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Fish Drug Analysis—Phish-Pharm: A Searchable Database of Pharmacokinetics Data in Fish

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ABSTRACT

Information about drug residues and pharmacokinetic parameters in aquatic species is relatively sparse. In addition, it is difficult to rapidly compare data between studies due to differences in experimental conditions, such as water temperatures and salinity. To facilitate the study of aquatic species drug metabolism, we constructed a Fish Drug/Chemical Analysis Phish-Pharm (FDA-PP) database. This database consists of more than 400 articles that include data from 90 species (64 genera) of fish. Data fields include genus, species, water temperatures, the average animal weight, sample types analyzed, drug (or chemical) name, dosage, route of administration, metabolites identified, method of analysis, protein binding, clearance, volume of distribution in a central compartment (Vc) or volume of distribution at steady-state (Vd), and drug half-lives ($t_{½}$). Additional fields list the citation, authors, title, and Internet links. The document will be periodically updated, and users are invited to submit additional data. Updates will be announced in future issues of *The AAPS Journal*. This database will be a valuable resource to investigators of drug metabolism in aquatic species as well as government and private organizations involved in the drug approval process for aquatic species.

KEYWORDS: aquatic, fish, drug, pharmacokinetics, residues, database, Web.

INTRODUCTION

There are currently very few drugs approved by the US Food and Drug Administration (FDA) for use in fish.[1-4] Although there are several reasons for this shortage, the primary factor is a lack of pharmaceutical sponsors willing to invest in the research needed to generate the data to support a drug approval. Such data include demonstration of drug efficacy and safety in the target species, human food safety, and environmental impact assessments.[5] The overall cost of obtaining the experimental data required for a New Animal Drug Application (NADA) can be in excess of $40 million.[6-8]

Efforts to increase the availability of therapeutic agents for fish and for other minor species include work being done by the *National Research Support Project No. 7*[6] and the *Proposals to Increase the Availability of Approved Animal Drugs for Minor Species and Minor Uses*.[9] One strategy being explored for aquaculture drug products is to group species according to those species of fish likely to present with similar safety profiles, effectiveness characteristics, or withdrawal times.[10-16] Several approaches have been suggested for this "crop grouping," and the proposed basis for grouping species has included taxonomic class, salinity tolerance, or water temperature.

The underlying theory for a taxonomic grouping is that organisms closely related phylogenetically might be expected to have similar drug metabolism and elimination. This is definitely the case in fish lacking certain renal elements such as glomeruli and distal tubules.[17] Drugs that are normally filtered by the glomerulus are retained much longer in these fish species. Other scientists suggest grouping fish based on their salinity preferences. Marine fish drink large quantities of salt water and produce little urine, while freshwater fish do not drink and produce copious urine. The amount a fish drinks can affect both absorption and excretion of drugs. For example, Sohlberg et al[18] found that flumequine plasma levels were much lower in salmon smolts treated during their transfer to saltwater as compared with smolts that were returned to freshwater. Cations from the water in the gastrointestinal tract were thought to bind and facilitate drug elimination.

The suggestion to group species by temperature is based on the ability of poikilothermic animals to dramatically change their rate of drug metabolism and depuration, depending on holding conditions. In general, the colder the environment, the slower most drugs are absorbed and excreted.[19-21] This is, however, dependent on the type of drug being examined.

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Compounds such as the anesthetic, benzocaine, have been shown to be eliminated just as rapidly in fish held at 7°C versus those held at 16°C.[22]

Once species groups have been developed, a model species could be chosen to represent the entire group in the target animal safety and/or effectiveness studies supporting product approval. The full human food safety data package could be generated in the same or different model species. Ultimately, some bridging studies would be needed to verify the appropriateness of the proposed grouping for the other species included in that group.

The concept of extrapolating data from one animal species to another is not unique. Preclinical data may be used to estimate a phase 1 dose to be administered to healthy human volunteers.[23] It is also used to generate allometric equations for predicting pharmacokinetic parameters in man,[24-25] or to determine action levels for environmental contaminants, toxicants, and carcinogens.[26-27] This approach has, however, only been incorporated into the drug-approval process for animal drugs in selected cases. During the past decade, the farming of minor species has become more popular and such nontraditional farm animals require veterinary care and therapeutic drugs. It is for these minor species, especially the aquatic species, that a reliable and predictable method of species grouping would be extremely advantageous.

A large amount of supportive data, however, must be compiled in order to demonstrate that information from a model species will accurately predict the responses of all the members of a group. Since these pharmacokinetic data are often used to make decisions about the conduct of human food safety studies, it is essential that conclusions are drawn from an adequately sized data set. There are several online databases available for human pharmacokinetic data.[28-33] One online resource, the Food Animal Residue Avoidance Databank,[30] provides residue information for food animals, primarily terrestrial species.[34-35]

Compared with what is available for mammals, there is a general lack of the literature describing drug depletion or pharmacokinetic studies in fish. There are also a few fish species, such as channel catfish and salmonids, which dominate the literature. The information that does exist needs to be organized in a way that will allow the reviewer to evaluate the many different study variables inherent in the aquatic animal literature. As part of the Center for Veterinary Medicine (CVM)/Office of Research's work on crop grouping, we have begun to develop such a literature database to detail information on drug metabolism, depuration, and pharmacokinetics in fish.

Materials and Methods

Features of FDA-PP

The current database consists of more than 400 articles, which include data from over 90 species (64 genera) of fish. The data set contains separate sortable fields for the following information:

1. Articles
   a. author(s)
   b. year of publication
   c. citation and Web links to the abstracts if available
2. Experimental animals and the holding conditions
   a. species common name
   b. species scientific name
   c. average water temperature(s)
   d. average animal weight
   e. type of sample analyzed
3. Drug/chemical and pharmacokinetic parameters
   a. drug name
   b. drug class
   c. dosage
   d. route of administration
   e. metabolites identified
   f. method of analysis
   g. protein binding
   h. clearance
   i. volume of distribution in a central compartment (Vc) or volume of distribution at steady-state (Vd)
   j. drug half-lives ($t_{½}$)

Values for $t_{½}$ were either entered as reported or extrapolated from data or graphs provided in the articles. If the $t_{½}$ was extrapolated, a notation was made in another column to identify such entries as estimates. The $t_{½}$, average temperature, and average weight fields are defined as numerical entries to facilitate plotting the data. Additional detailed fields were incorporated at the end of the master spreadsheet to expand the information from numerical columns. For example, the actual range of water temperatures is entered in the "detailed water temperature" field, while numerical averages are entered into "average water temperature" field. So too, the detailed weight and detailed dosage fields allow additional, nonnumerical information to be included.

The database is provided in 2 formats. In its simplest "raw" form of a Microsoft Excel spreadsheet, the data should be readily accessible to most scientists. A searchable Microsoft Access Database is also available.

Contents and Structure of the Spreadsheet

The field names and a description of their contents are listed below.

Drug. The database contains drugs/chemicals approved for use in fish in the United States as well as many other drugs/chemicals for which there is published information. The field "Drug" uses the name of the drug or chemical most

commonly used in the literature. For clarity, chemical names have sometimes been included after the commonly used abbreviated names, for example "DDT (Dichlorodiphenyltrichloroethane)."

Metabolite. Metabolites are frequently unidentified or may be described as "a polar metabolite." If no metabolites were mentioned in the article, nothing was entered in this field. If the authors described finding a metabolite but did not identify it, it was listed as "unknown metabolite," with other descriptors such as polar or sulfated added.

Fish Species. Commonly used name.

Dep-time. This column represents the time to deplete any measurable residues from the sample, which usually includes the edible portions of the fish. These numbers are NOT withdrawal times and are highly method dependent. Withdrawal times were calculated factoring dosing, route of administration, marker residue, target tissue, tolerance, and regulatory method. For more information, refer to the CVM Guidance No. 3 (http://www.fda.gov/cvm/guidance/guideline3toc.html).[36]

$t_{½}$ hr. This value provides the half-life in hours of the drug or metabolite in the sample listed in that row. If a range of times was given, the longest interval was entered into this column, not the average. This is to ensure the most conservative data are used. If no half-life was calculated by the authors, but concentration versus time data were provided in the form of residue tables or graphs, we estimated half-lives from these published data. Any such estimate is identified in the following column as an estimate. This was done to keep the data in this column numerical to allow users to graph data.

Estimate. This column identifies any $t_{½}$ listed in the previous field as an estimated value if the $t_{½}$ was extrapolated from data published in tables or graphs. This field was left blank if the $t_{½}$ was calculated and reported in the citation.

Sample. This is the tissue type analyzed, providing as much detail as was available in the original article. For example, some authors state that they sampled blood, while others state that they used serum or plasma. To facilitate sorting through different but related samples such as these, we began the entry with the word blood and followed with descriptors if further information was available (eg, blood; blood, plasma; blood, serum).

Average Weight (g). Some studies included fish that covered a range of sizes. If the data were combined in their report, we averaged the weights and rounded to the nearest gram. If no weights were reported, we left the field blank. If ranges were provided, we entered that information in the "Weight-Detail" field.

Average Water Temp (°C). Temperatures, if ranges were provided, were averaged and rounded to the nearest integer. If the temperature was not specified, the field was left blank. Detailed temperature ranges are listed in the "Water Temp-Detail" field.

Water. The water salinity is reported as Saltwater (generally >17 parts per thousand (ppt), usually 25-36), Brackish (generally between 3 and 17 ppt), and Freshwater (0-2 ppt). If the authors did not specifically site the type of water used in the experiment, "not specified" was entered into the field, unless the species is routinely housed only under certain conditions (eg, channel catfish are routinely housed in freshwater systems or ponds).

Dosage. There is great variability in the dosing methods. Thus, this is a descriptive field, and additional details may be provided in the comments field. If a single dose was given, the entry is followed by "sd" The abbreviations BID and TID are used as an abbreviation for twice daily and 3 times per day, respectively.

Route. The routes are Bath (immersion), PO (oral; includes gavage or in feed), IC (intracardiac), IPC (intrapericardial), IV (intravascular), IVC (intravascular cannulated), IM (intramuscular), IP (intraperitoneal), IS (intrasinus), SC (subcutaneous), and In Vitro (cell culture studies).

Comments. This field is used to provide additional information about the study or to provide an explanation for unusual data.

Protein binding. The data in this field are rarely reported.

CL. The total body clearance rates are rarely reported.

Vc. The volume of distribution of the drug in the central compartment is rarely reported.

Vd. The volume of distribution of the drug at steady state (Vdss) is infrequently reported. The type of model used to develop the pharmacokinetic data is currently not listed in the table but will be included in subsequent versions.

Authors.

Year.

Citation.

Title.

Link. Links to abstracts of the articles on the Web are included where available. Much of the older literature about residues in fish is not yet readily available using online search engines.

Genus species (scientific name). The current name is used, even if the authors had used an older name, for example, *Salmo gairdneri* is now *Oncorhynchus mykiss*.

Drug Class. This field refers to use as well as chemical structure. Antibiotics are identified by the general term "antibiotic" but are followed by the class; for example, Ampicillin is listed as "Antibiotic-Penicillin." Main classes include antibiotics, antifungals, antiparasitics, metals, and organic chemicals, which include dyes, herbicides, pesticides, and other compounds.

Method. This field identifies the method used to detect the drug/chemical. Abbreviations used are AAS (atomic absorption spectrophotometry), GC (gas chromatography), GLC (gas liquid chromatography), GC-EC (electron capture gas chromatography), HPLC (high-performance liquid chromatography), ICP (inductively-coupled plasmaspectrometer), LC (liquid chromatography), MS (mass spectrometry), LC/APCI-MS (liquid chromatography with atmospheric pressure ionization mass spectrometry), LC/ED-LC/ESI-MS (liquid chromatography with electrochemical detection, liquid chromatography with electrospray ionization-mass spectrometry), Micro (microbiological), Rad (radioactive chemical), and TLC (thin layer chromatography).

Detail fields. (Discussed previously.)

Contents and Structure of the Access Database

The database, in the form of a Microsoft Access Database, is available for download. To use this file, the user must have Access Version 2002 or higher installed on their computer. If this program is unavailable, the Excel spreadsheet can be downloaded and imported into another database program. *(These files are available online at http://www.aapsj.org/view.asp?art=aapsj070230.)*

The FDA-PP Access Database opens to a page from which the user can choose several options. The user can (1) view instructions and information about the database, (2) view the main table, or (3) enter the search page. The search page contains 8 fields to use for searching.

Drug/Chemical	Fish Species
Drug Class	Genus Species
Route	Sample
Authors	Water

The user can combine any of these fields in their search by selecting an entry from a drop-down list or by typing in part of the entry. For example, to find all citations that used any species of catfish, typing all or part of the word surrounded by asterisks (ie, *catfish* or *cat*) into the Fish Species field will result in a report of all citations that have entries with the text "cat" in them, such as "channel **cat**fish" and "blue **cat**fish."

The search report is presented in either a table or a form-style format. The user can choose the format in which the report will appear. The table can be further sorted by any of the fields. This facilitates additional manipulations to organize the material. In addition, the table format allows rapid comparisons between entries. The form-style report shows all the data for an entry on 1 page. This eliminates the side-to-side scrolling necessary when viewing the data in the table format.

RESULTS

Examples of Data Charts

The data, being organized into such a searchable database, can be readily manipulated. The option to sort and extract data from such a large number of articles allows the researcher to see trends that would otherwise be difficult to visualize. By plotting data that have been mined from the database, one can readily observe that $t_{½}$ clusters for some drug classes. For example, Figures 1 and 2 show the $t_{½}$ of several nonantibiotic drugs sorted either by drug (Figure 1) or by animal species (Figure 2). Based on Figure 1, it is evident that as a general rule, either parent drug or total drug residues associated with the benzimidazoles, such as albendazole, fenbendazole, and mebendazole, have $t_{½}$ values of less than 8 days in muscle tissue. In Figure 2, we see that the animal species considered in these plots include Atlantic salmon, tilapia, channel catfish, rainbow trout, and eels. The 2 longer $t_{½}$'s are attributable to the presence of metabolites found in the tilapia and the eel (note that as described in the CVM Guidance No. 3, withdrawal time factors not only the parent compound but also is based on the depletion of the total residue). Some extremely long retention times are observed for the halogenated pesticides found in the center of the figure.

These figures can also be useful for comparing the $t_{½}$ of a single drug in multiple species of fish. Figures 3 and 4 are examples of this type of comparison, in either muscle or blood. The $t_{½}$ for oxytetracycline (OTC) in muscle (Figure 3) ranges between 1 and 13 days, depending on aquatic animal species. Of interest, within rainbow trout alone, $t_{½}$ values can vary between 2 and 13 days. Thus, both the within and between species variations in $t_{½}$ values appear to be similar when conducting a cross-study comparison. These studies have been conducted using a variety of methods including HPLC and microbial assays.

A closer examination of the data in the spreadsheet shows that the studies associated with some of the longest muscle $t_{½}$ estimates for OTC used fish held at the colder temperatures. Figure 4 contains the $t_{½}$ estimates for OTC in the blood of several species. The $t_{½}$ values range from 1 to 24 days, with the range for trout being approximately 2 to 20 days. The species with reported $t_{½}$ values exceeding 10 days are Atlantic salmon, Arctic charr, Chinook salmon, rainbow trout, sockeye salmon, and walleye.

A general overview of all compounds and all species (Figure 5) demonstrates that other than DDT, most compounds have muscle $t_{½}$ estimates of less than 14 days. An exception to this generalization is ormetoprim, where the $t_{½}$ value in the muscle tissue of rainbow trout is reported to be 19 days. Such findings warrant closer examination of the study to determine a reason for this deviation. Similarly, in Figure 6 (all antibiotics in blood of all species), the $t_{½}$ for gentamicin in toadfish is approximate-

ly 25 days as compared with the $t_{½}$ estimates of 0.5 to 2 days for goldfish, channel catfish, and brown sharks.[17,37-38] The fundamental reason for this interspecies deviation is the unusual anatomy of toadfish kidneys. Gentamicin, in mammals and most fish, is excreted primarily by glomerular filtration. Toadfish have aglomerular kidneys and therefore cannot filter plasma to excrete drugs. This difference in renal physiology accounts for the unusual retention time for gentamicin observed in these animals. What is remarkable, however, is that fish as diverse as goldfish, channel catfish, and even brown sharks all have similar short $t_{½}$'s. Again, taking the general overview of all the drugs, most of the compounds (except the pesticides and metals) have $t_{½}$ values in blood of less than 2 weeks.

Additional figures have been included that demonstrate the $t_{½}$ of drugs in either muscle or blood or of multiple drugs in an individual species:

Figure 7 - All Drugs in Muscle by Species

Figure 8 - All Drugs in Muscle by Drug

Figure 9 - Antibiotics - Chloramine T - Quinolones in Muscle by Species

Figure 10 - Antibiotics - Chloramine T - Quinolones in Muscle by Drug

Figure 11 - Antibiotics - Sulfa Drugs in Muscle by Species

Figure 12 - Antibiotics - Sulfa Drugs in Muscle by Drug

Figure 13 - Antibiotics -Tetracyclines in Muscle by Species

Figure 14 - Antibiotics -Tetracyclines in Muscle by Drug

Figure 15 - Nonantibiotics in Muscle by Species

Figure 16 - Nonantibiotics in Muscle by Drug

Figure 17 - All Antibiotics in Blood by Species

Figure 18 - All Antibiotics in Blood by Drug

Figure 19 - Antibiotics - Gentamicin-Thiamphenicol in Blood by Species

Figure 20 - Antibiotics - Gentamicin-Thiamphenicol in Blood by Drug

Figure 21 - Antibiotics - Quinolones in Blood by Species

Figure 22 - Antibiotics - Quinolones in Blood by Drug

Figure 23 - Antibiotics - Sulfa Drugs in Blood by Species

Figure 24 - Antibiotics - Sulfa Drugs in Blood by Drug

Figure 25 - Antibiotics - Tetracyclines in Blood by Species

Figure 26 - Antibiotics - Tetracyclines in Blood by Drug

Figure 27 - Antibiotics - Nonantibiotics in Blood by Species

Figure 28 - Antibiotics - Nonantibiotics in Blood by Drug

Figure 29 - All Drugs in Rainbow Trout Muscle

Figure 30 - All Drugs in Tilapia Muscle

Figure 31 - All Drugs in Channel Catfish Muscle

Figure 32 - All Drugs in Atlantic Salmon Muscle

Figure 33 - All Drugs in All Salmon Muscle by Species

Figure 34 - All Drugs in All Salmon Muscle by Drug

Conclusion

We present here a compilation of data from more than 400 articles. This database was developed to facilitate studies on drug metabolism, pharmacokinetics, drug development, and therapy for aquatic species. We have tried to organize the data in ways that allow the investigator to rapidly search the literature for information about drug metabolism across a range of fish species and under a variety of exposure conditions. To make this database readily available, we are publishing this material online. As the field of fish pharmacokinetics grows, so too will the need to standardize the methods of study and the presentation of these data to the scientific community. Currently, few fish studies include the detailed pharmacokinetic parameters routinely found in mammalian studies. It is our hope that more complete pharmacokinetic data will be included in future fish drug metabolism studies. As such data become available, this database may be amended to include those parameters. Announcements of these updates will be posted in future issues of *The AAPS Journal*.

