OR flavored OR microcapsul\* OR 3rs OR 'Three Rs' OR 'animal use alternatives')

## Other Databases

(gavage OR alternative\* OR refinement\* OR "voluntary ingest\*" OR "voluntary oral ingest\*" OR "voluntary intake" OR "voluntary oral administration" OR "voluntary oral dosing" OR "syringe feeding" OR "oral infection" OR "ingest\* voluntarily") AND ("adverse effect\*" OR "animal welfare" OR anxiety OR anxious OR humane OR "less invasive" OR "less aversive" OR "non invasive" OR noninvasive OR "reduce stress" OR "stress-free" OR "non aversive" OR "less aversive" OR "less stressful" OR voluntary OR 3Rs OR "Three Rs" OR "animal use alternatives") AND (mice OR rat OR rats OR rodent\* OR murine OR "Mus musculus" OR "M musculus" OR rattus OR "Rattus norvegicus" OR "R norvegicus") AND (bread OR "bread feeding" OR dough OR gelatin OR gel OR jelly OR cookie OR wafer\* OR pellet\* OR "peanut butter" OR Nutella OR "chocolate milk" OR "condensed milk" OR juice OR jello OR syrup OR paste OR jam OR mealworm\* OR micropipette OR refinement\* OR "tablet formulation" OR "Medicated Dosing System" OR "medicated diet" OR "alternative dosing method" OR "Bio Serv" OR bioserv OR microcapsul\* OR flavored OR flavoured OR "drinking water" OR palatable OR palatability OR treat OR treats OR liquid)

## How to Use These Hedges

Below are instructions on how to use these hedges in a few selected databases.

### PubMed

1. Select and copy the hedge.
2. Go to <https://pubmed.ncbi.nlm.nih.gov/> and select Advanced to access the Advanced Search Builder
3. Paste the hedge into the Query Box and select Search.
4. You will see the results listed by title and sorted by relevance ("Best Match"). Usually the most relevant citations (the ones that contain multiple keywords from the hedge) appear at the top of the results while less relevant citations tend to be towards the end. Make sure to screen the whole record, because sometimes the refinement is discussed in the abstract and not the title.

## Scopus

1. Scopus is a subscription database produced by Elsevier which also publishes peer-reviewed journals and books. You will need to access Scopus through your library's website. Keep in mind that not all institutional libraries subscribe to Scopus. Check with your institution's librarian for advice on how to access Scopus on your library's platform.
2. Go to Scopus' main search page and follow the link for the Advanced Document Search option.
3. Copy and paste the search hedge into the Advanced search query box where it says "Enter query string" and select Search. Scopus will then display the results.
4. By default, Scopus sorts results by default to show the highest cited articles first. Switch the sort order to Relevance so that the most on-target citations display first.

## Web of Science

1. Web of Science is a subscription database produced by Clarivate Analytics. You will need to access Web of Science through your library's website. Keep in mind that not all institutional libraries subscribe to Web of Science. Check with your institution's librarian for advice on how to access Web of Science on your library's platform.
2. Go to Web of Science's search page and select the Advanced Search option below the query box.
3. Copy the search hedge and paste it into the Advanced Search Query Builder. Then select the purple Search button.
4. Search results will be displayed sorted by Relevance.

## Embase

Embase is the largest subscription biomedical database, produced by Elsevier. It also searches Medline and has its own controlled vocabulary, Emtree, which is based on MeSH.

Copy the search hedge and paste it into Embase's Quick Search dialog box and select the Show Results button. The Search History and a list of results will appear on the next screen.

## For additional help

1. You can also translate search strings using [Polyglot](#), a free online tool from Bond University's Institute for Evidence-Based Healthcare.
2. For more information on conducting searches in PubMed, please refer to the Network of the National Library of Medicine's [How PubMed Works](#) instructional video series and [PubMed's User Guide](#).
3. For additional information on search best practices, search syntax, and related topics, see the [Literature Searching: How to Find Animal Use Alternatives](#), on the National Agricultural Library's (USDA) website.
4. If you have questions or suggestions, please reach out to AWIC at [awic@usda.gov](mailto:awic@usda.gov).