The attached document represents CTP's then-current thinking on certain aspects of tobacco regulatory science. The information contained herein is subject to change based on advances in policy, the regulatory framework, and regulatory science, and, is not binding on FDA or the public. Moreover, this document is not a comprehensive manual for the purposes of preparing or reviewing tobacco product applications. FDA's review of tobacco product applications is based on the specific facts presented in each application, and is documented in a comprehensive body of reviews particular to each application.

Given the above, all interested persons should refer to the Federal Food, Drug, and Cosmetic Act, and its implementing regulations, as well as guidance documents and webinars prepared by FDA, for information on FDA's tobacco authorities and regulatory framework. This document does not bind FDA in its review of any tobacco product application and thus, you should not use this document as a tool, guide, or manual for the preparation of applications or submissions to FDA.

MEMORANDUM

FROM: Todd L. Cecil, Ph.D.
Chemist
Division of Product Science, Office of Science

Todd L. Cecil -S
Digitally signed by Todd L. Cecil -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Todd L. Cecil -S, 0.9.2342.19200300.100.1.1=2001734216
Date: 2016.02.16 13:59:20 -05'00'

THROUGH: Tim M. Brewer, Ph.D.
Team Leader
Division of Product Science, Office of Science

Timothy M. Brewer -A
Digitally signed by Timothy M. Brewer -A
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2001549595, cn=Timothy M. Brewer -A
Date: 2016.02.17 04:36:03 -05'00'

Matthew Holman, Ph.D.
Director
Division of Product Science, Office of Science

Digitally signed by Matthew R. Holman -S
Date: 2016.02.17 07:45:28 -05'00'

TO: David L. Ashley, Ph.D.
Director
Office of Science

SUBJECT: Use of CigaretteDesigner and other Models to Predict HPHC Yields in SE Reports

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Purpose

The purpose of this memo is to consider the use of CigaretteDesigner and other models to predict TNCO and other HPHC yields from combusted cigarettes. This memo will describe the process for developing and validating such models and identifying the limitations of CigaretteDesigner. This memo will also provide deficiency language for use in scientific reviews of SE Reports.

Background

Modeling software like CigaretteDesigner have increasingly been used to estimate smoke yields of tar, nicotine, carbon monoxide (TNCO) and other harmful and potentially harmful constituents (HPHCs) in tobacco products that are not available for testing or where comprehensive testing is considered cost prohibitive. The applications reported to date have ranged from multiple linear regressions to more complex semi-empirical models like that employed by CigaretteDesigner.

The CigaretteDesigner software is a freely available tool that claims to predict tar, nicotine, and carbon monoxide (TNCO) smoke yields of a modified cigarette based upon a reference cigarette. It is designed and developed as a tool to provide estimates of the effects that physical design changes might have upon smoke yields. However, this program is not a traditional statistical or predictive model. Instead, it more closely resembles a multi-factorial data transform. Where a data transform is a mathematical equation or series of equations that converts a data point from one data form to another (similar to a Fourier transform). A multi-factorial data transform is, therefore, a data transform that uses many different variables (factors) to transform the data.

Predictive model or data transform

Both predictive models and data transforms are complex mathematical tools used by many industries to understand their data and predict outcomes. Although these tools are complementary and have similar uses, their application, strengths and weaknesses are very different. A data transform is a useful tool where a rough estimation is desired and where the number of differences between the starting point and the calculated endpoint are limited. Examples of simple data transforms are the “log”, “sine”, and “cosine” mathematical functions. The strengths of this type of tool include: ease of understanding relationships between cause and effect, adaptability, and small data sample sizes. The weaknesses of a data transform include: the cost of development (due to the need for theoretical understanding of the system), effective blindness to all variables not included in the equation(s), lack of statistical relevance (it produces an answer every time, but whether it is a good answer is not known), and inflexibility. A predictive statistical model is a series of statistical tools using the power of large data sets to make predictions. These predictions are based solely of statistical observations and are delivered with a probability that the answer is accurate. These tools are used when there are complex questions and where cause and effect relationships are complicated. Examples of predictive models include actuarial tables used in the insurance industry or weather predictions. The strengths of this type of model include: the ability to make predictions with an associated confidence, adaptability, flexibility, ability to predict beyond the boundaries of the model (in certain conditions). Weaknesses of predictive models include the need for a large data set, ongoing maintenance of the models, need for a statistical specialist to develop the models.

CigaretteDesigner 4.1[1]

CigaretteDesigner as a multi-factorial data transform uses many different pieces of data and a complex series of equations to convert TNCO data from a reference cigarette to TNCO values for a “test product.” These conversions (transforms) are based on a

[1] http://www.cigarettedesigner.com/download/cigarettedesignermanual.pdf. Accessed 1/26/2016.

number of assumptions that cannot be varied and do not necessarily reflect the complex changes taking place in the cigarette. To illustrate the point; CigaretteDesigner assumes that all cigarettes yield 10 mg of nicotine per gram of tobacco filler and then applies equations to calculate the amount of tobacco burned in each puff to calculate the nicotine delivered to the smoker. However, if the tobacco used is higher in nicotine per gram or burns at a different temperature than the model, or includes burn modifiers to burn faster, or other un-modelled components, the transform will not be accurate. A data transform, unlike a predictive model, does not acknowledge the presence (or potential for the presence) of variables that are not included in the data transform. While CigaretteDesigner is not a predictive model, it could be used as a component of a potentially powerful predictive model. When this predictive model is appropriately developed and validated, it should provide a prediction with a probability or prediction uncertainty value. There are a number of limitations that will need to be overcome before CigaretteDesigner will provide sufficient prediction confidence to serve as a replacement for measured values in a regulatory filing. These limitations include:

1. (b) (4)
2. CigaretteDesigner does not and cannot be used to predict HPHC values as these are outside of the design parameters of the model. While CigaretteDesigner claims to approximate tar content, and changes in tar content may be correlated to changes in overall HPHC content, there is no data to indicate that the relative content of individual HPHC values is linked to tar content (i.e., tar values for a product may be lower, but may actually contain increases in B[a]P or NNN content relative to the predicate). If specific HPHC measurements are made and added to a fully-validated predictive model, then modelled values for may be accurate (see Appendix A).
3. The calculated results used by CigaretteDesigner are dependent upon a reference product or surrogate product. This is a limitation because selection of a reference product is not trivial. The scientific rationale for the selection of the reference cigarette and evidence that the correct reference cigarette was chosen would also be needed. Because CigaretteDesigner cannot adjust an estimate based upon any type of chemical changes (e.g., tobacco blend, additive), the selection of an appropriate reference product becomes the most critical choice in the successful application of the model.(b) (4)

(b) (4)

4. Because CigaretteDesigner is a data transform, each application is a singlet determination and is not statistically significant without replicates. In essence CigaretteDesigner takes the measured results from a single cigarette and extrapolates from that cigarette to one other cigarette. This extrapolation is only applicable to that one cigarette. Even where the average nicotine content of 10,000 cigarettes is entered into CigaretteDesigner, the result will be a single number. There is no way to tell if that single calculated nicotine value is representative of a batch of predicted cigarettes because all of the information about the variability of the 10,000 cigarettes is lost. This concept put in statistical terms means that a singlet determination does not allow extrapolation to a population and therefore should not be used to represent an individual lot or brand of products. A predictive model relies upon multiple single determinations of cigarettes (or averages of cigarettes) to accurately predict an outcome and more importantly extrapolate to a larger number of products.
5. CigaretteDesigner is not designed to account for changes in tobacco blend, additives, tobacco moisture levels, or flavors. (b) (4)

(b) (4)

(b) (4)

The effect of tobacco blend, casing, flavor, and moisture should be considered in any model that is developed to predict TNCO values.

6. (b) (4)

Recommendations

Predictive modeling provides a the greatest opportunity to successfully predict TNCO values in modelled cigarettes when designed and validated as described in Appendix A. However, there is inherent risk in the use of modeling as opposed to direct measurement because these models rely on the statistics to draw relationships to expected outcomes[2]. These models do not work well where outliers or anomalous results occur or where unexpected factors are present. If these models are not well-designed[3], then the results are likely to be inaccurate and can lead to false conclusions

[2] Statsoft.com/textbook. An Electronic statistics textbook available since 1995. Accessed 1/24/2016.
[3] For example, does not include critical variables, applies inaccurate assumptions, is based on inadequate data sets, overreaches their design capability.

and decisions. Before a model can be accepted in an SE Report, the applicant must do the following:

- Define the application (e.g., prediction of TNCO, prediction of specific HPHC values, prediction for all X brand cigarettes)
- Define the acceptable error in the predicted values
- Identify assumptions in the model and provide rationale for each assumption, including, if possible, objective testing evidence to support assumptions
- Demonstrate the adequacy of modeling prediction for replicate measurements of the "Reference Cigarette" or the data set used to develop the model
- Validate the model by comparing predicted values to actual measurements of products being modeled for each predicted variable
- Calculate and report the Confidence Interval and the Prediction Interval (calculation of these values are available in a variety of statistical texts and describes the quality of the prediction [4])

The use of predictive models, if properly designed, tested and validated, provide a valuable means to demonstrate significant equivalence of predicate products that are no longer available and for new products within the design parameters of the model. However, because predictive models can be viewed as a "black box" predictor, applicants may misuse or extend the model beyond its design parameters thus making inaccurate or misleading statements about new or predicate products. If the applicant provides adequate demonstration of their understanding of the design and application of predictive models through the validation process, the reviewers will be better able to determine if changes cause the new product to raise different questions of public health.