We welcome the submission of additional material by e-mail to the corresponding author (renate.reimschuessel@fda.hhs.gov).

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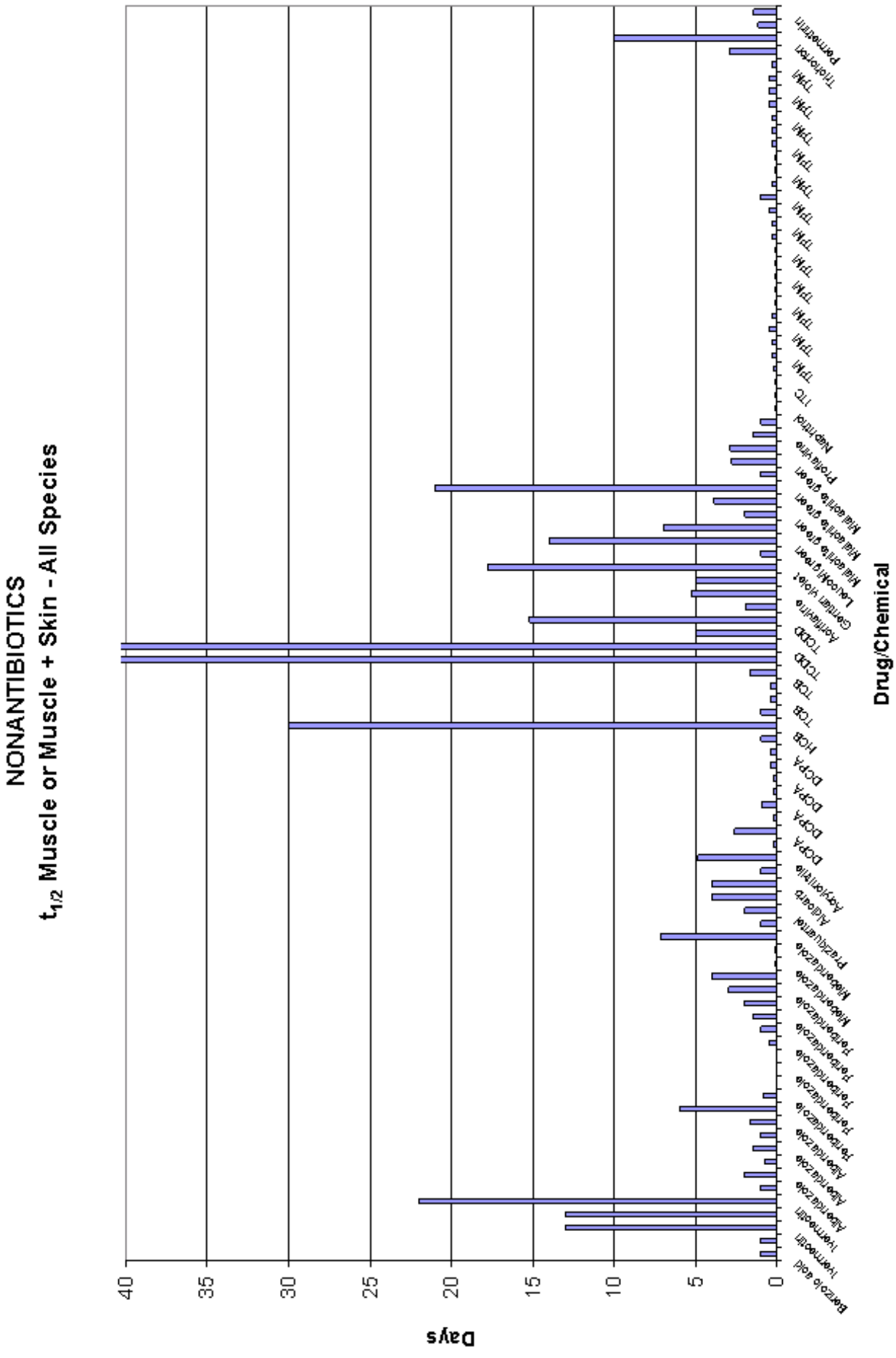
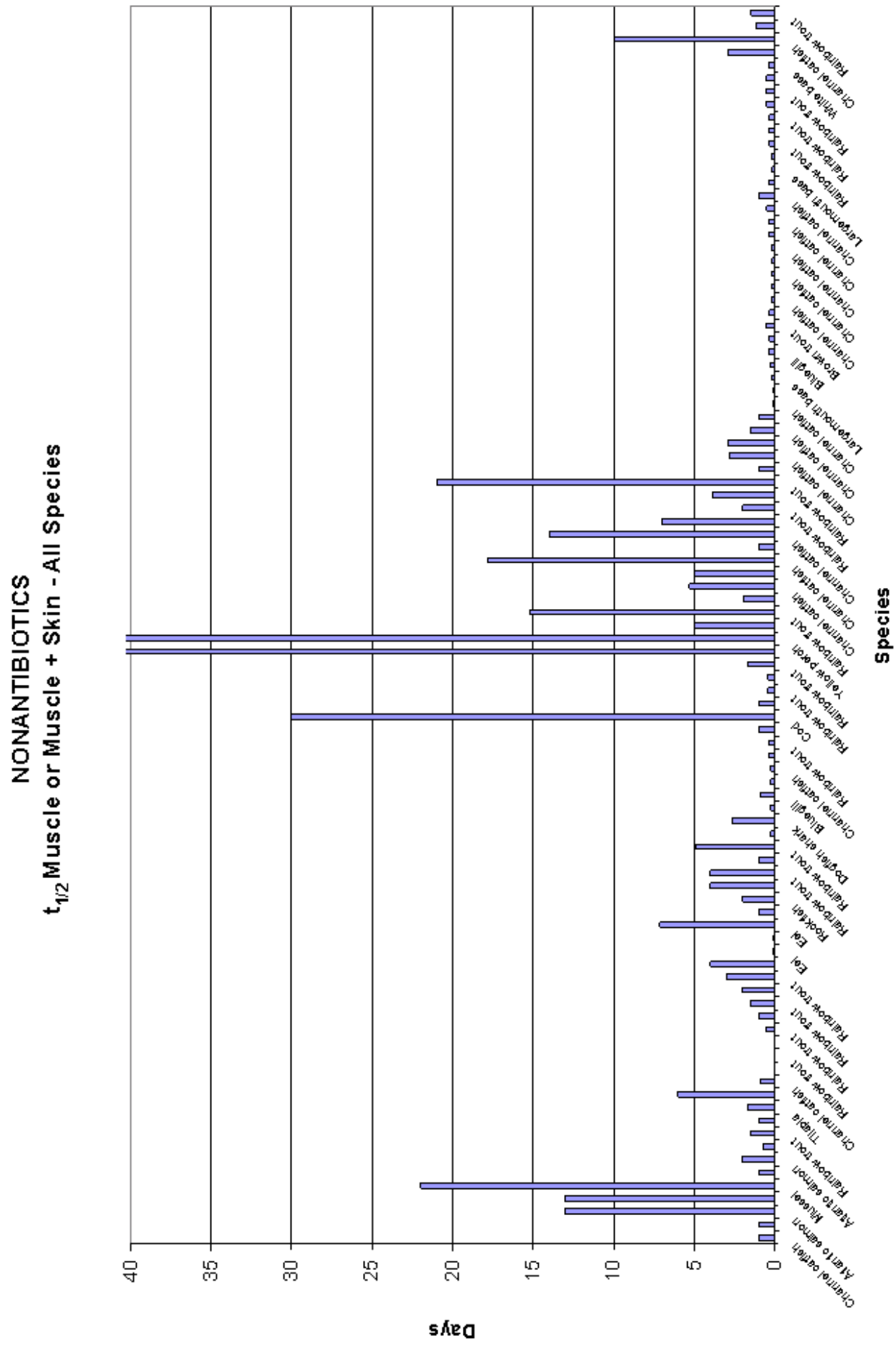

NONANTIBIOTICS
$t_{1/2}$ Muscle or Muscle + Skin - All Species
Days
0
5
10
15
20
25
30
35
40
Drug/Chemical
Enrofloxacin
Tilmicosin
Penmocillin
TMP
TMP
TMP


NONANTIBIOTICS
$t_{1/2}$ Muscle or Muscle + Skin - All Species
Days
0
5
10
15
20
25
30
35
40
Species
Chlortrio/ oxytetrach
Atlantic salmon
Rainbow trout
Halibut
Atlantic salmon
Rainbow trout
Tilapia
Chlortrio/ oxytetrach
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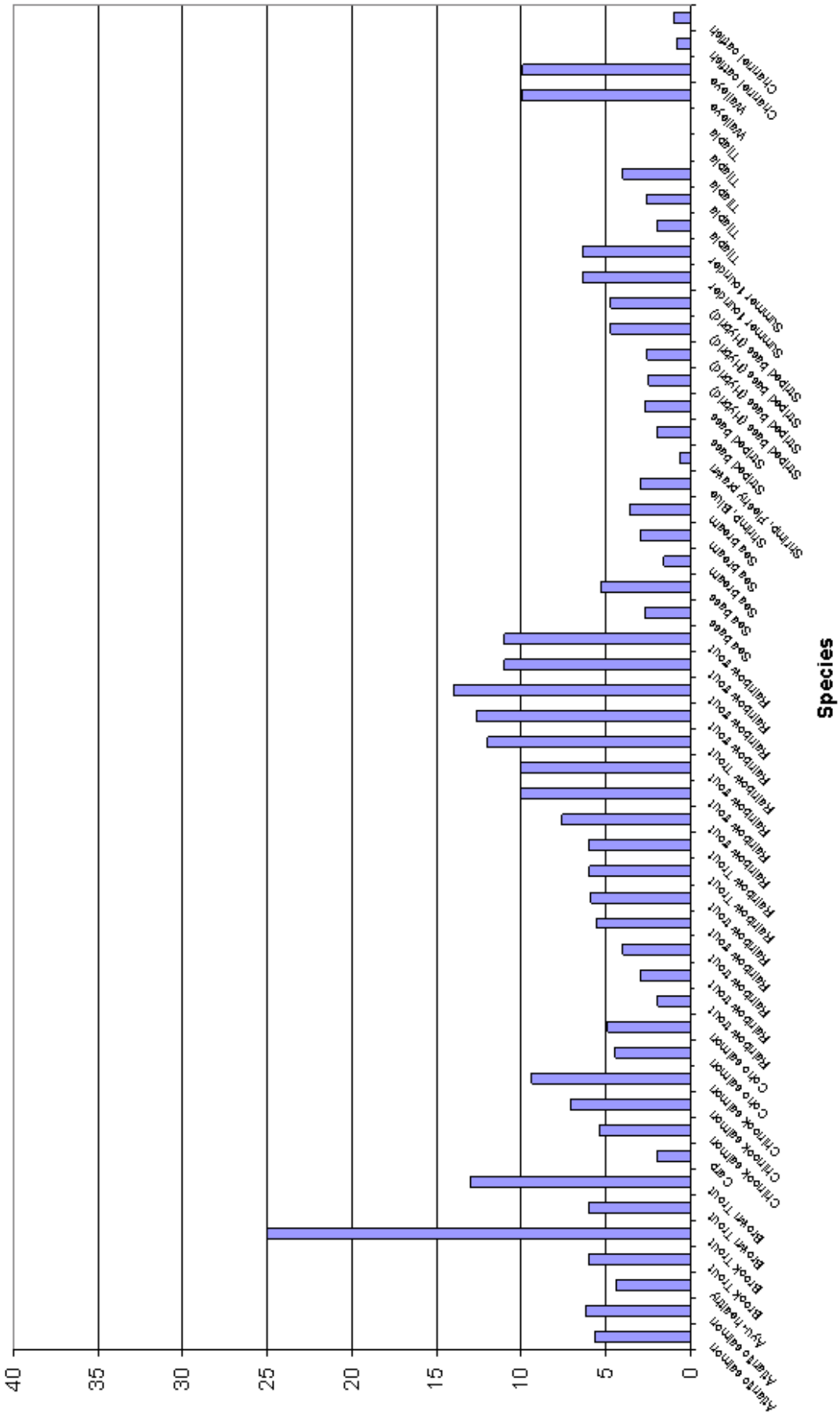
Eel
Eel
Rainbow trout
Rainbow trout
Rainbow trout
Chlortrio/ oxytetrach
Rainbow trout
Rainbow trout
Rainbow trout
Chlortrio/ oxytetrach
Rainbow trout
Rainbow trout
Yellow perch
Rainbow trout
Cod
Rainbow trout
Chlortrio/ oxytetrach
Bluegill
Rainbow trout
Dogfish shark
Rainbow trout
Rainbow trout
Rainbow trout
Rainbow trout
Eel
Rainbow trout
Rainbow trout
Rainbow trout
Chlortrio/ oxytetrach


ANTIBIOTICS - Tetracyclines
t1/2 Muscle or Muscle + Skin - All Species
Days
0
5
10
15
20
25
30
35
40
Species
Atlantic salmon
Atlantic salmon
Ayu, hoeating
Brook Trout
Brook Trout
Brook Trout
Brook Trout
Carp
Chinook salmon
Chinook salmon
Chinook salmon
Chinook salmon
Coho salmon
Coho salmon
Rainbow trout
Rainbow trout
Rainbow trout

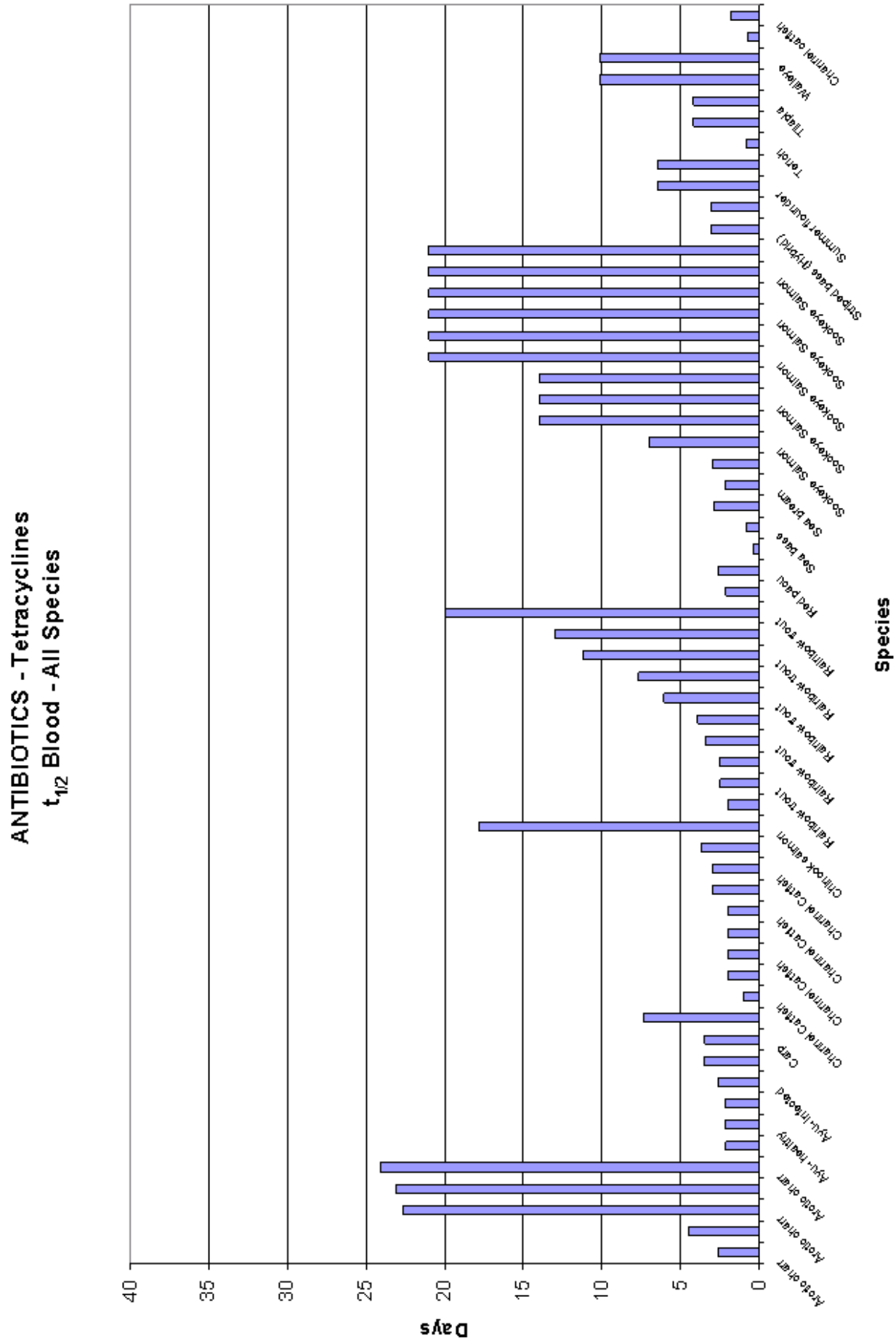


Figure 4. Estimates for OTC in Blood by Species.

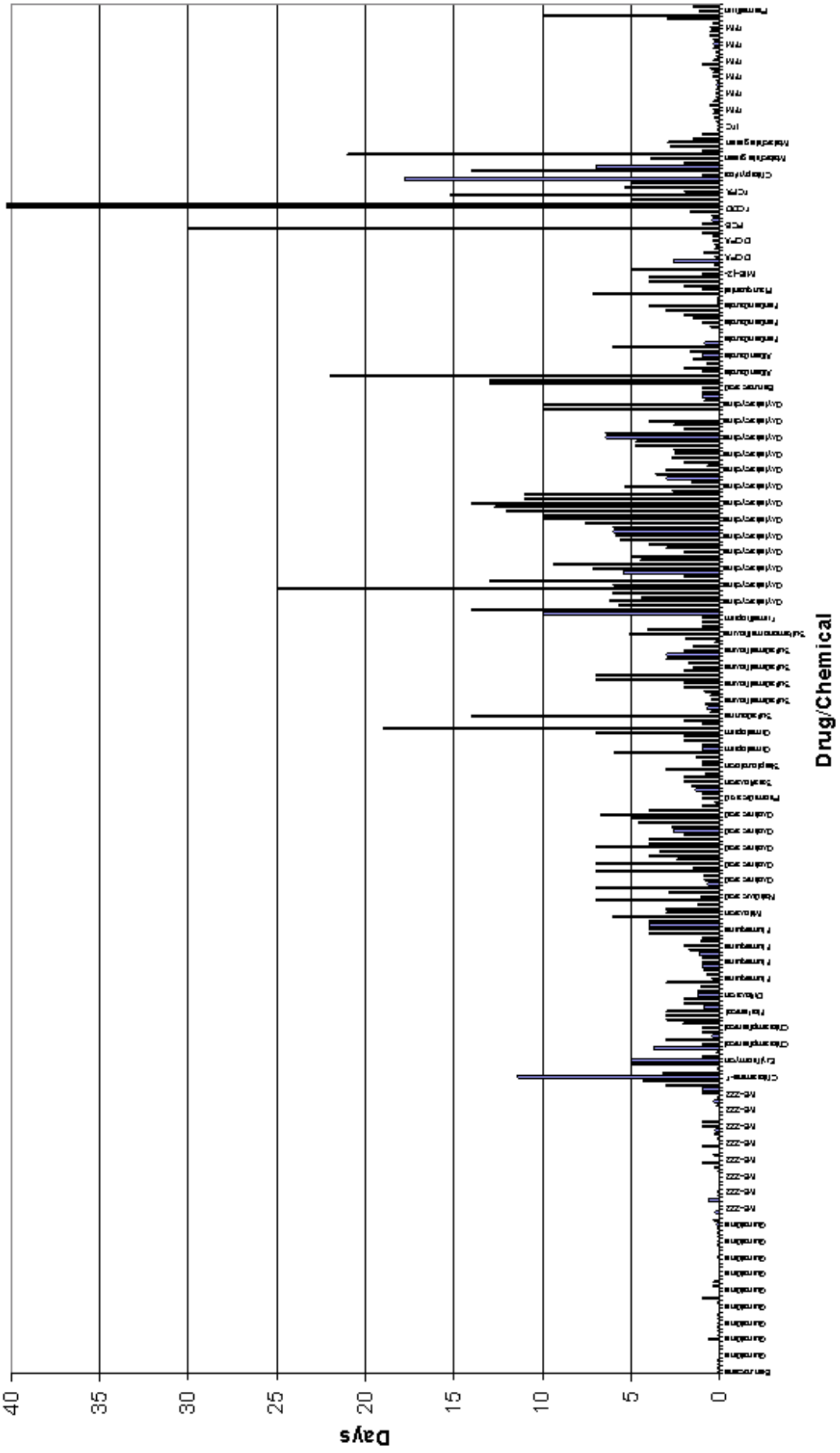


Figure 5. Overview of All Compounds and All Species.