1. Applicable SE Reports

Any applicant that would like to employ a predictive model including but not limited to CigaretteDesigner must provide the following information about their development and application of the model.

a. A description of the critical design characteristics used in the model
b. A description of the variables that the model is designed to predict
c. A listing of assumptions and rationale for excluding a variable
d. The acceptable prediction error for each modelled variable
e. A description of the test set to include the prediction and measured values for each member of the set (Validation)
f. A calculation of the predictive error (Confidence Interval and the Prediction Interval) for each modelled variable

[4] Rencher AC, Christensen WF, *Methods of Multivariate Analysis (3rd ER),* Wiley and Sons, 2012, Chapter 10. or other text books on the topic

If the predicted values in the new and/or predicate products are substantially different, it will be necessary for the applicant to provide discussion and scientific rationale to justify why the differences do not cause the new product to raise different questions of public health.

2. Proposed Boilerplate Deficiency Language

Where CigaretteDesigner or other predictive models are used to predict TNCO or HPHC values

All of your SE Reports include TNCO [and HPHC] values, which were calculated from the design characteristics of the new and predicate products. Your SE Reports claim that the model was developed using a broad range of cigarette types and are therefore applicable to both your new and predicate products. However, your SE Reports do not provide sufficient evidence to demonstrate the accuracy of the model in predicting actual smoke yields. Furthermore, changes to the tobacco blend and ingredients other than tobacco were not taken into account in your analyses. Therefore, the TNCO [and HPHC] values in your SE Reports do not provide adequate justification or evidence that the new products do not raise different questions of public health.

Provide the following information about the predictive model so that we can evaluate the capabilities of model to adequately predict TNCO values.

a. A description of the critical design characteristics used in the model
b. A description of the variables that the model is designed to predict
c. A listing of assumptions and rationale for excluding a variable
d. The acceptable prediction error for each modelled variable
e. A description of the test set to include the prediction and measured values for each member of the set (Validation)
f. A calculation of the predictive error (confidence interval and the prediction interval) for each modelled variable

Alternatively, you may provide the following information about TNCO testing so that we can fully evaluate the differences in TNCO quantities in the predicate and new products:

g. Quantitative test protocols and method used
h. Validation data of analytical methods used to measure TNCO
i. Testing laboratory and their accreditation(s)
j. Length of time between date(s) of manufacture and date(s) of testing
k. National/international standards used and any deviations(s) from those standards. If deviation(s) is not the same for methods used for the new and predicate products, provide scientific evidence demonstrating that the

testing result for the new and predicate products are accurate and comparable.

l. Number of replicates
m. Standard deviation(s)
n. Complete data sets
o. A summary of the results for all testing performed
p. Storage conditions prior to initiating testing

If your predicate product is not available for testing, there are options which you may choose to pursue to try to demonstrate substantial equivalence. Below are some options, though other alternative options may be acceptable. For example, the predicate product can be manufactured at present day consistent with the product composition and design specifications in place at the time the grandfathered predicate product was originally manufactured. In this case, the mainstream smoke TNCO and HPHC data should be accompanied by documentation demonstrating that the manufacture of the predicate product at present day is reflective of the grandfathered predicate product at the time of original manufacture. Another option would be to submit mainstream smoke HPHC data for products other than the predicate and new products (referred to as surrogate tobacco products) that can be extrapolated to the predicate and new products. In this case, data for the surrogate tobacco products could be submitted in place of data for the predicate and new tobacco products; the data should demonstrate that the differences in characteristics between the predicate and new products do not cause the new tobacco product to raise different questions of public health. In order to extrapolate such data, the TNCO or HPHC smoke data should be produced from surrogate tobacco products as similar as possible in characteristics to the predicate and new products and enough information should be provided to demonstrate that these comparisons are valid. In addition to the smoke data, information comparing the surrogate tobacco products to the predicate and new products should also be submitted.

Appendix A. Developing and Validating a Predictive Model

Developing and validating a predictive model involves a number of steps. These steps include designing a model, data collection, model development and testing on a training set, validation of the model on a test set, calculation of "goodness of fit" or fitness for purpose.

Designing a Predictive Model[5]

The selection of the predictive model is based upon considering the desired outcomes, the variables that may affect the outcomes, the quality of the information available, the acceptable amount of error in the prediction, and the intended use of the predicted values. Models range from a simple linear regression to multi-linear regression, principle components regression, various forms of parametric and non-parametric models, and even branching neural networks. The selection and means to make a selection of the variables and model are the responsibility of the applicant.

Defining Outcomes and Variables

The complexity of the model is related to the complexity of the data and accuracy of the expected outcomes. Where the outcome is expected to be measured with a 95% confidence interval, then the number of critical variables to be included in the model and the training set will be larger than if, for example, a 70% confidence interval is expected. Further, the predicted outcome of a tobacco product not previous evaluated requires a much more complex training set and a more complete variable set than determining the impact of changing one or a limited number of variables to a well-characterized product.

The number of variables used in a model will also be dependent upon how specific (or detailed) the result needs to be. A very detailed result will require more descriptors (variables). A simple illustration is provided by the spoken language. A simple description a male child could be "boy", while a detailed description might be a "20-Kg, 10-Year old, Aleut boy wearing a blue shirt and blue jeans". The number of descriptors (or variables) in the second example provide a more accurate picture of a male child. In the same manner, a predictive model needs a sufficient number of variables to adequate predict the desired result. The size of the training and test sets and their ability to accurately reflect the population will also improve the accuracy of the prediction (more is better).

[5] Multiple text books exist to provide complete details. The recommendations herein come from: *Applied Predictive Modeling*, Kuhn M. and Johnson K., Springer-Verlag New York, 2013. DOI: 10.1007/978-1-4614-6849-3

Training Set[6]

Once the critical variables have been designated and the model identified, the model is developed using a training set of "reference" cigarettes results. The training set will be measured for each of the critical variables (e.g., tobacco weight, % bright content, paper permeability). The training set should include examples of the types of cigarettes that the model will be used to predict HPHC values. The training set in many ways defines the scope of the model. A varied data set with lots of data points allows the greatest prediction across cigarette type but with lower specificity. A focused data set that is similar to the predicted product will allow a prediction with greater specificity and lower associated error, but is less generally applicable.

There is no published criteria to describe a minimum size for a training set, however, large data sets (>50 samples) typically provide better results than smaller data sets and therefore will provide better predications. The larger a data set is, the better the data will represent the population of the sample from a purely statistical perspective. The larger data set allows more statistical power when making predictions thereby reducing prediction error, in theory. Small data sets can be employed, but any predictions obtained from these models are not reliable because outliers and deviations carry too much statistical weight and skew the predictions[7]. Where a large enough data set is available, it is possible to partition a random sampling to be used as a test set. This type of test set can be used to demonstrate that the model is applicable to the population of the training set, but does not necessarily show that the model is capable of making predictions outside the boundaries of the training set.

Validation of the Model

Once a model has been developed and tested using the training set, it must then be tested using a "test" data set. This is a data set that that has not been used in development of the model. From the test set, it is possible to determine how well the model can predict variables in a controlled environment. This process includes:

1. Testing the cigarettes in the test set. This testing must include measurements of all of the values that the model has been designed to predict.
2. The model is used to make a prediction for each measurement it is intended to model.
3. The prediction interval and confidence interval are calculated. An excellent and comprehensive description are provided in the Rencher AC and Christensen WF

[6] Chemometrics: a Textbook, Massart D, Amsterdam ; New York : Elsevier ; New York, NY, U.S.A, 1988.
[7] Tengli A, Dubrawski A, Chen L, Proceedings of the International Conference on Information and Automation, December 15-18, 2005, Colombo, Sri Lanka.

book[8].

The confidence and prediction intervals should meet the acceptable level determined during the initial design of the model.

[8] Rencher AC, Christensen WF, Methods of Multivariate Analysis (3rd ER), Wiley and Sons, 2012, Chapter 10. or other text books on the topic

Attachment 1

[Note: the attached document has not been altered in any manner. Therefore the table of contents in the attachment does not reflect the correct page numbers. In addition, the Confidentiality statement included at the bottom of the next page applies to all of the following pages.]

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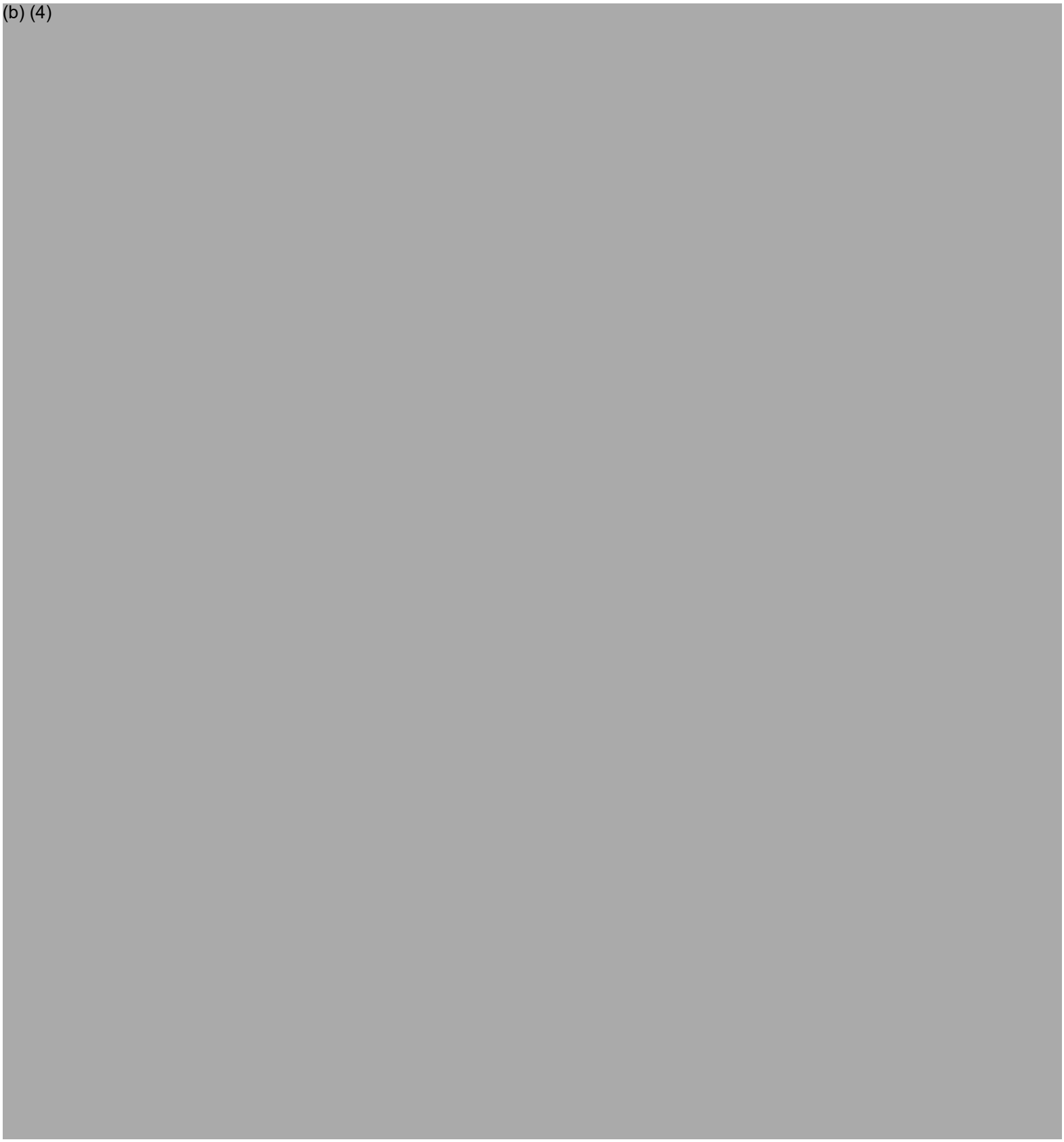

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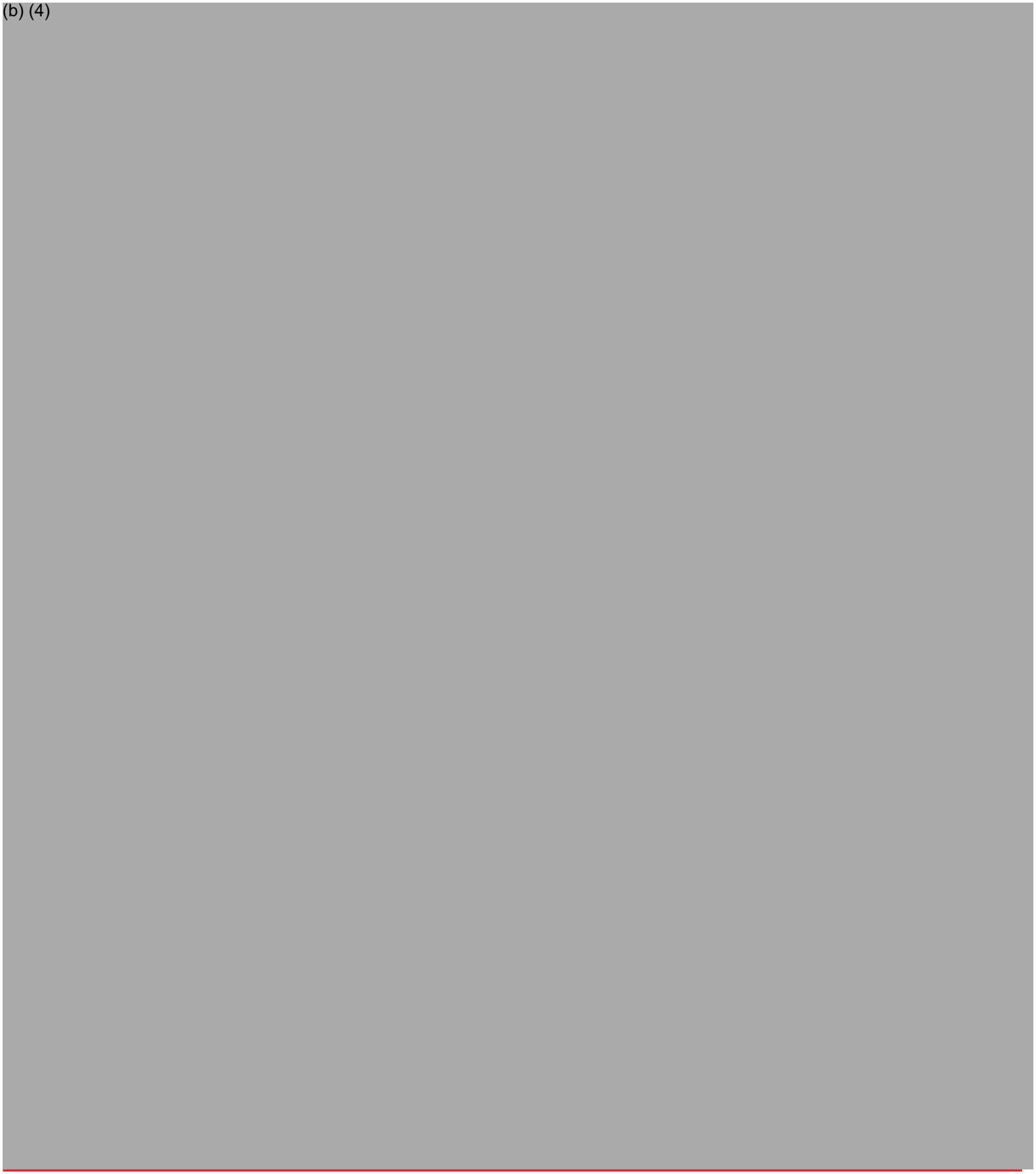