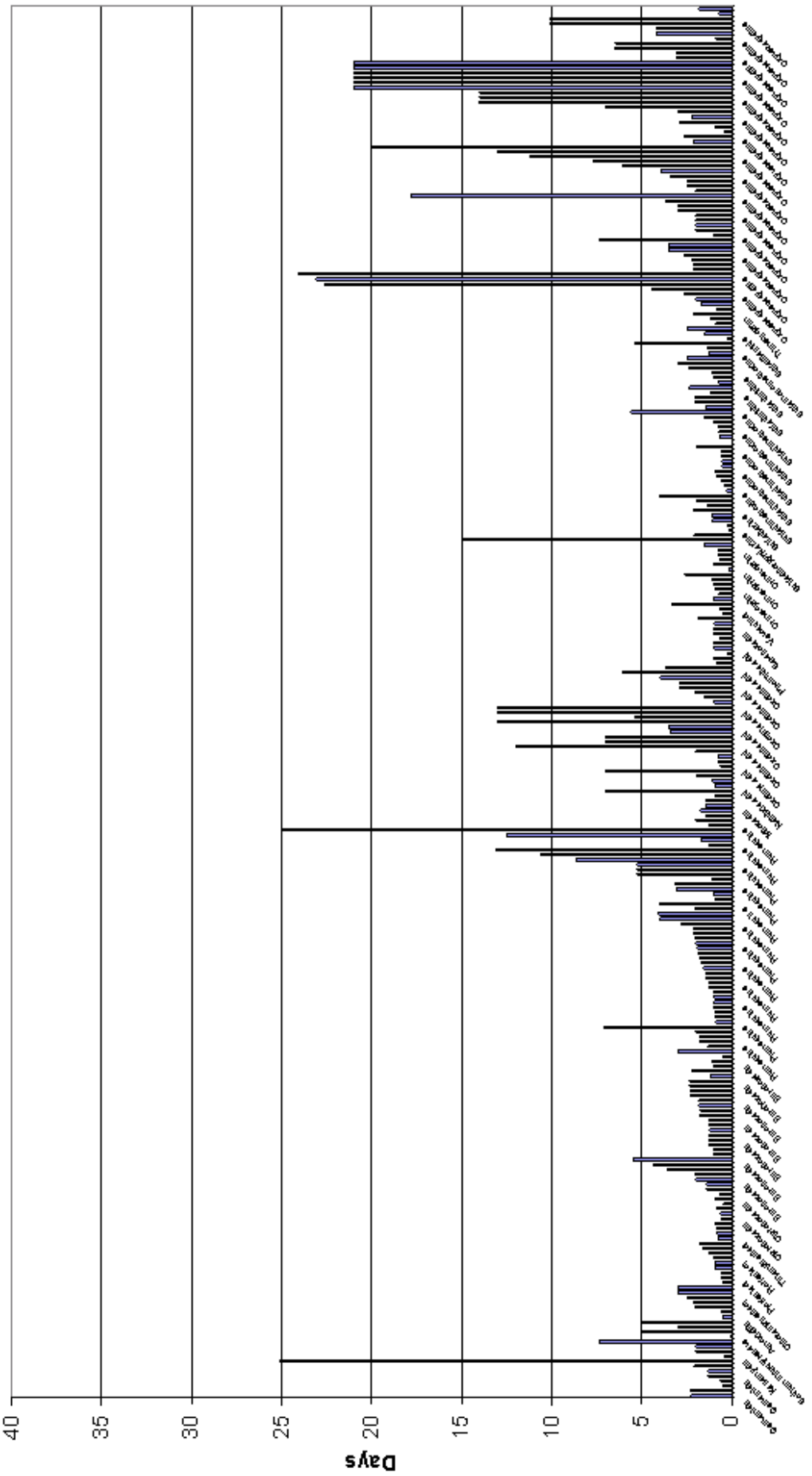


Figure 6. All Antibiotics in Blood of All Species.

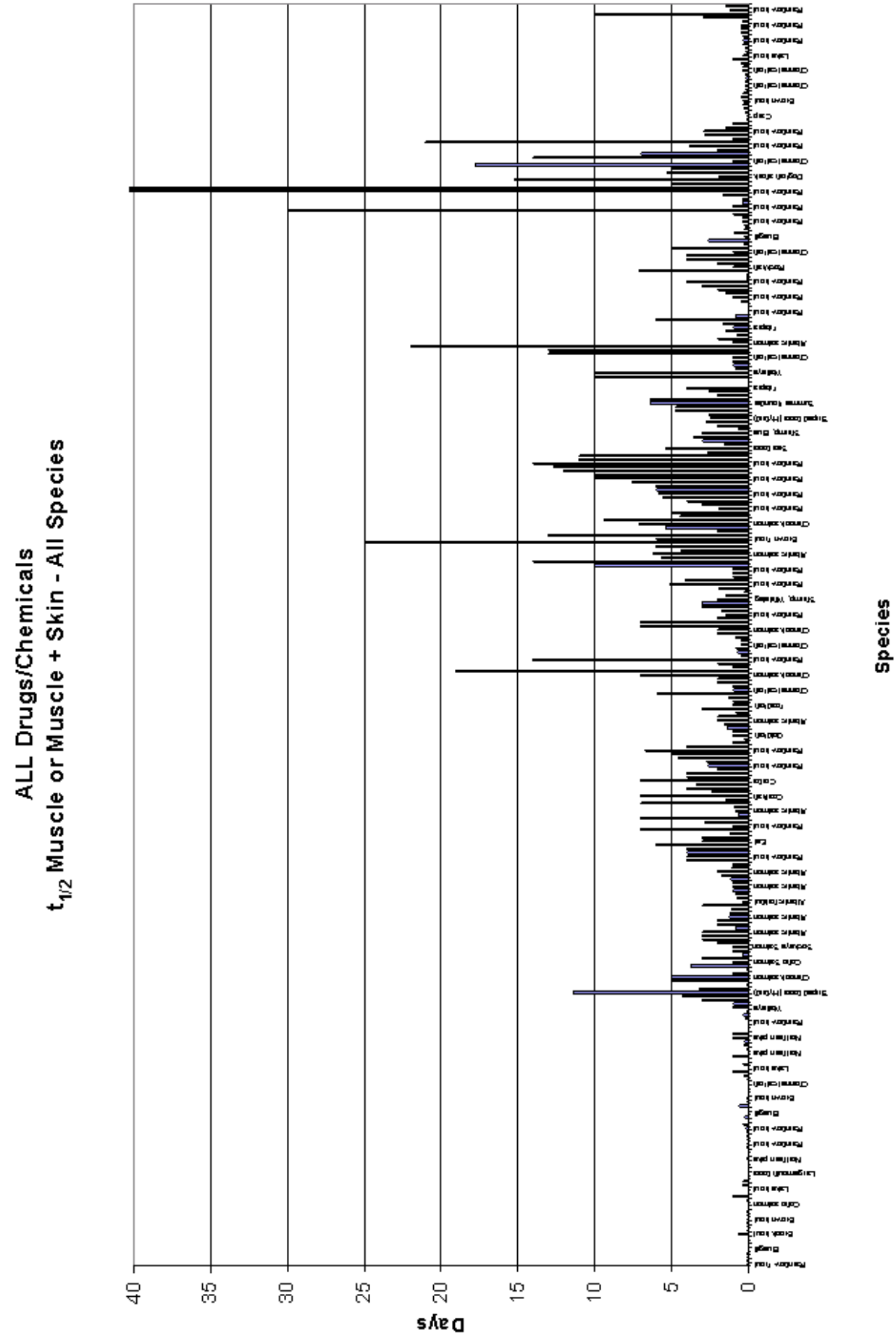


Figure 7. All Drugs in Muscle by Species.

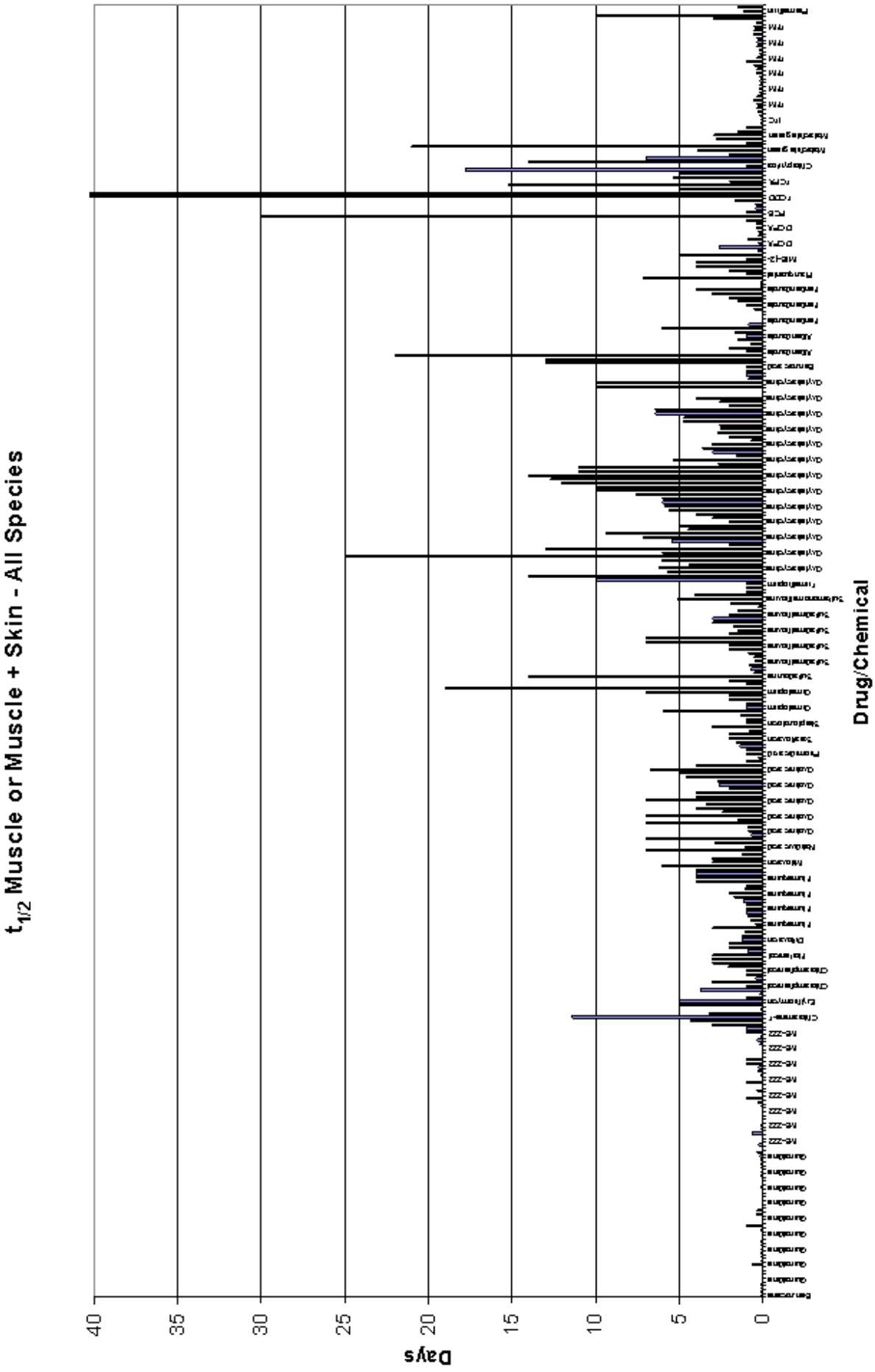


Figure 8. All Drugs in Muscle by Drug.

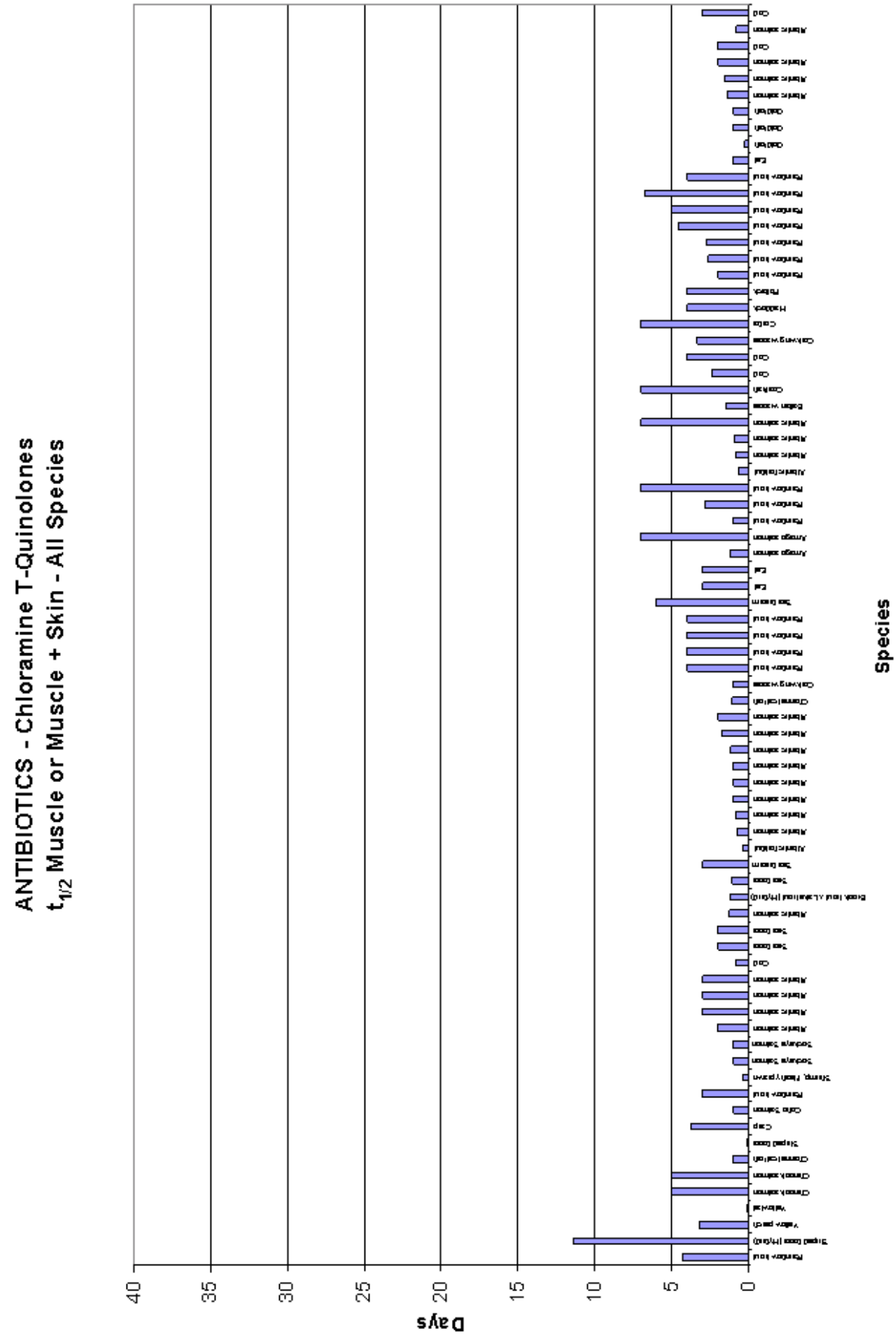


Figure 9. Antibiotics - Chloramine T - Quinolones in Muscle by Species.

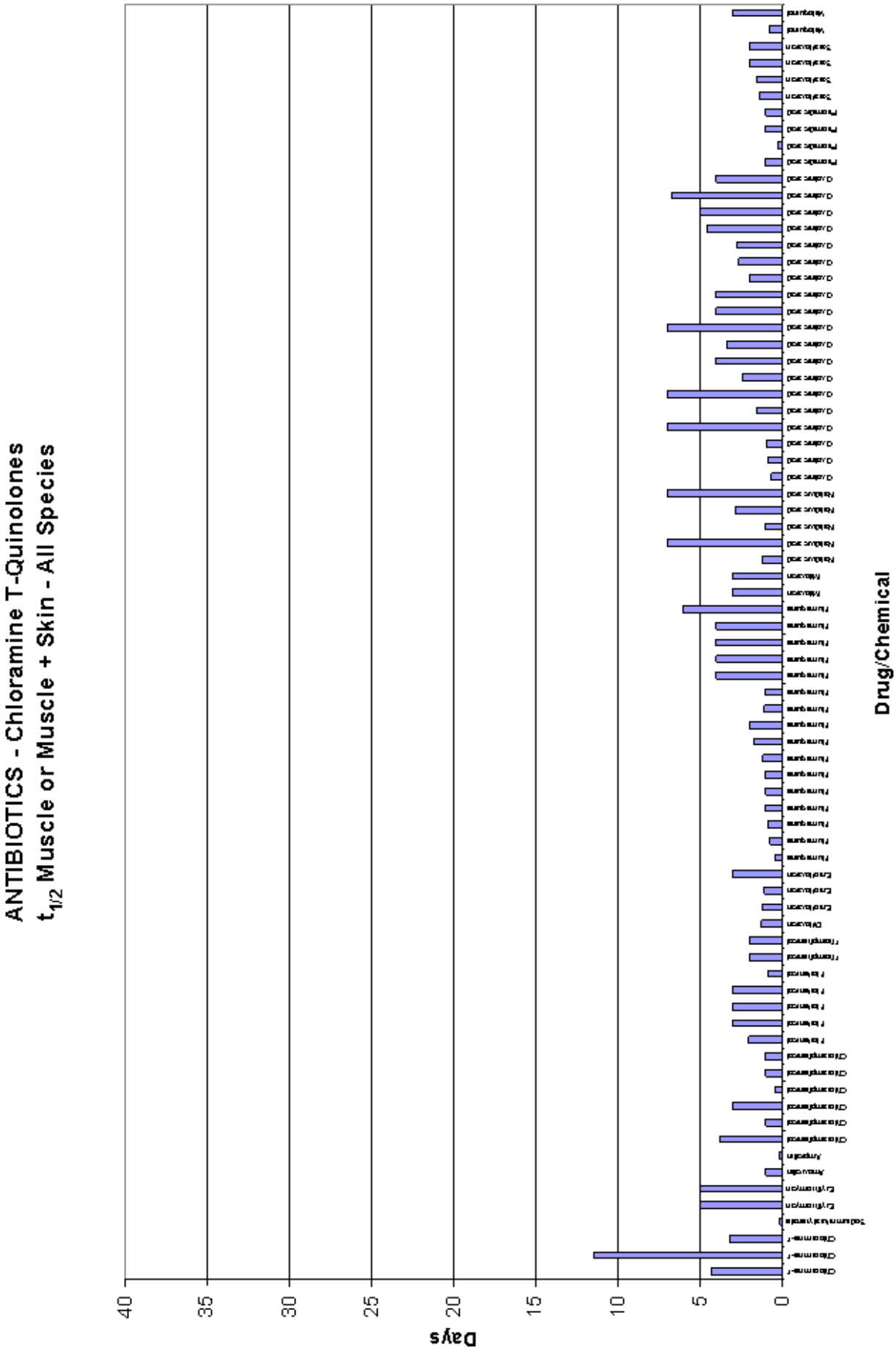


Figure 10. Antibiotics - Chloramine T - Quinolones in Muscle by Drug.

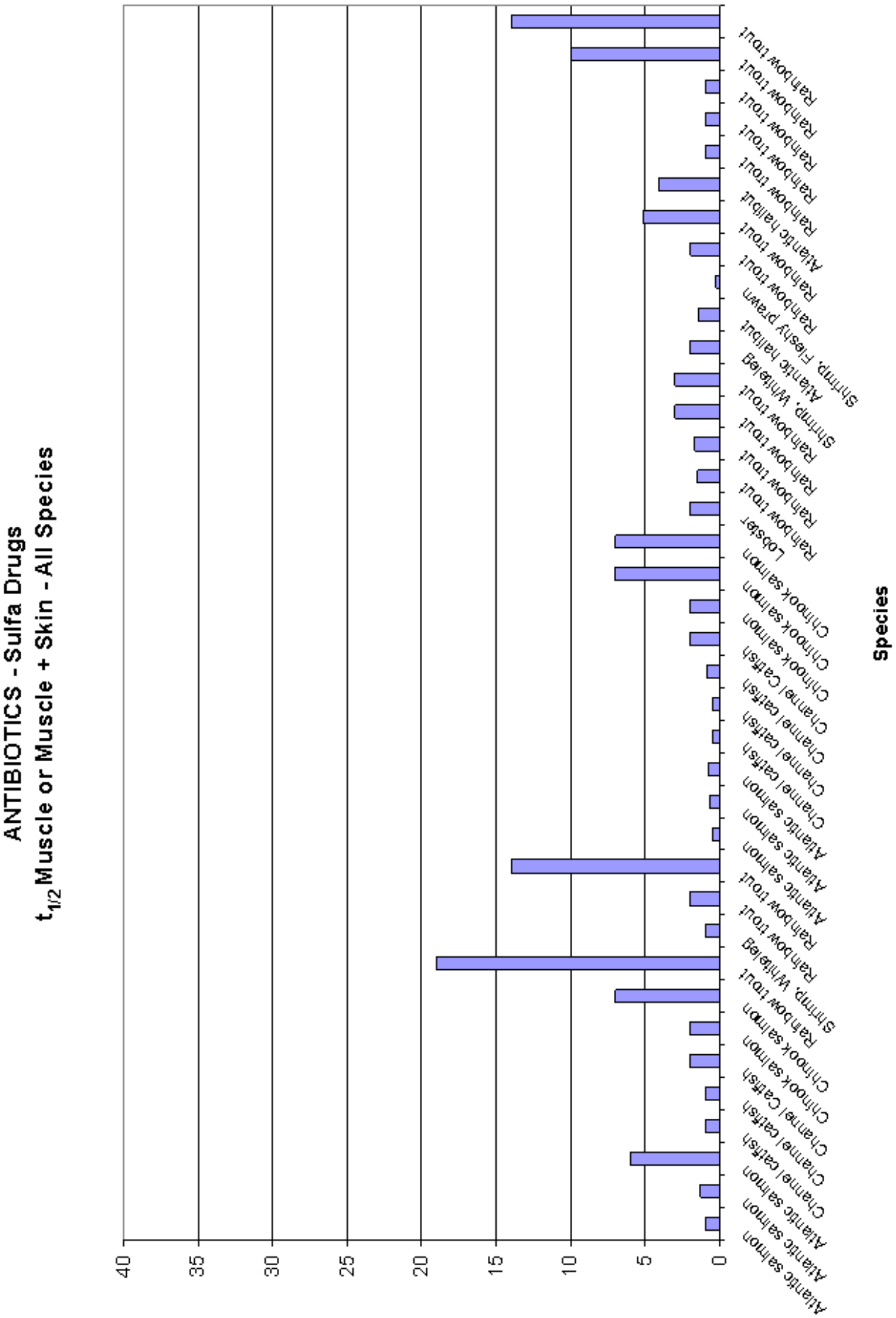


Figure 11. Antibiotics - Sulfa Drugs in Muscle by Species.

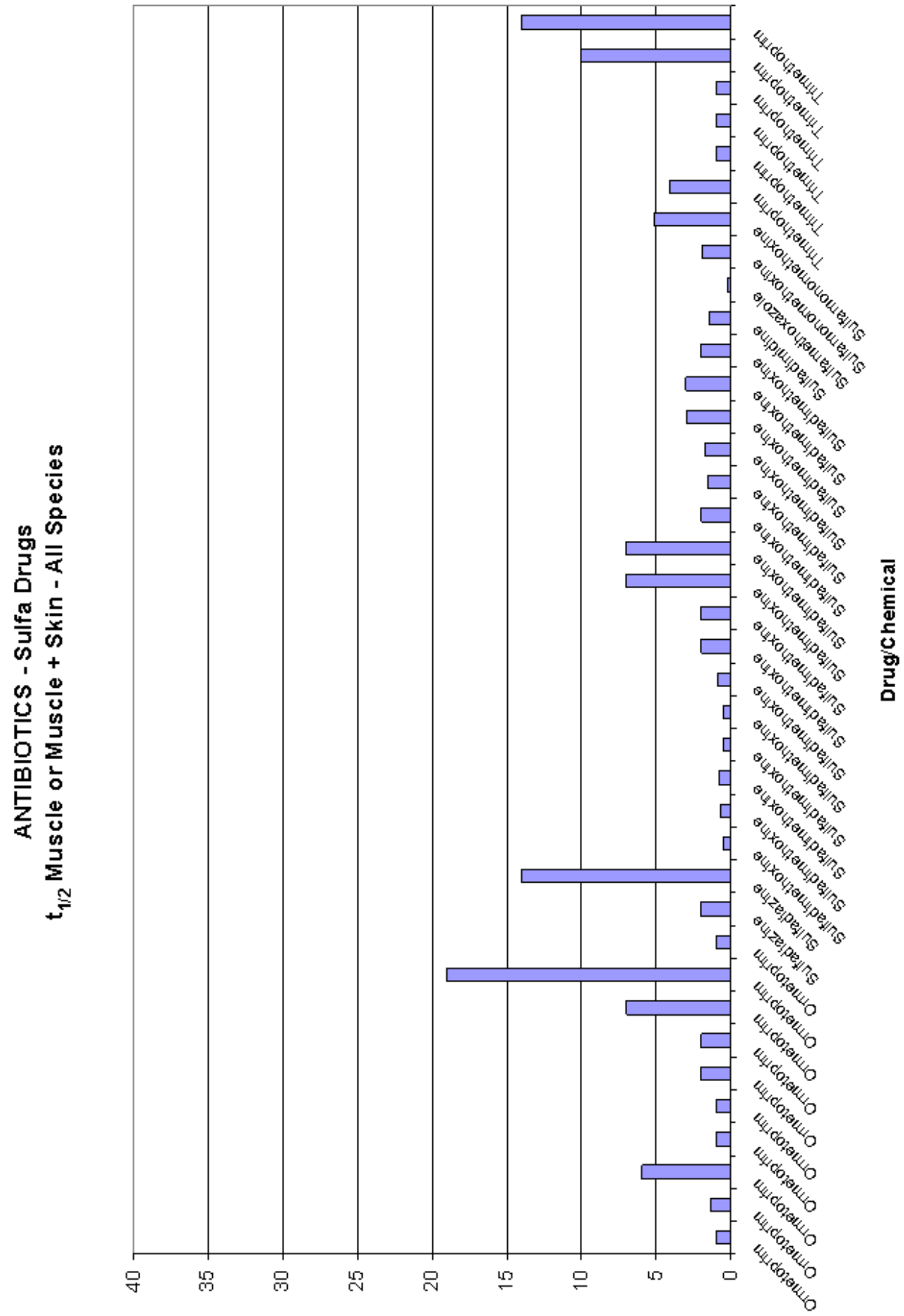
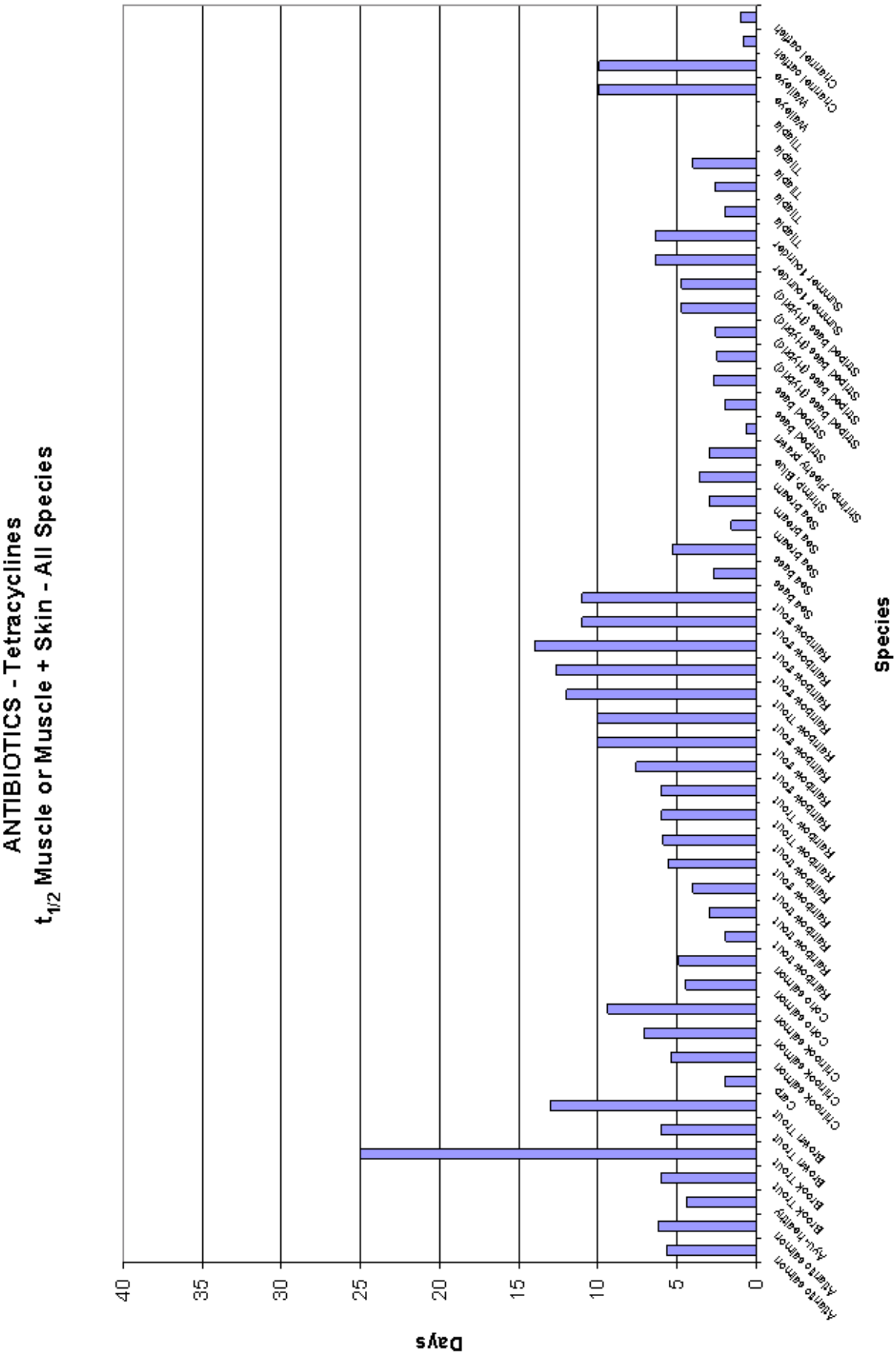


Figure 12. Antibiotics - Sulfa Drugs in Muscle by Drug.


ANTIBIOTICS - Tetracyclines
t1/2 Muscle or Muscle + Skin - All Species
Days
0
5
10
15
20
25
30
35
40
Species
Atlantic salmon
Atlantic salmon
Ayu, freshly
Brook Trout
Brook Trout
Brook Trout
Brown Trout
Brown Trout
Carp
Chinook salmon
Chinook salmon
Chinook salmon
Coho salmon
Coho salmon
Rainbow trout
Rainbow trout
Rainbow trout

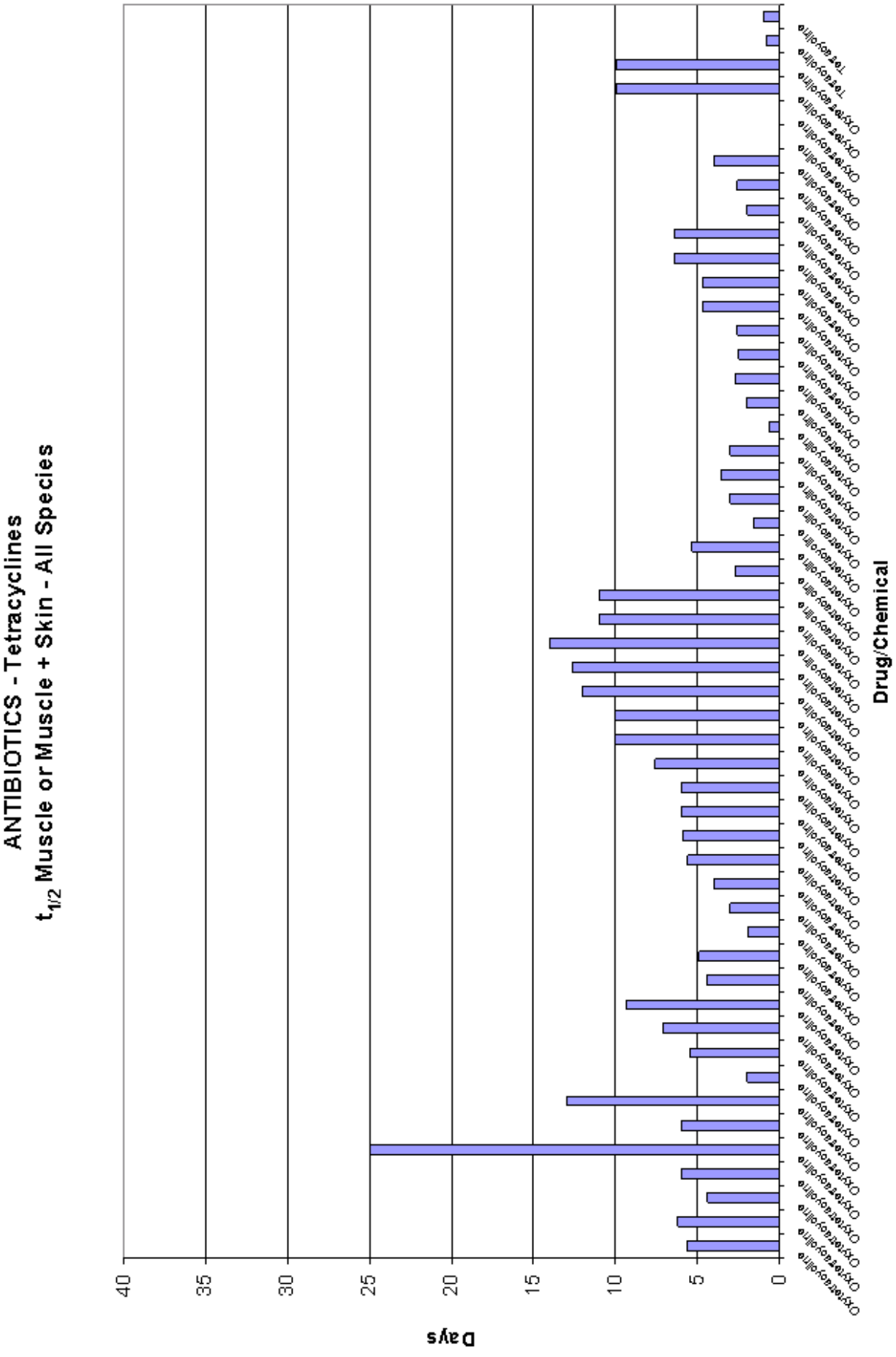


Figure 14. Antibiotics -Tetracyclines in Muscle by Drug.

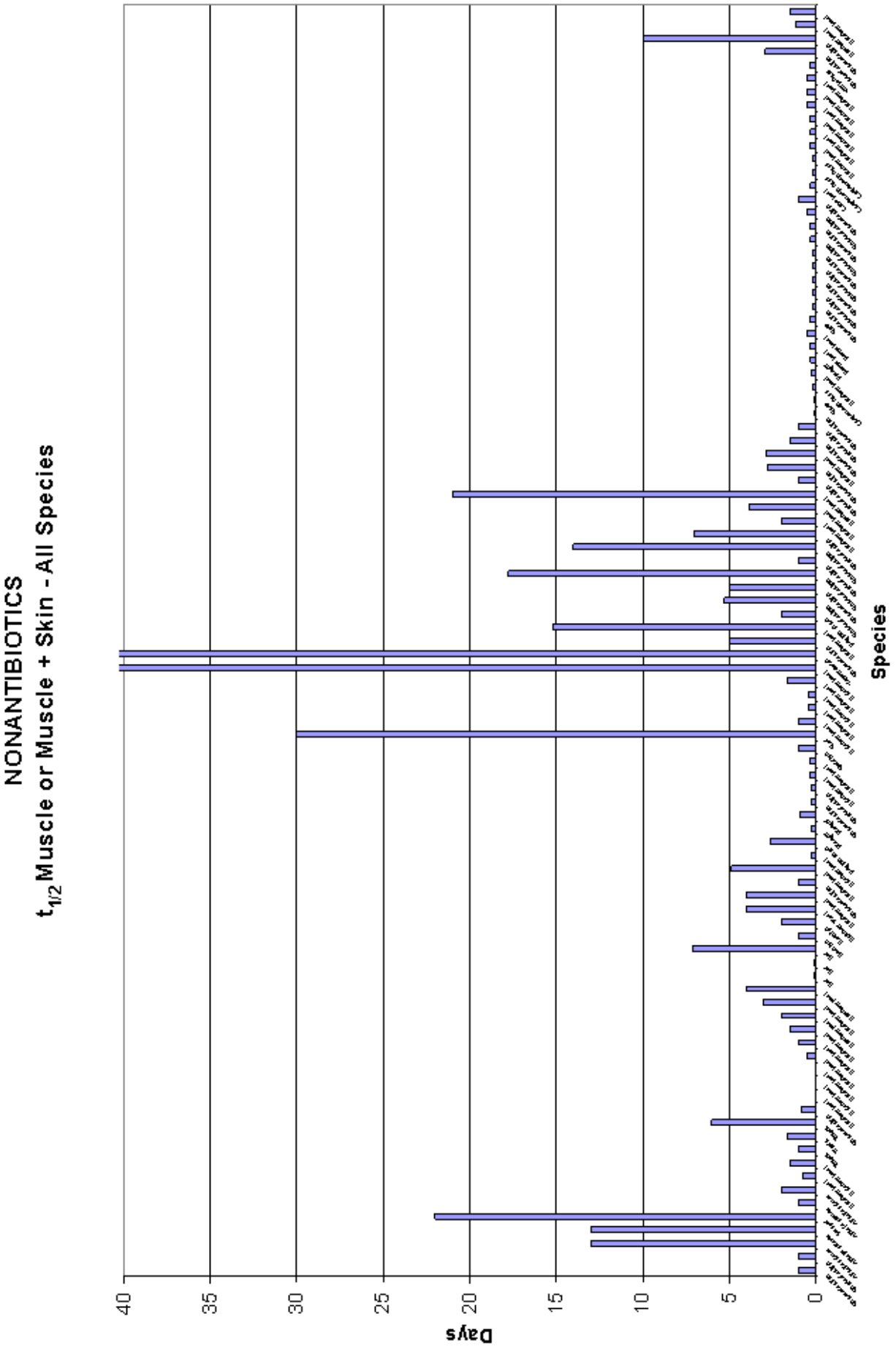


Figure 15. Nonantibiotics in Muscle by Species.