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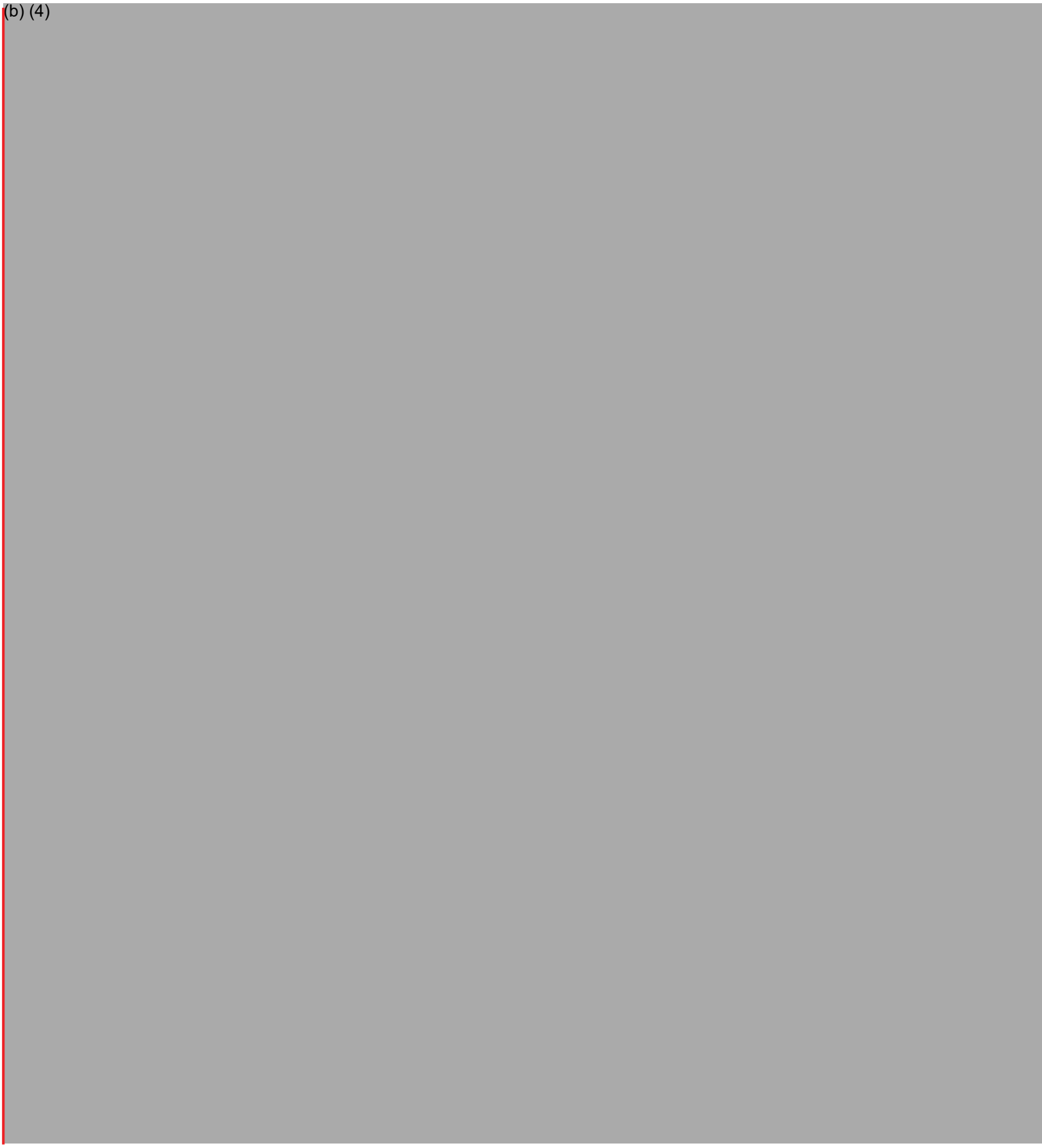

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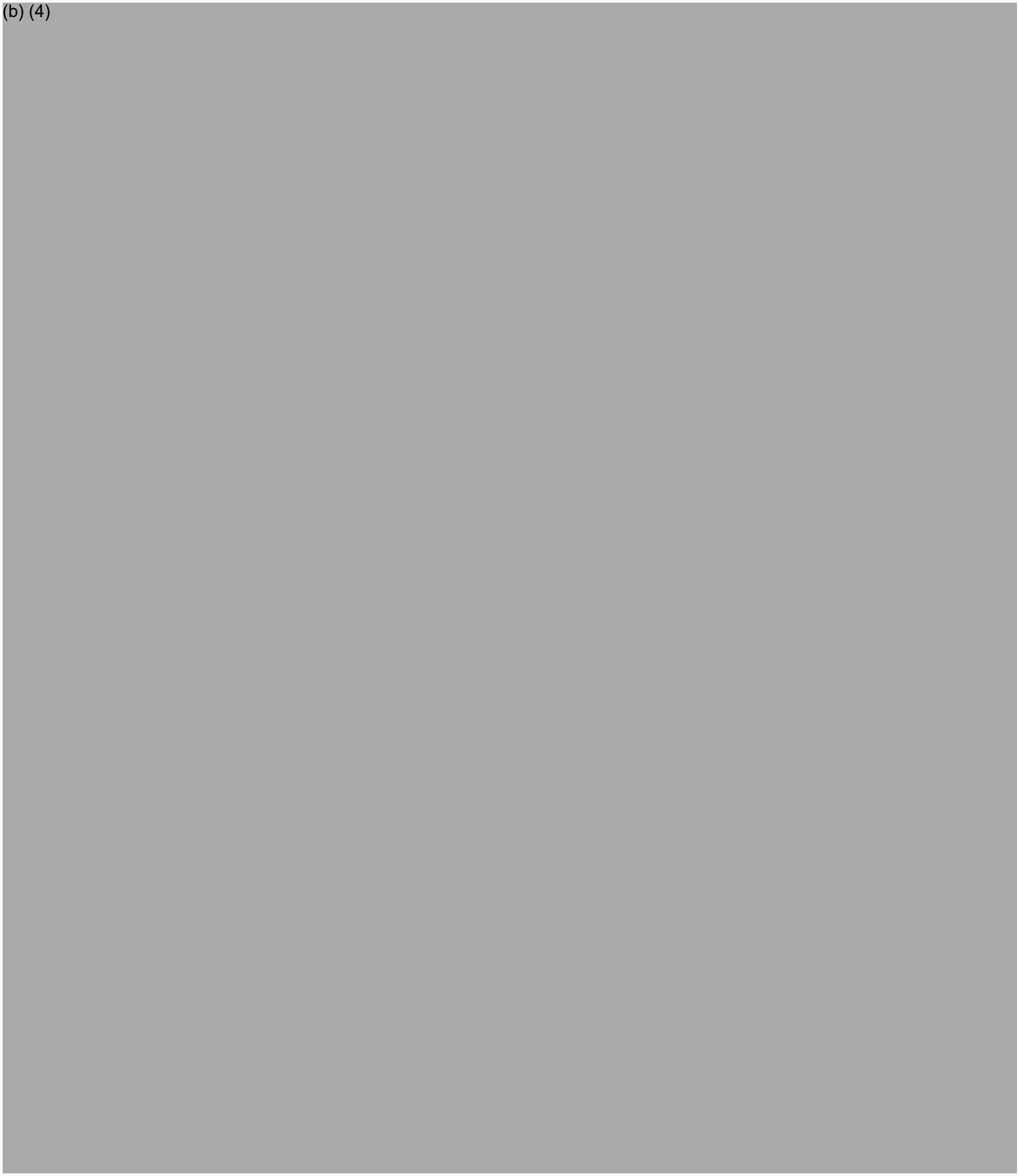

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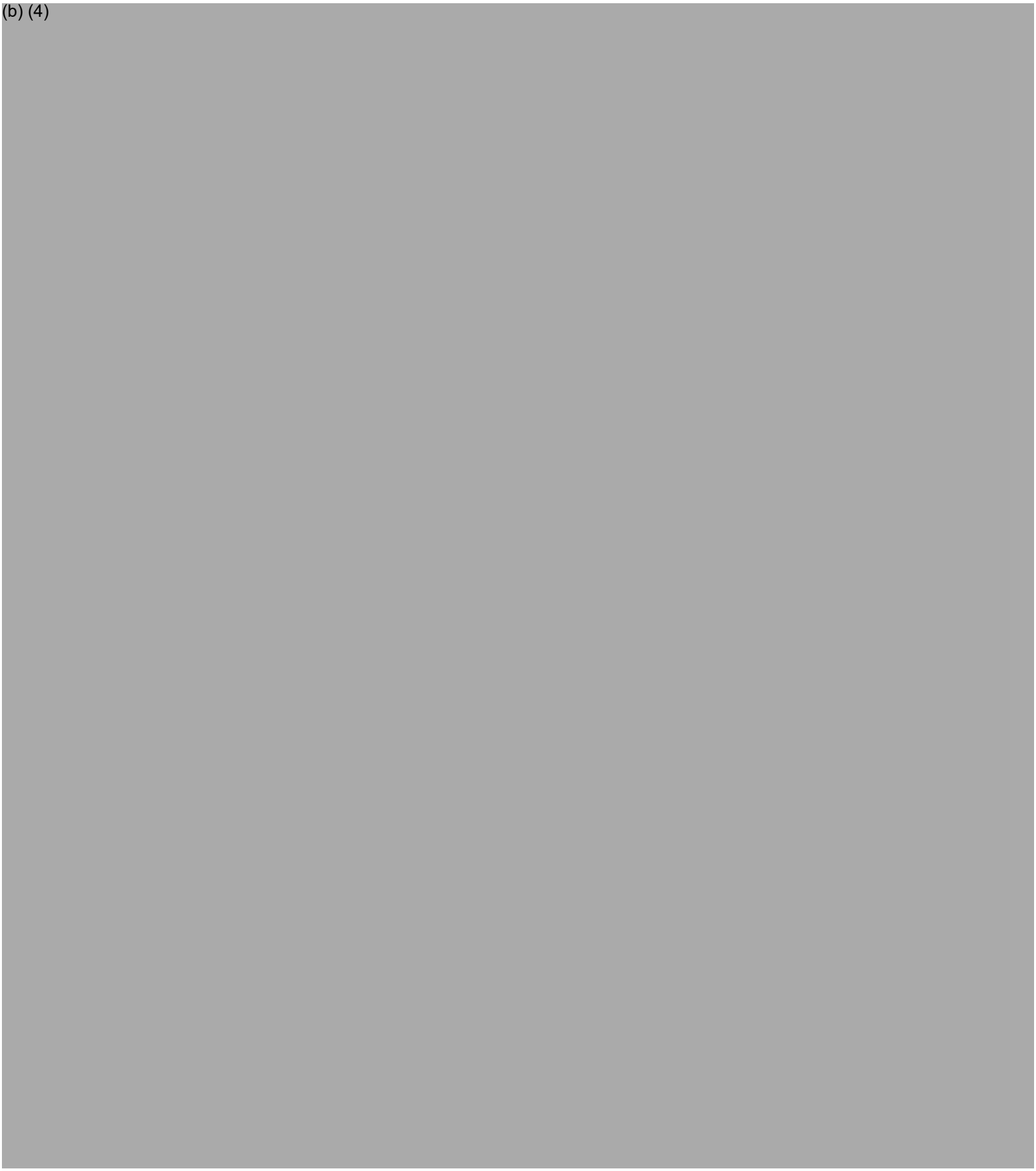

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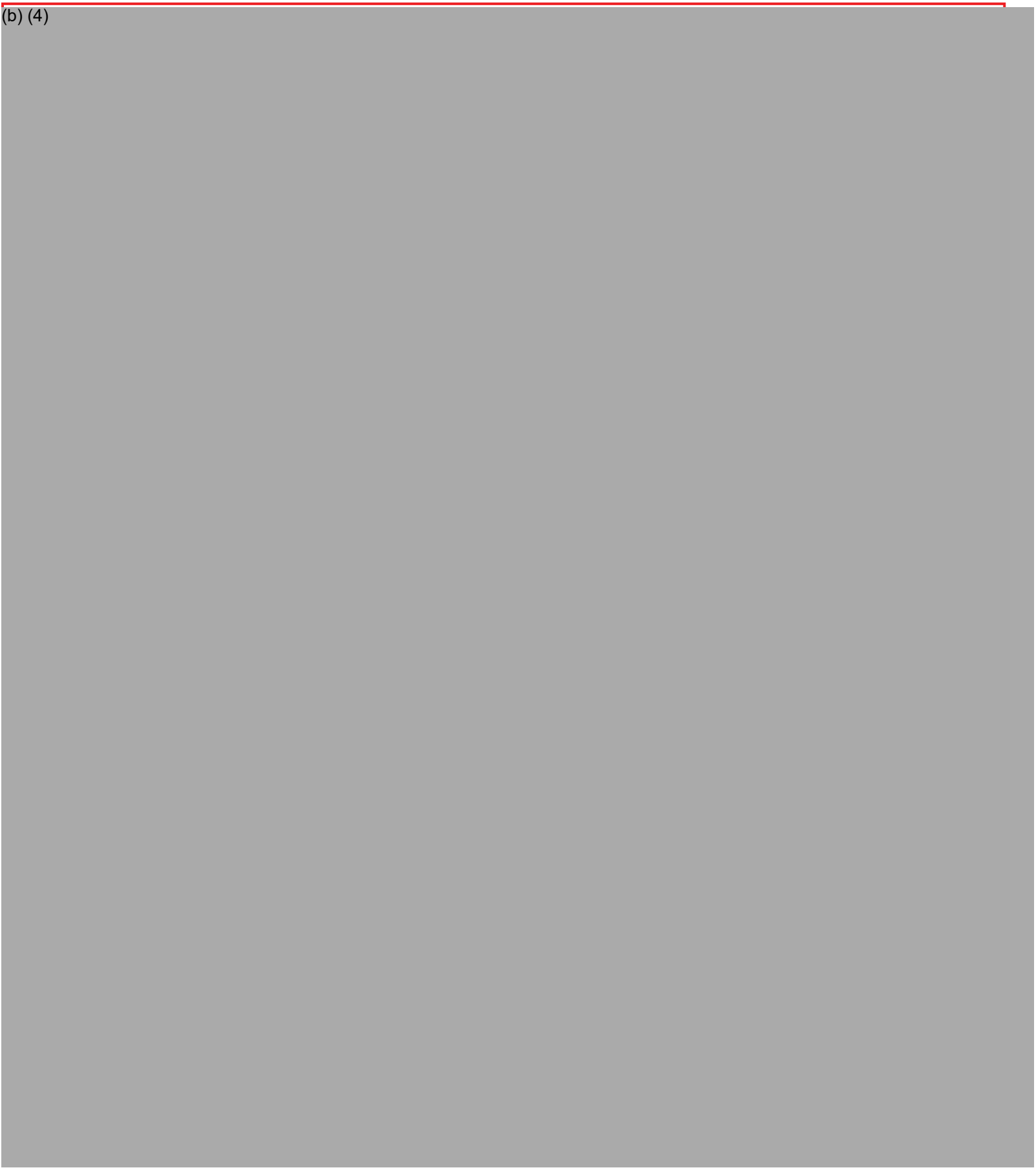

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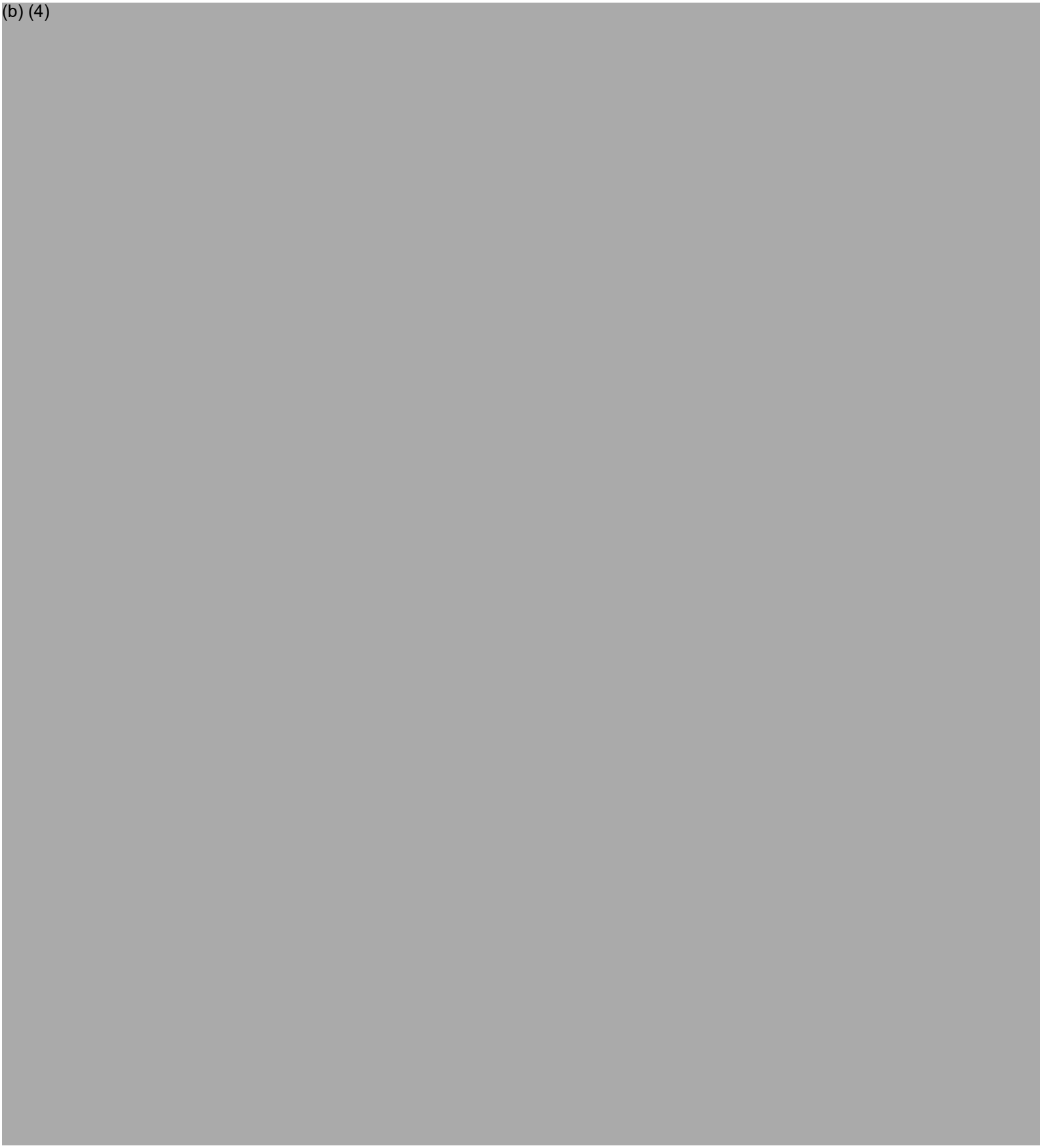