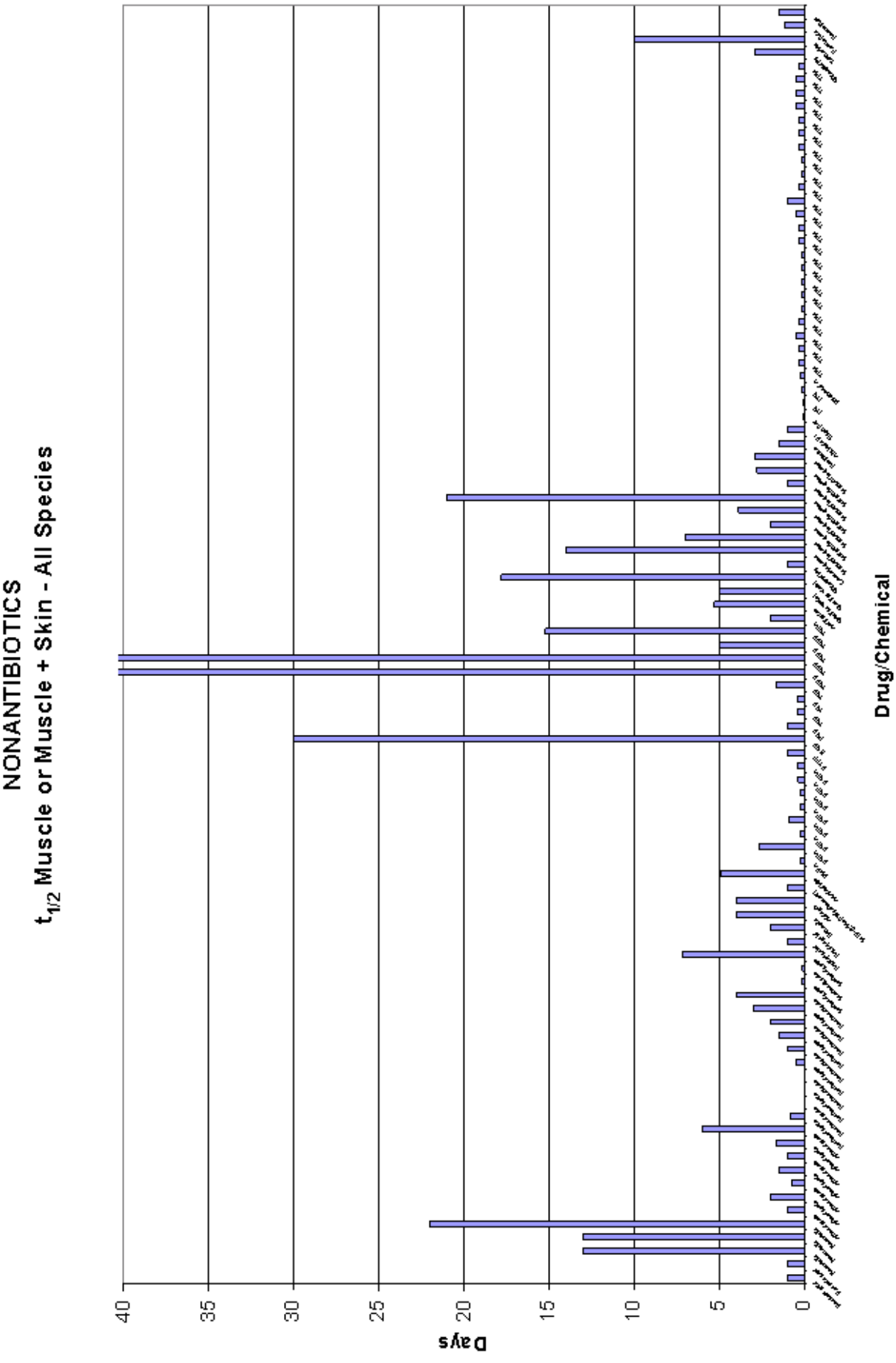


Figure 16. Nonantibiotics in Muscle by Drug.

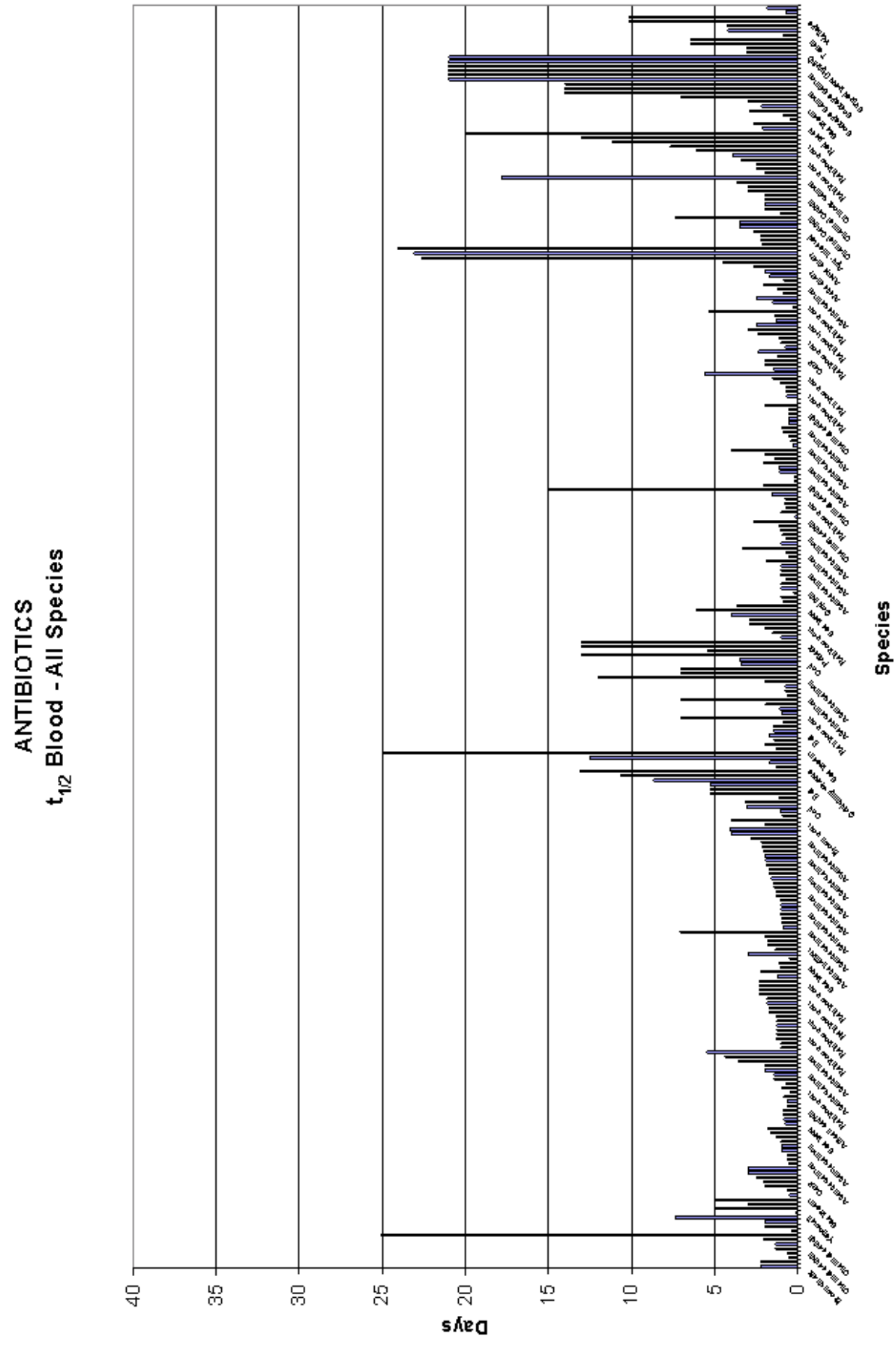


Figure 17. All Antibiotics in Blood by Species.

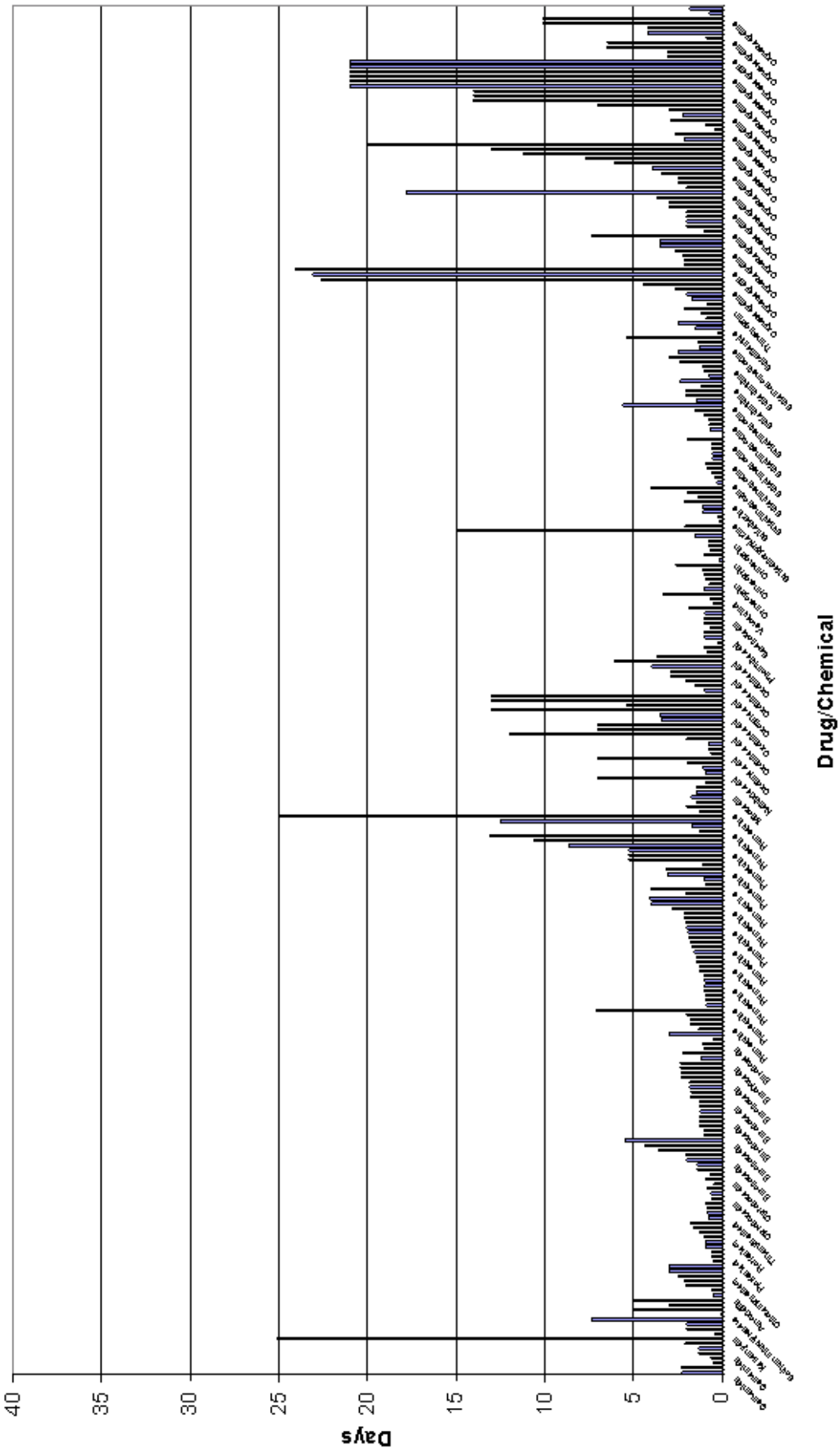


Figure 18. All Antibiotics in Blood by Drug.

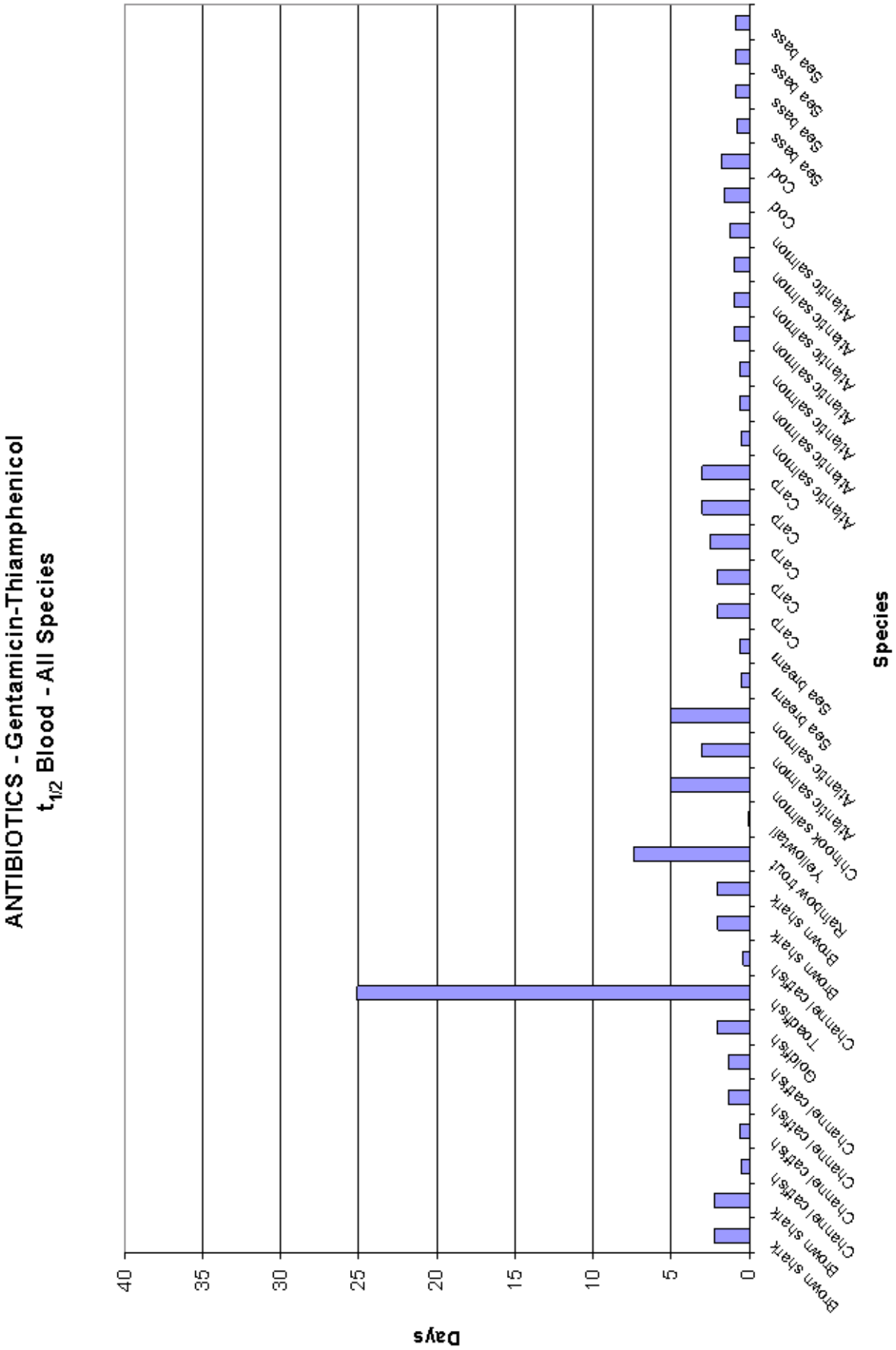


Figure 19. Antibiotics - Gentamicin-Thiamphenicol in Blood by Species.