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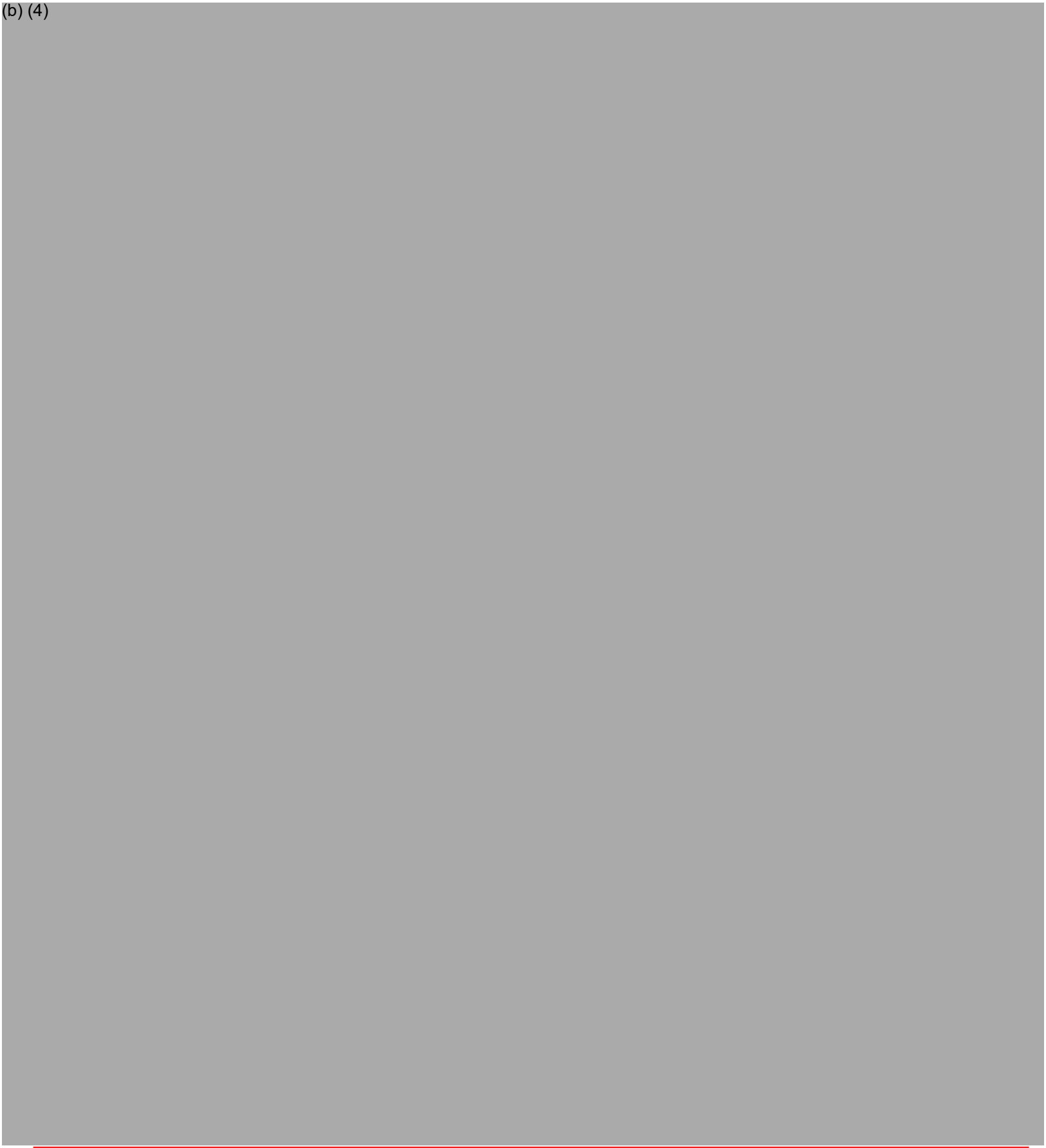

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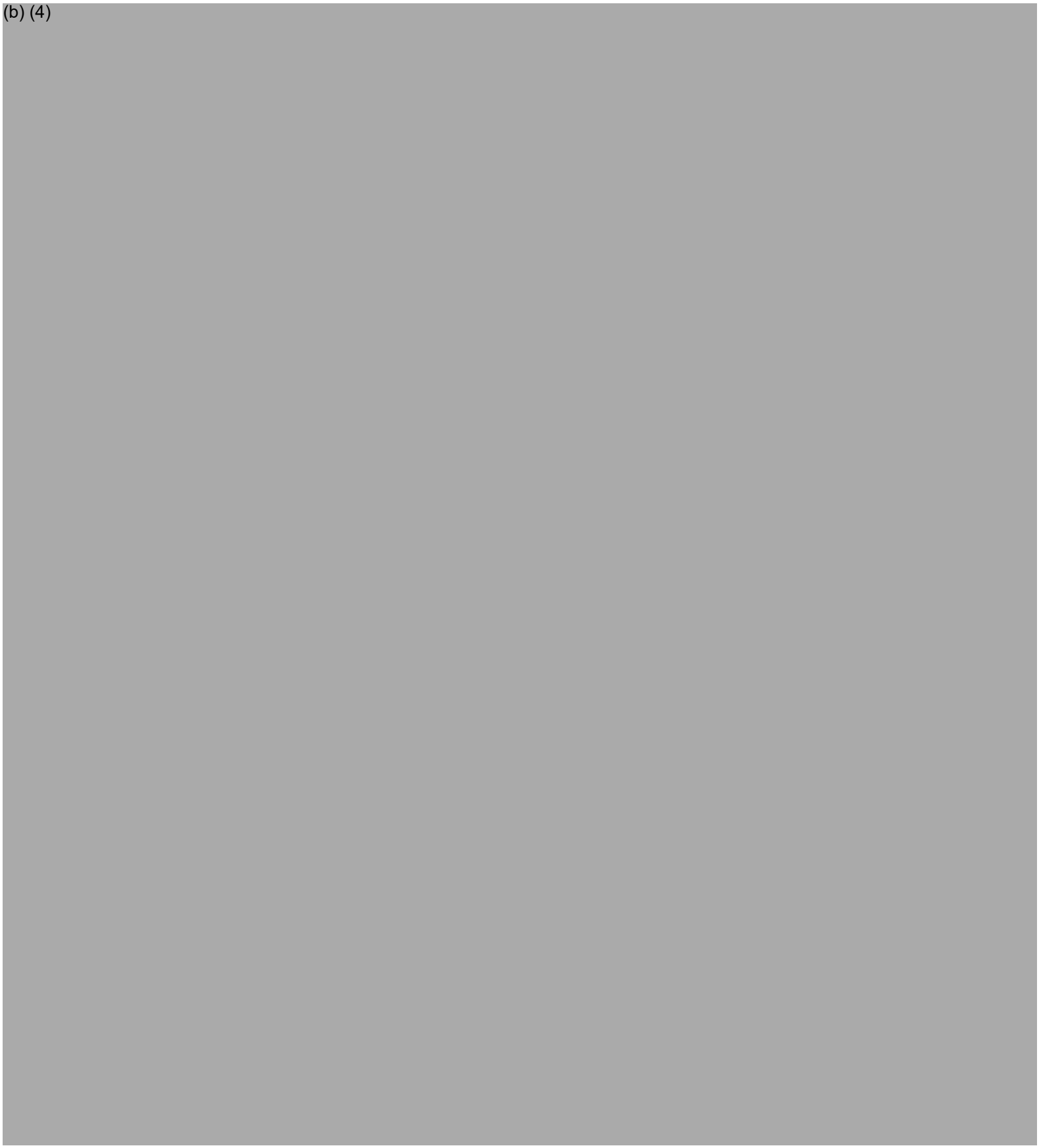