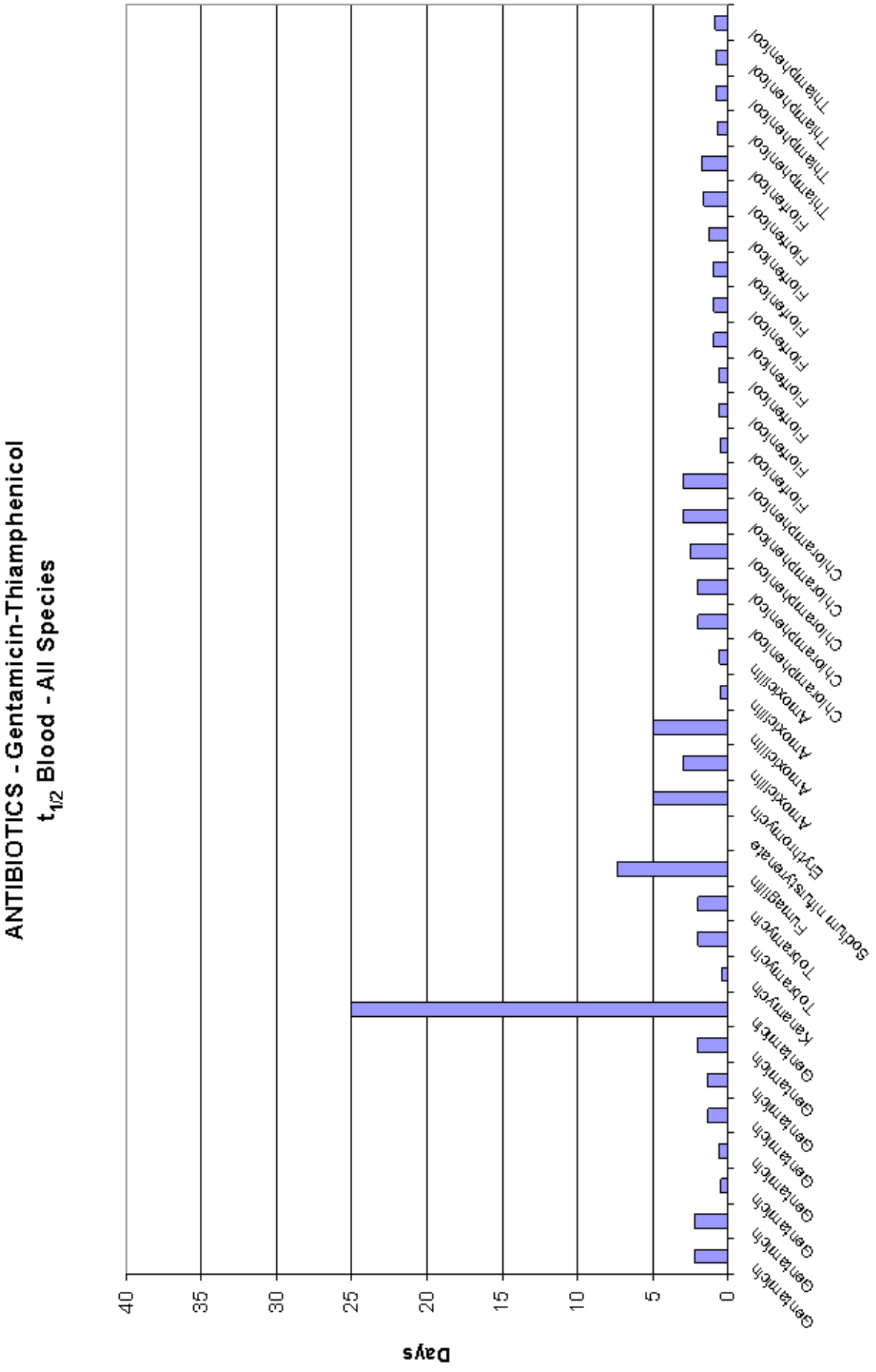
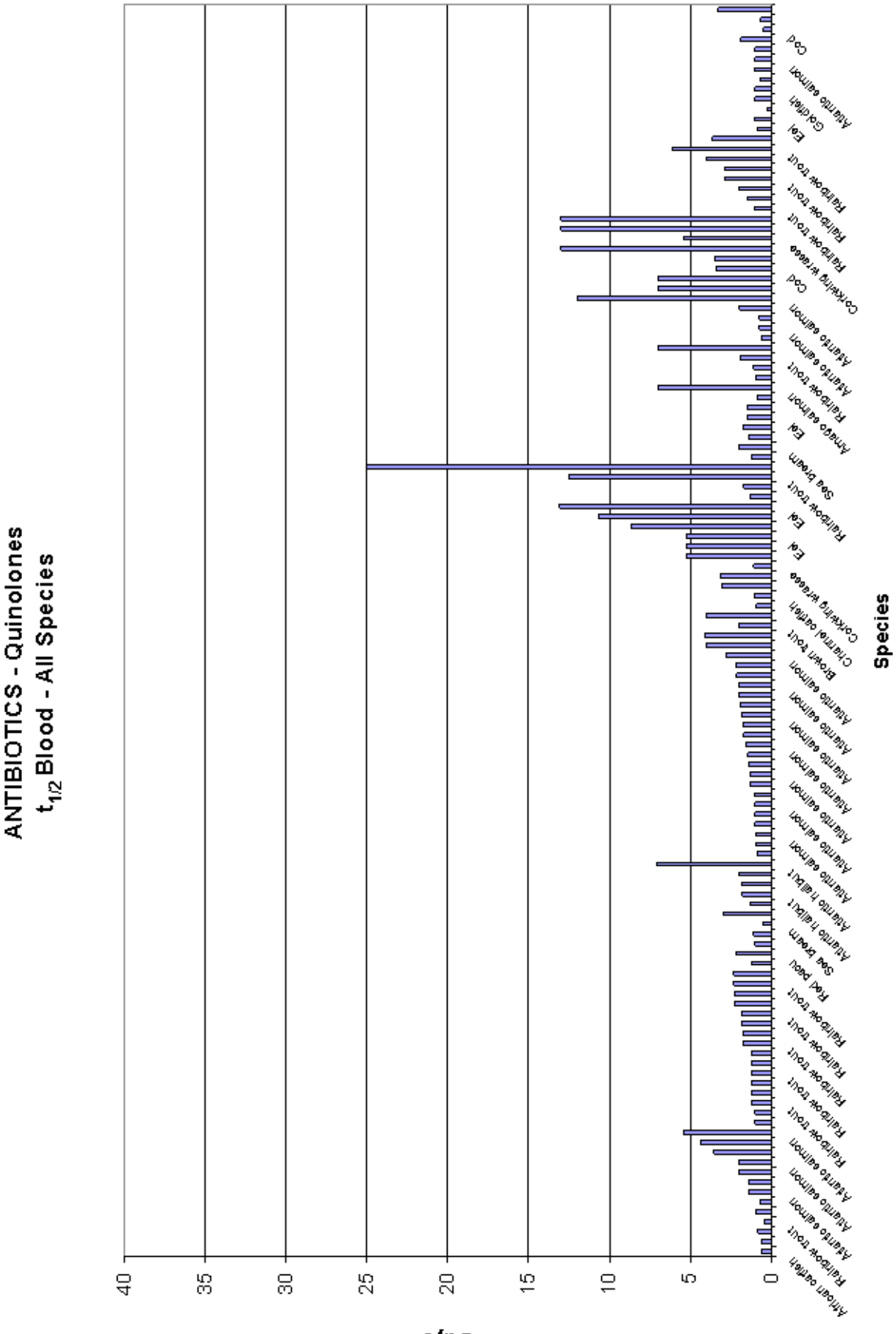
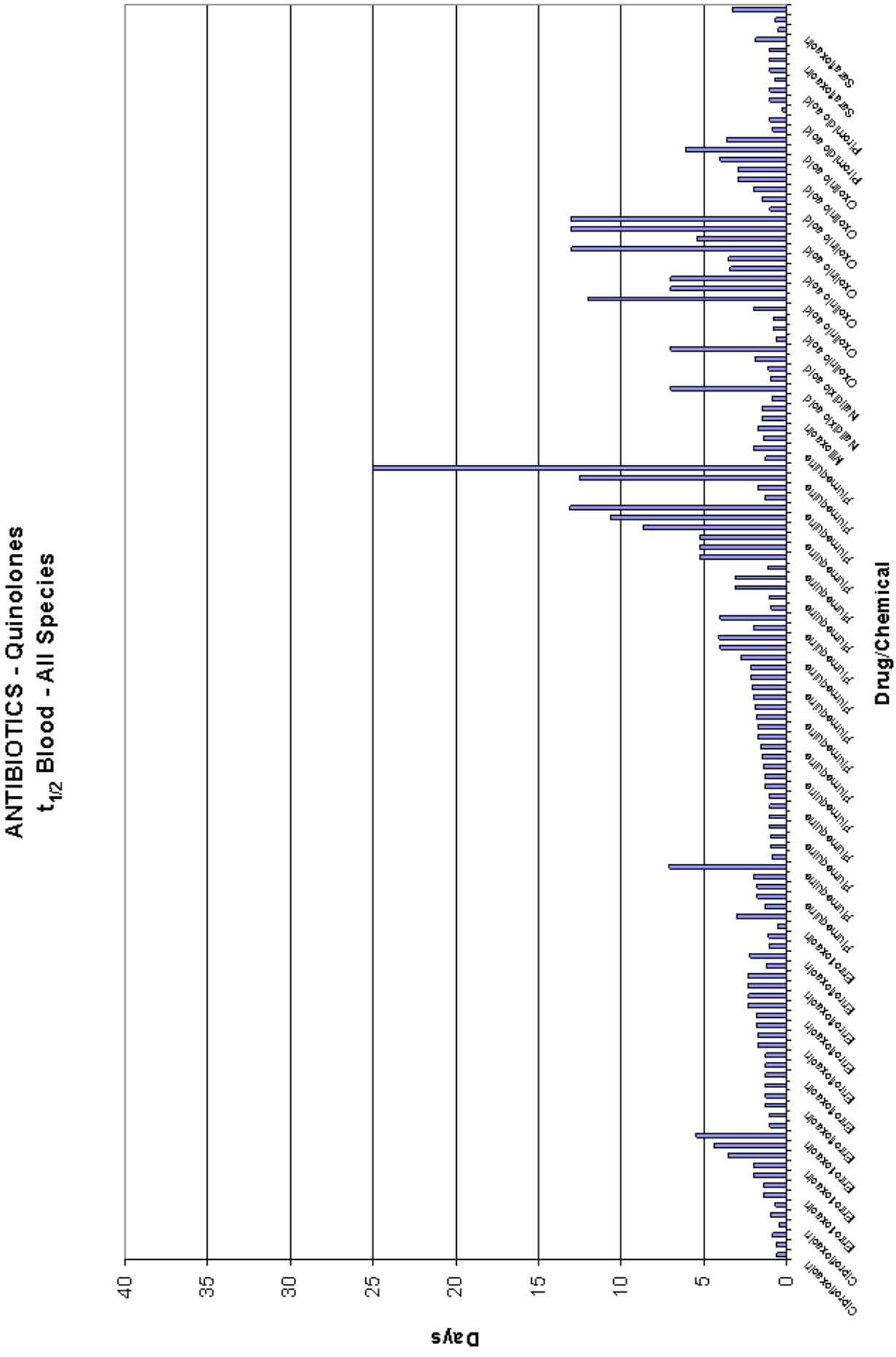


Figure 20. Antibiotics - Gentamicin-Thiamphenicol in Blood by Drug.


ANTIBIOTICS - Quinolones
$t_{1/2}$ Blood - All Species
Days
0
5
10
15
20
25
30
35
40
Species
African catfish
Rainbow trout
Asiatic salmon
Asiatic salmon
Asiatic salmon
Asiatic salmon
Asiatic salmon
Rainbow trout
Rainbow trout
Rainbow trout
Rainbow trout
Rainbow trout
Rainbow trout
Rainbow trout
Rainbow trout
Rainbow trout
Rainbow trout
Asiatic salmon
Asiatic salmon
Asiatic salmon
Asiatic salmon
Asiatic salmon


ANTIBIOTICS - Quinolones
$t_{1/2}$ Blood - All Species
Days
Drug/Chemical
0
5
10
15
20
25
30
35
40
Ciprofloxacin
Enrofloxacin
Enrofloxacin
Enr

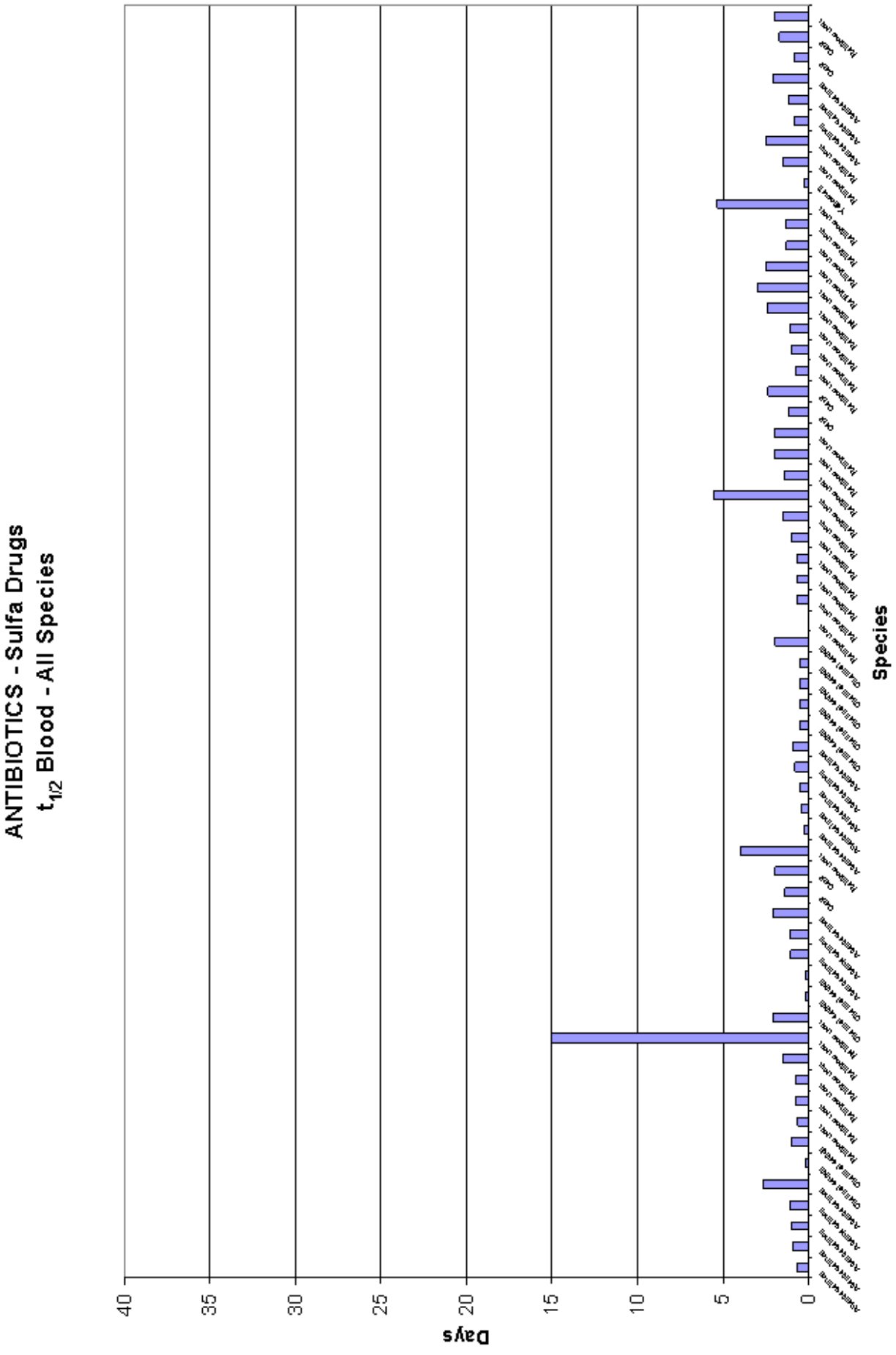


Figure 23. Antibiotics - Sulfa Drugs in Blood by Species.

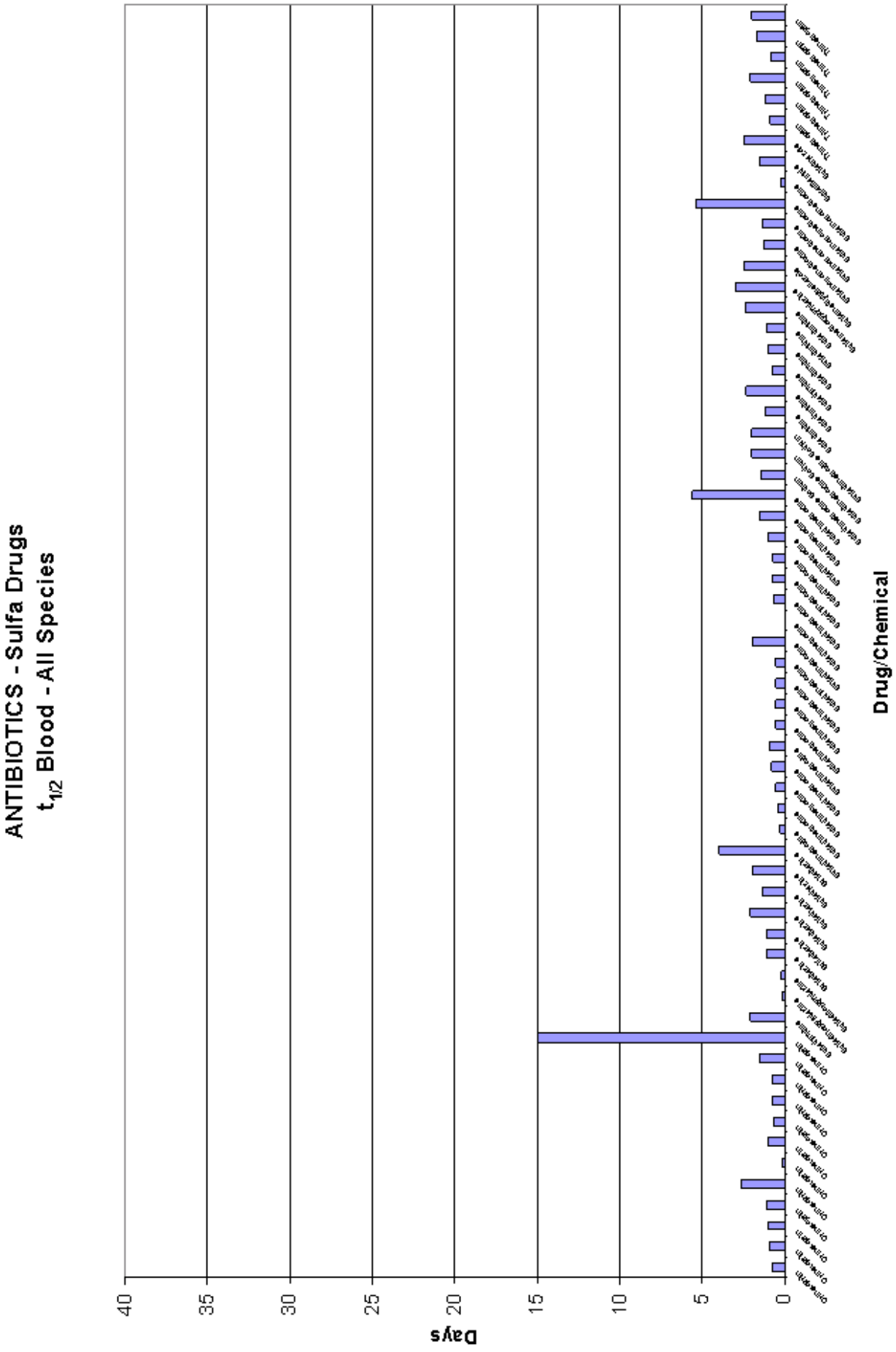


Figure 24. Antibiotics - Sulfa Drugs in Blood by Drug.

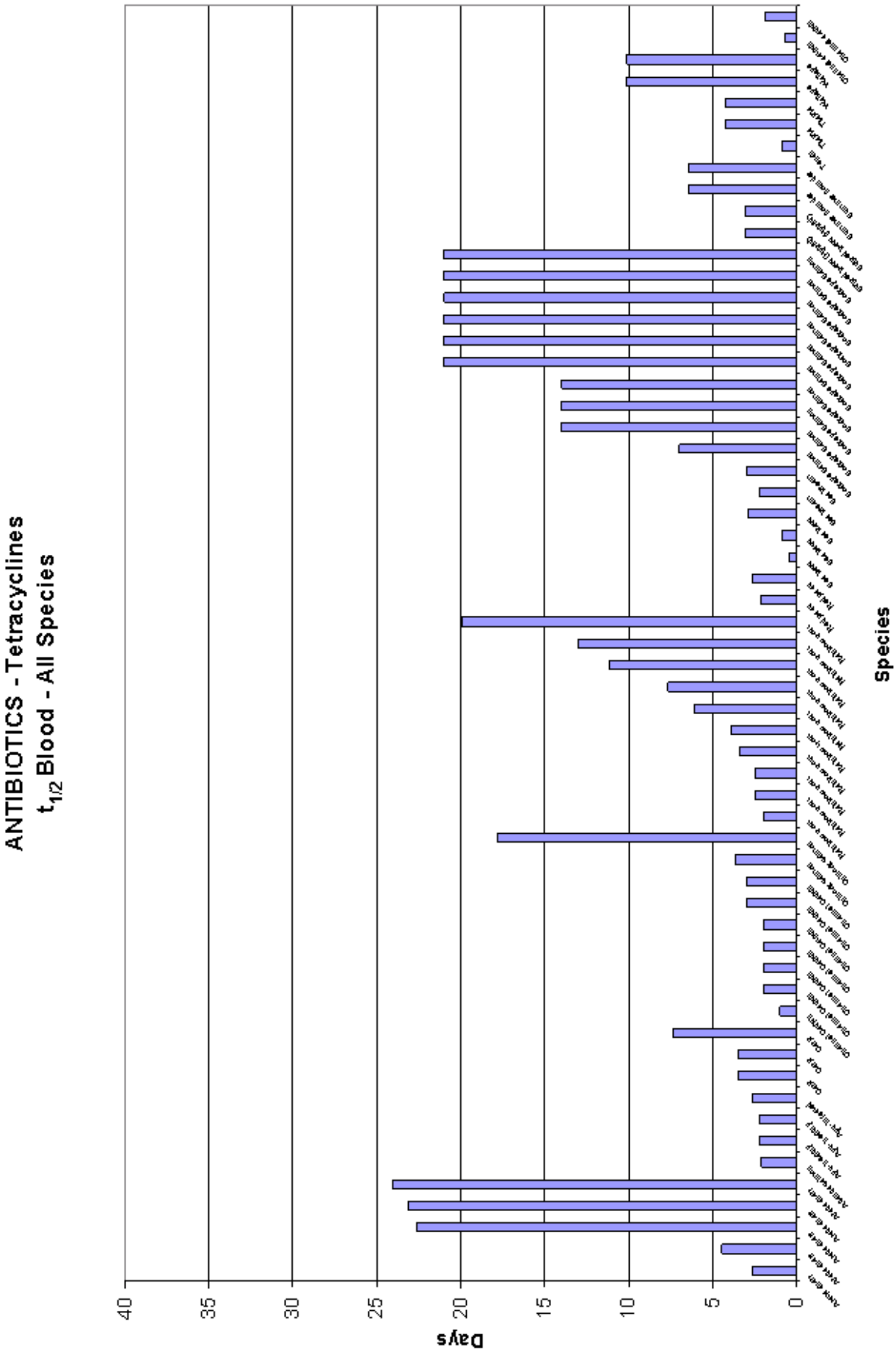


Figure 25. Antibiotics - Tetracyclines in Blood by Species.

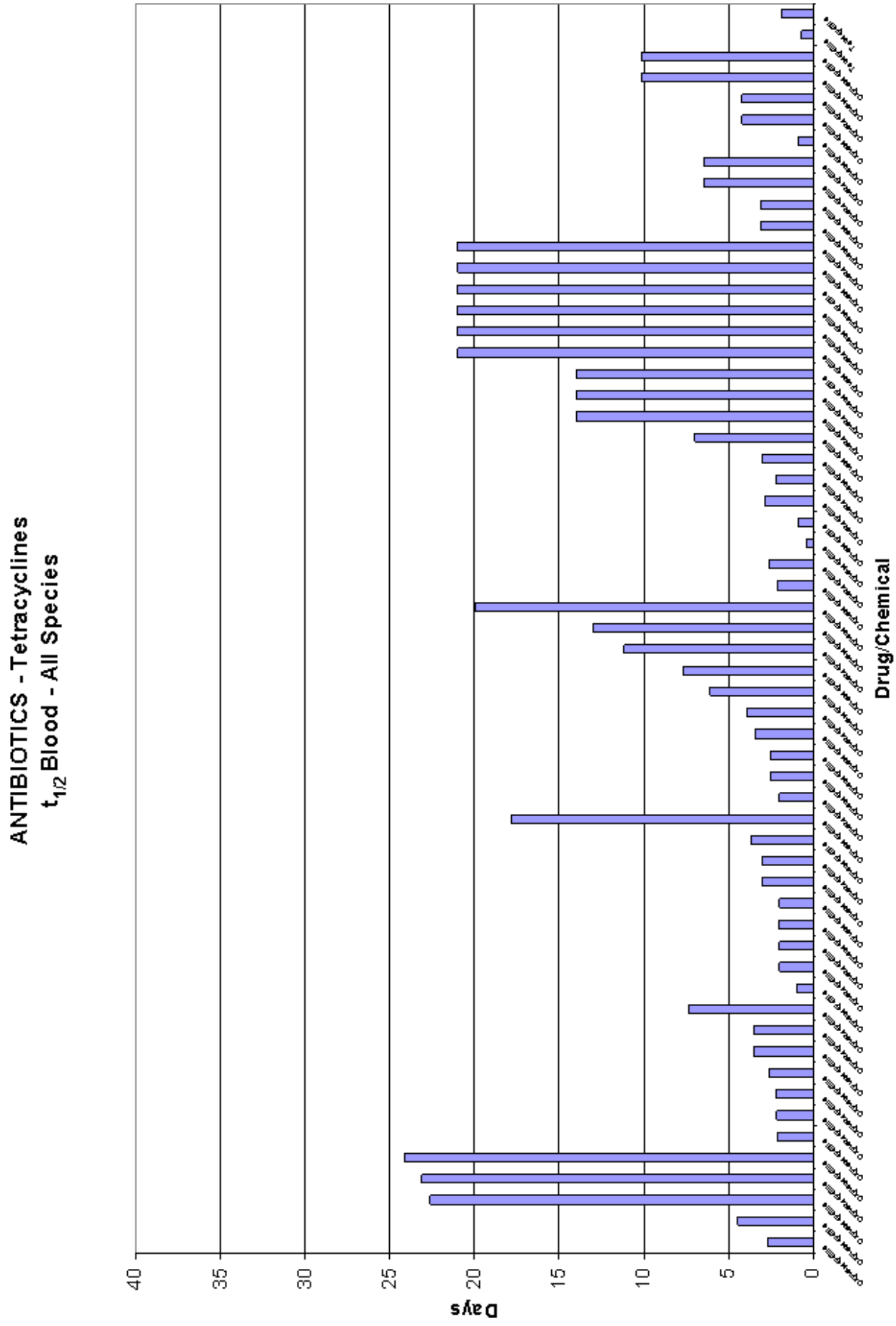


Figure 26. Antibiotics - Tetracyclines in Blood by Drug.

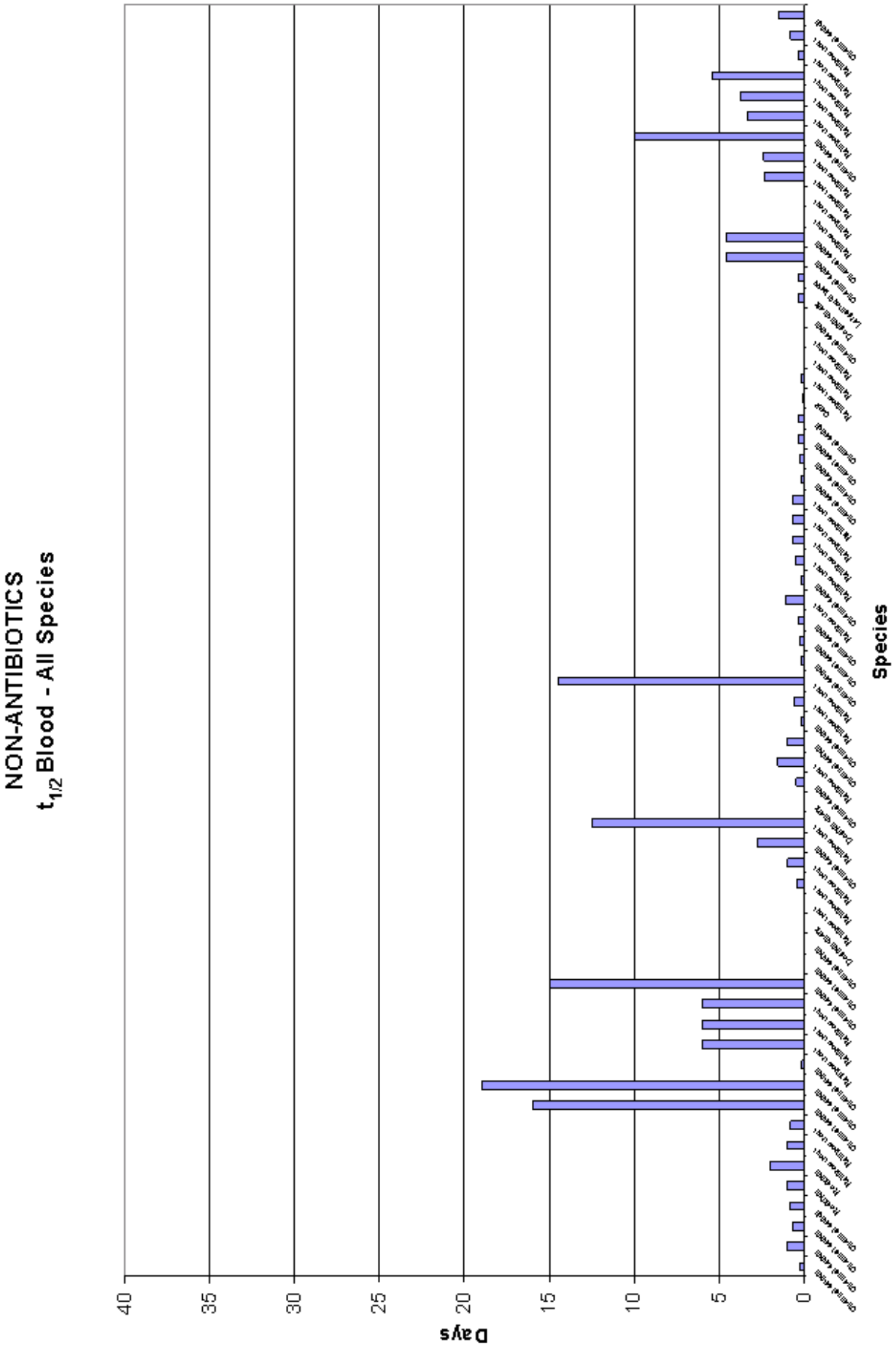


Figure 27. Antibiotics - Nonantibiotics in Blood by Species.

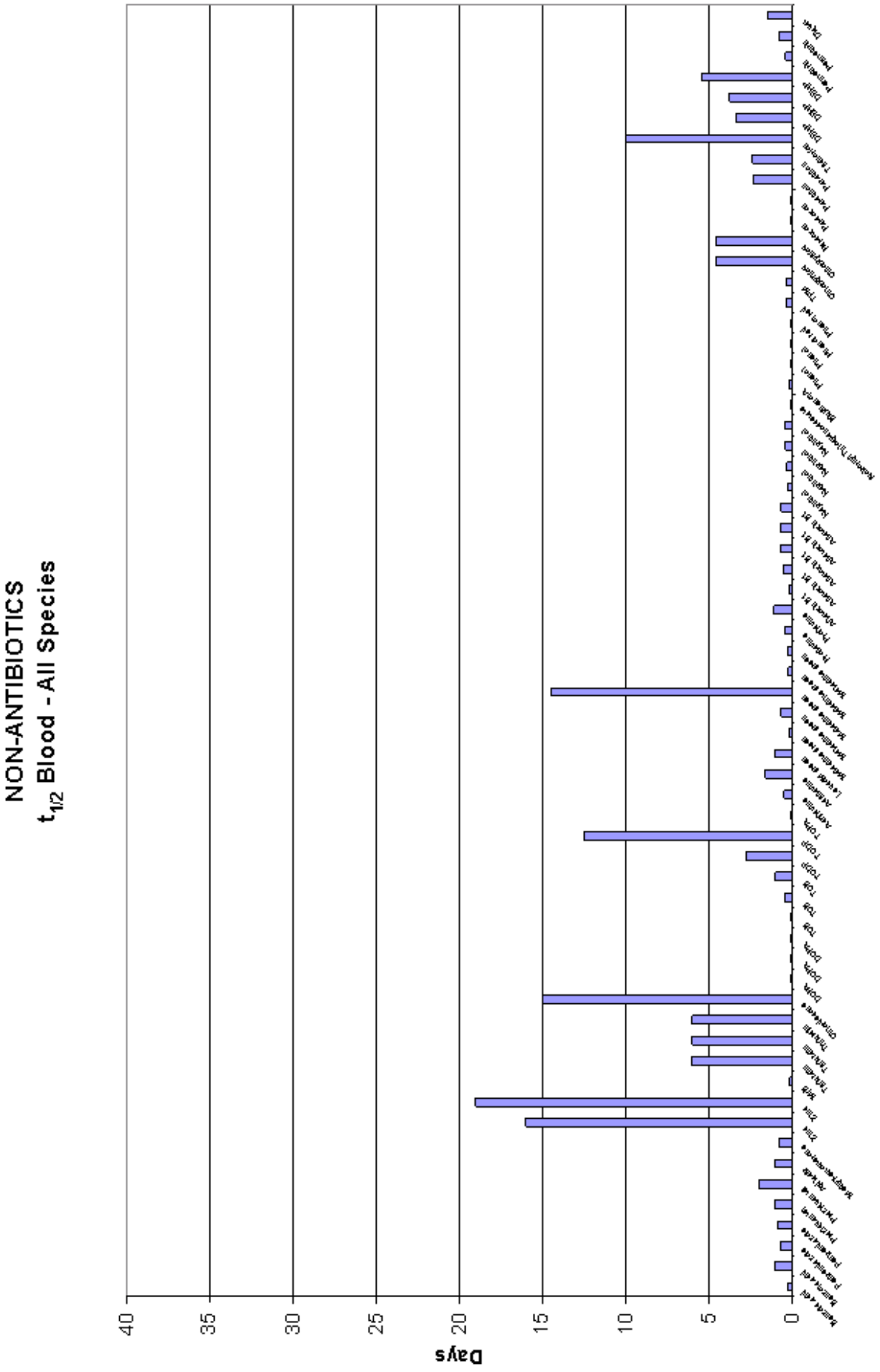


Figure 28. Antibiotics - Nonantibiotics in Blood by Drug.

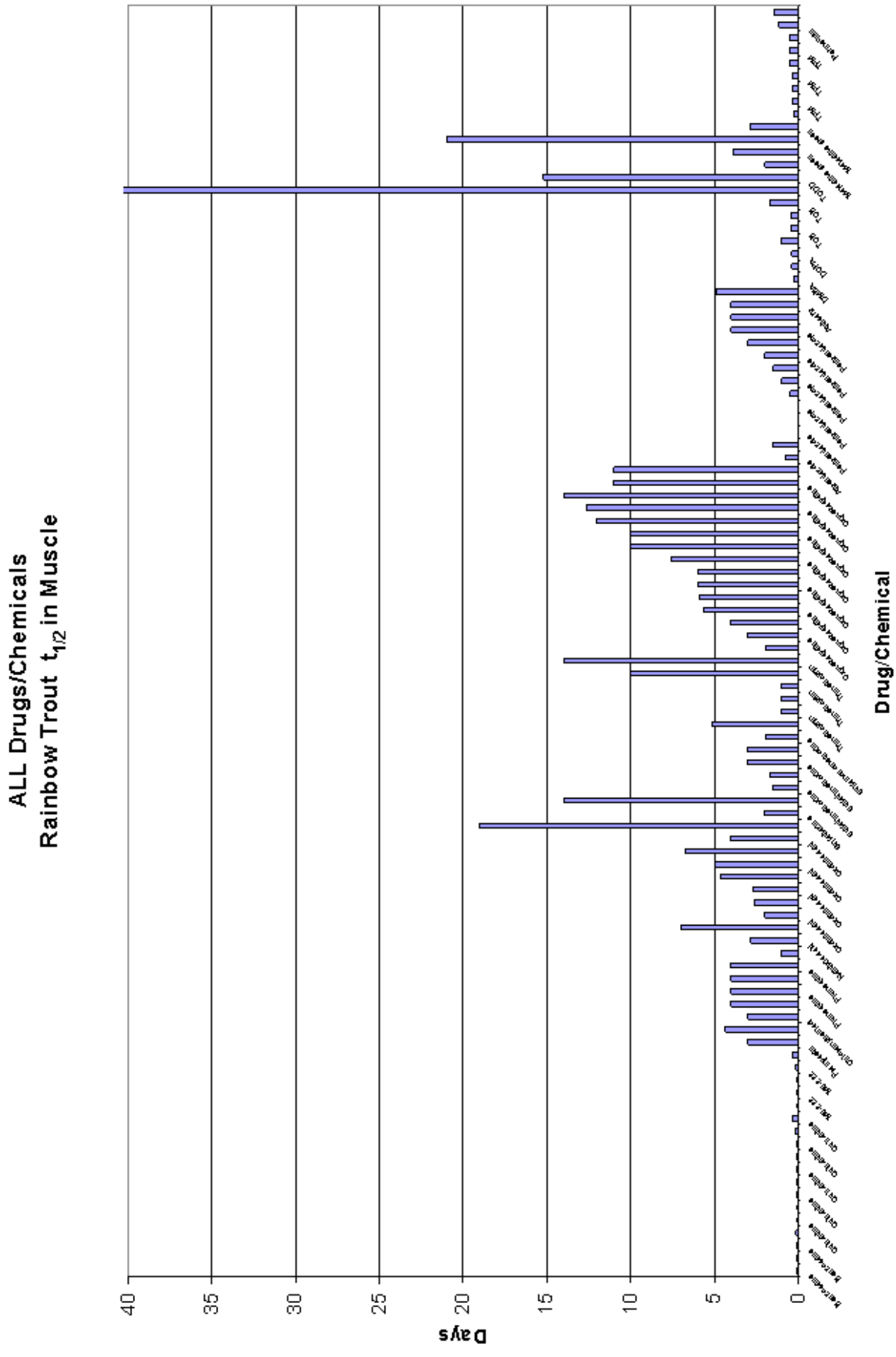


Figure 29. All Drugs in Rainbow Trout Muscle.