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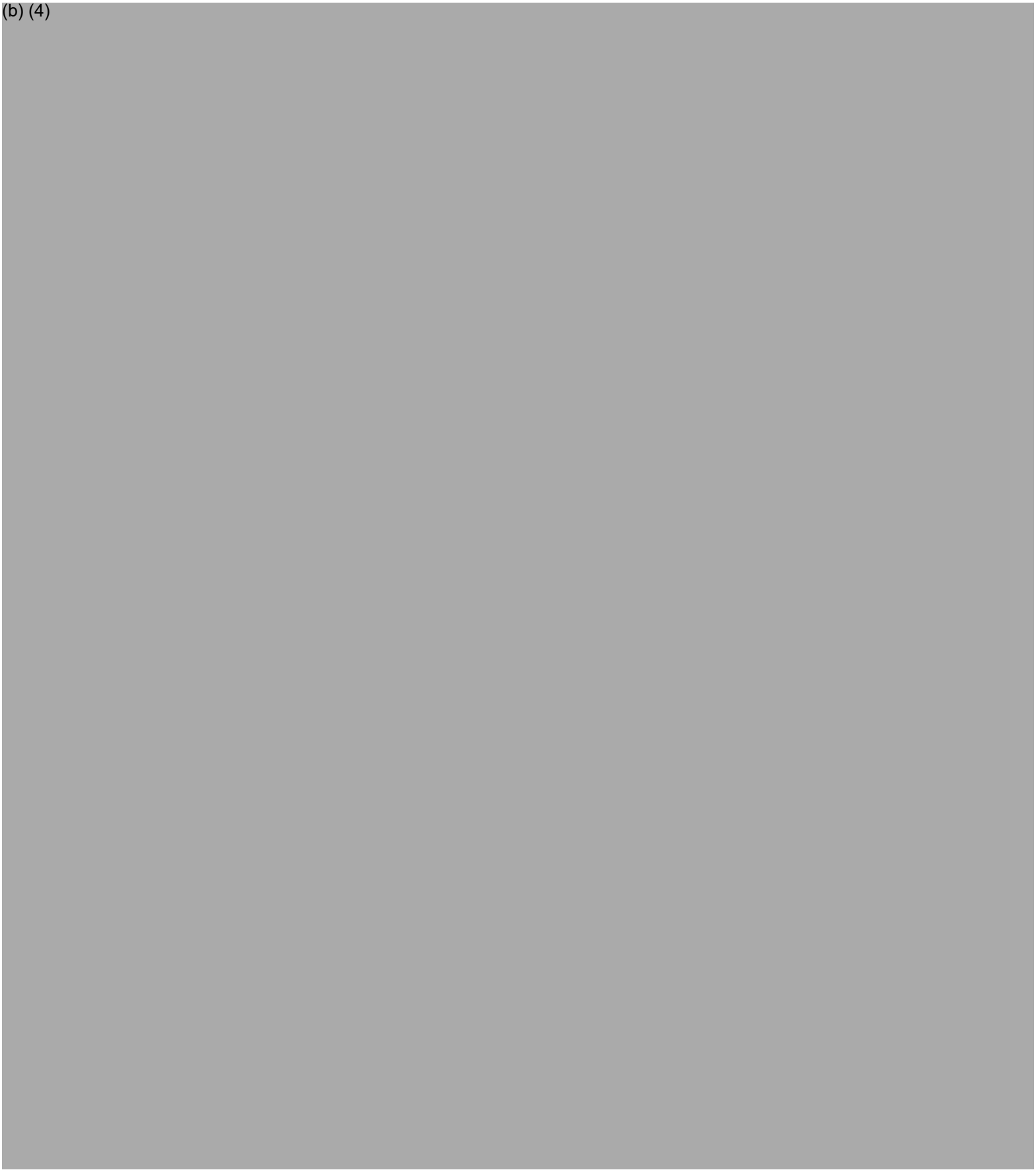

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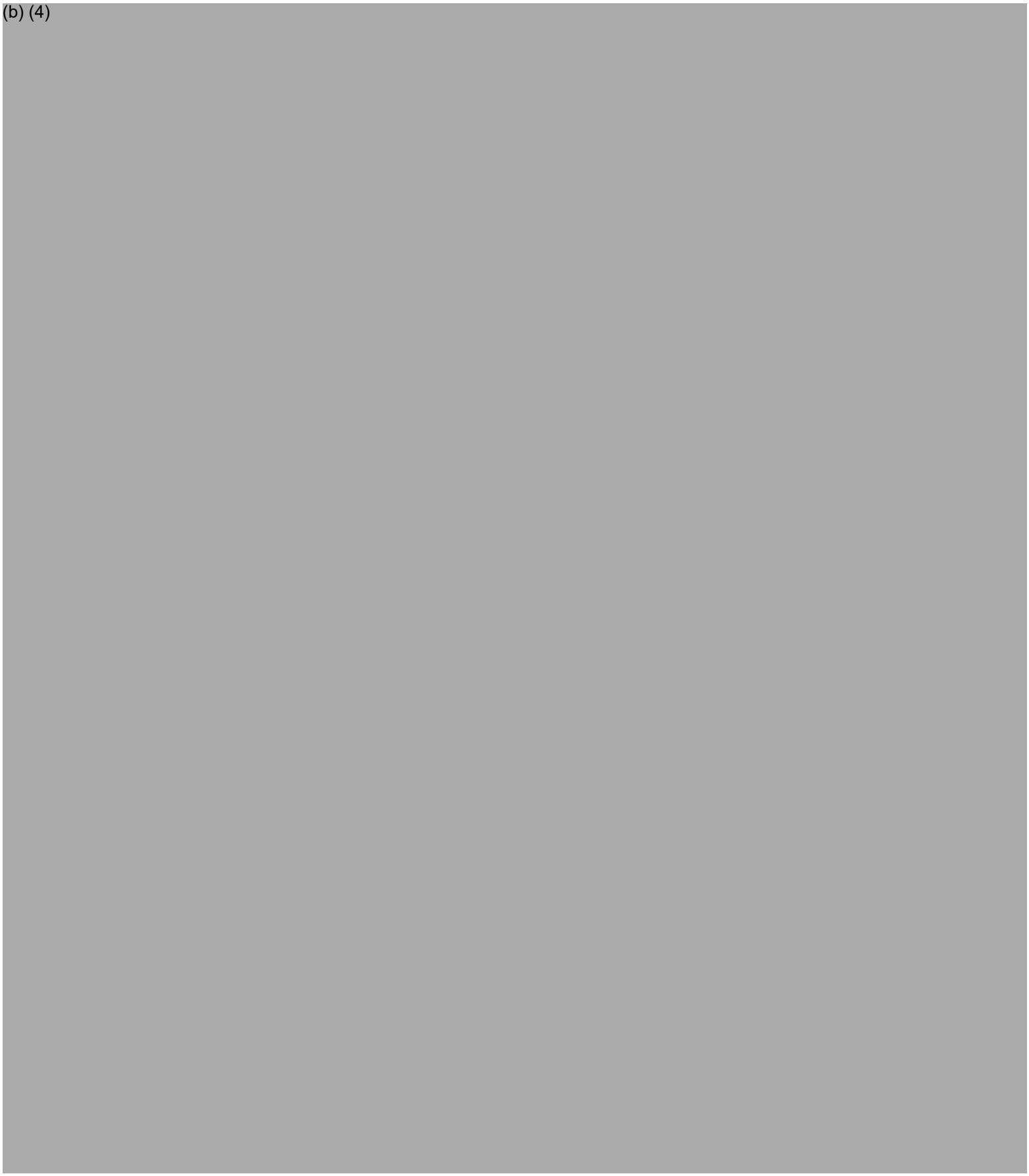

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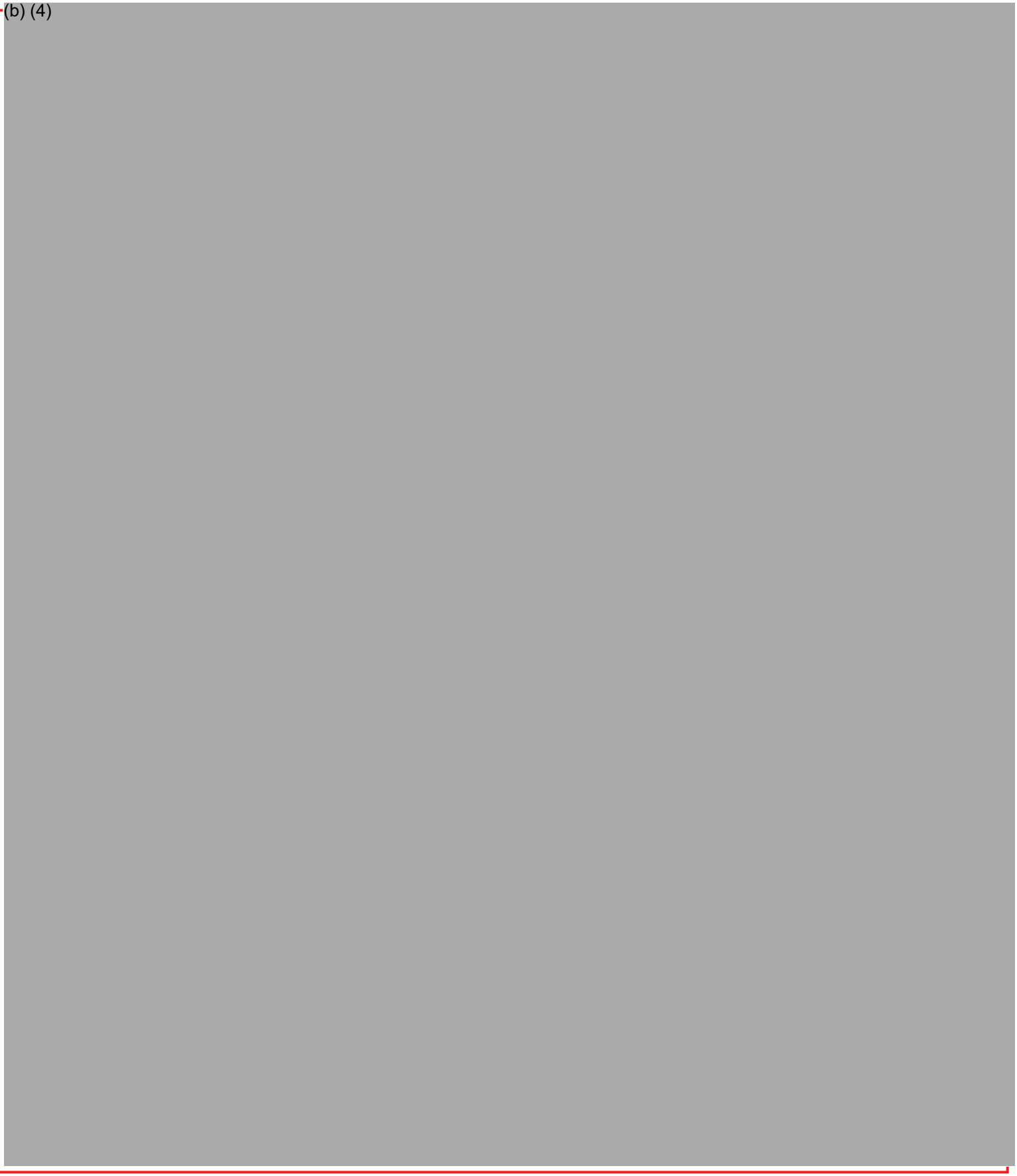