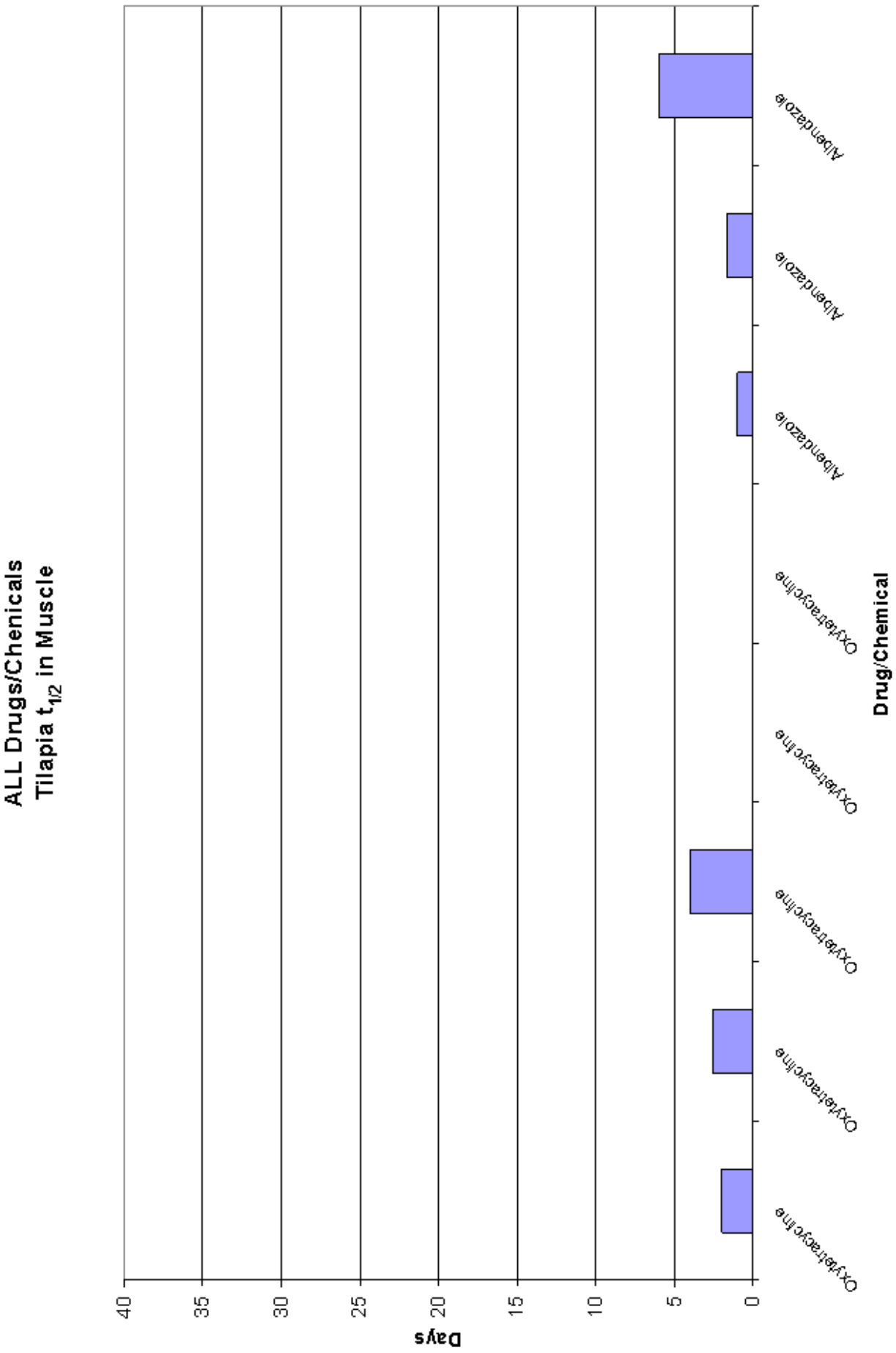
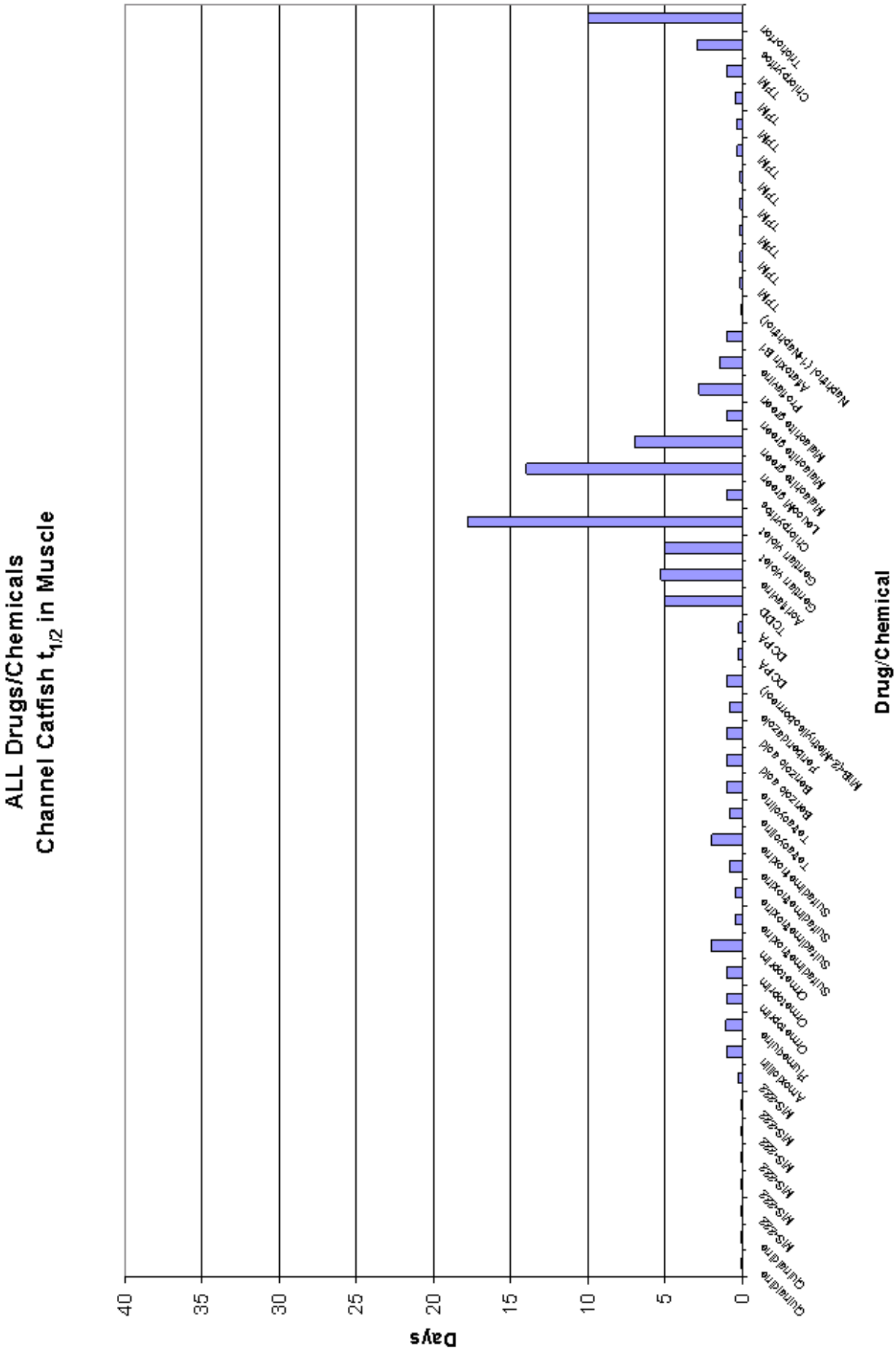


Figure 30. All Drugs in Tilapia Muscle.


ALL Drugs/Chemicals
Channel Catfish $t_{1/2}$ in Muscle
Days
0
5
10
15
20
25
30
35
40
Drug/Chemical
Quinaldine
Malachite green
Leucomalachite green
Chloropyrifos
Gentian violet
Acriflavine
TCDD
DCPA
Nitrofurazone
Benzocaine
Benzoic acid
Ivermectin
Oxytetracycline
Oxolinic acid
Sulfadimethoxine
Sulfamerazine
Sulfathiazole
Sulfamethoxazole
Trimethoprim
Oxytetracycline
Amoxicillin
Flumequine
Oxolinic acid
Oxytetracycline
Sulfadimethoxine
Ormetoprim
Sulfamerazine
Sulfathiazole
Sulfamethoxazole
Trimethoprim

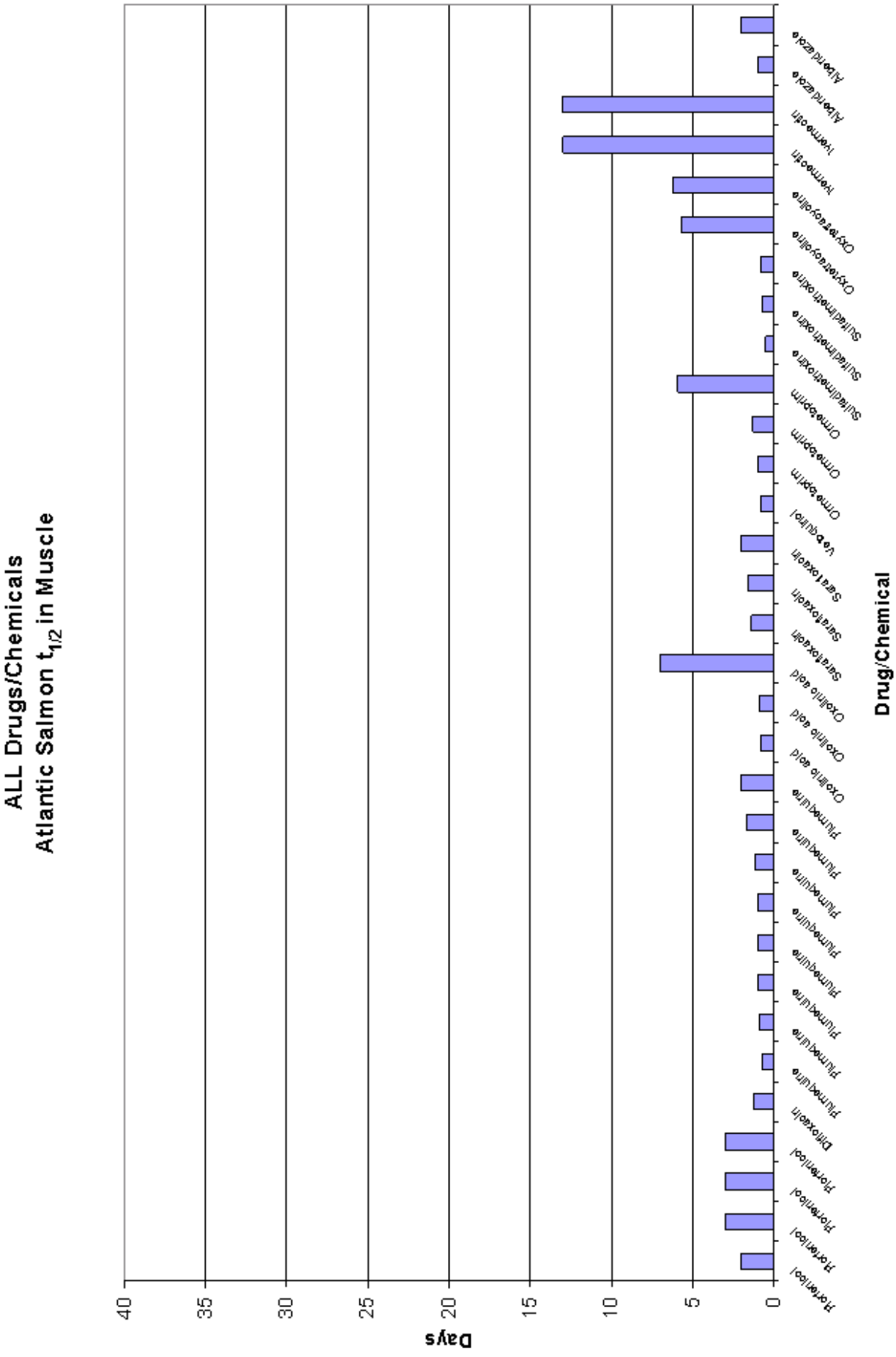


Figure 32. All Drugs in Atlantic Salmon Muscle.

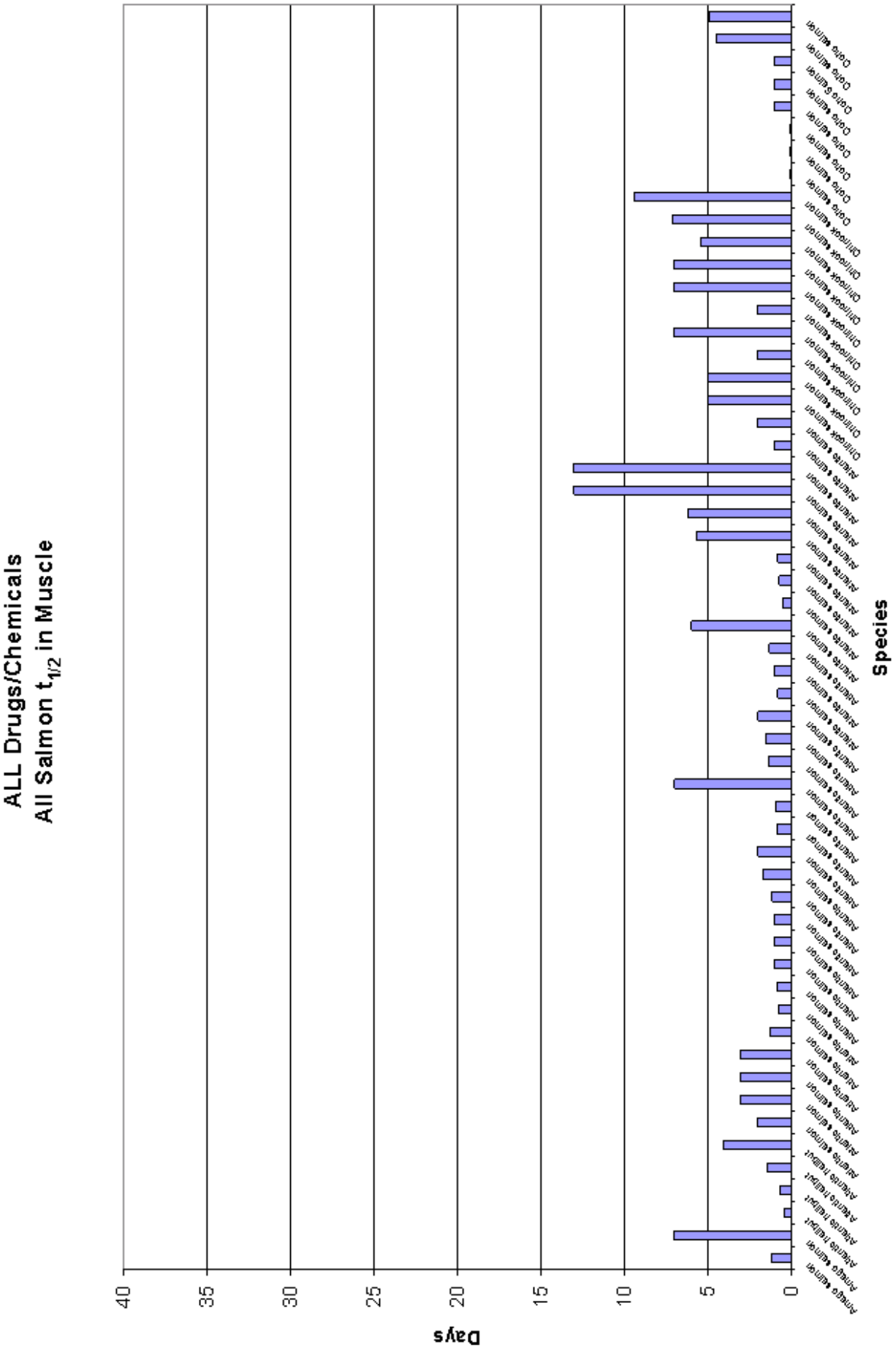


Figure 33. All Drugs in All Salmon Muscle by Species.

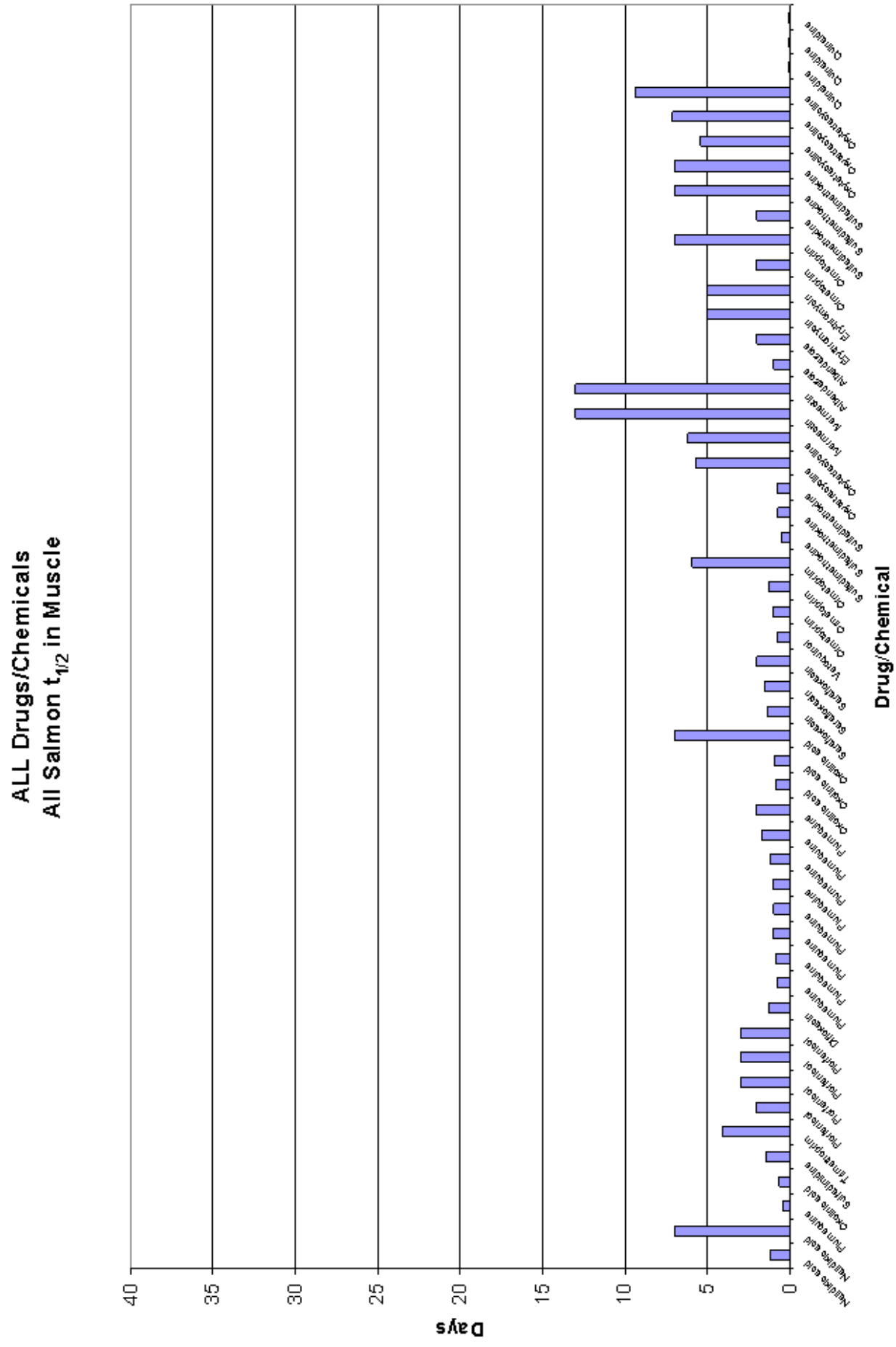


Figure 34. All Drugs in All Salmon Muscle by Drug.