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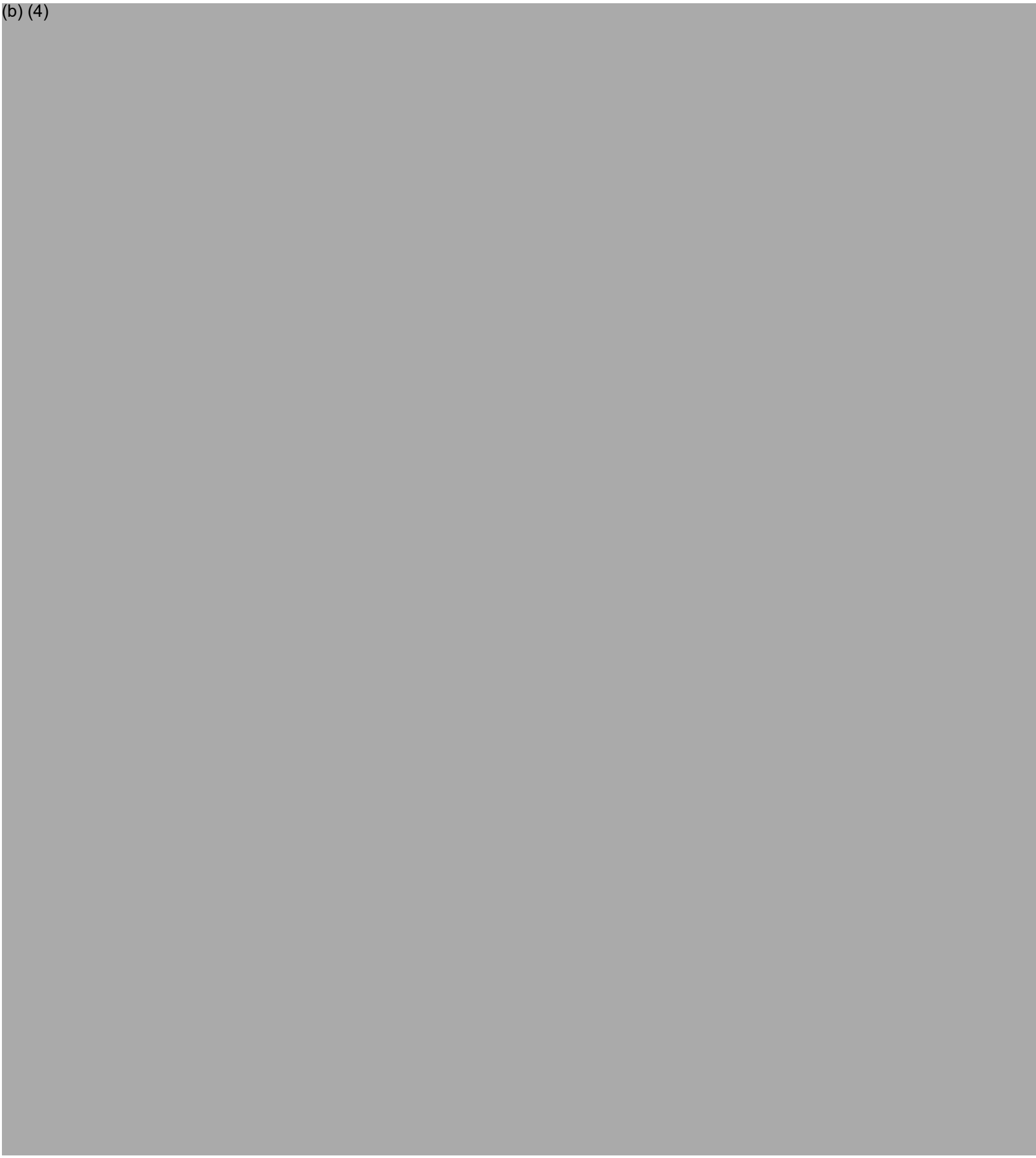

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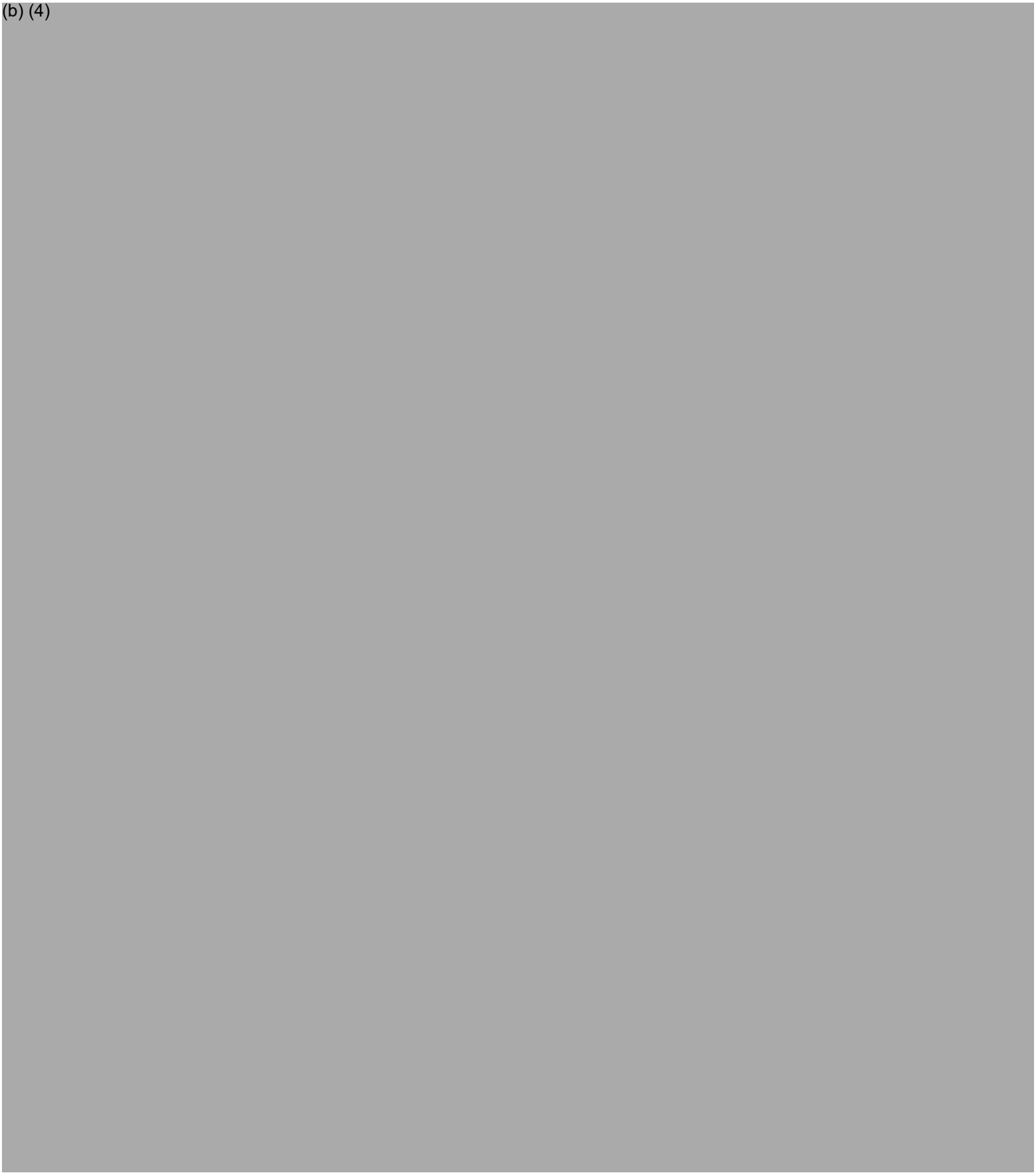

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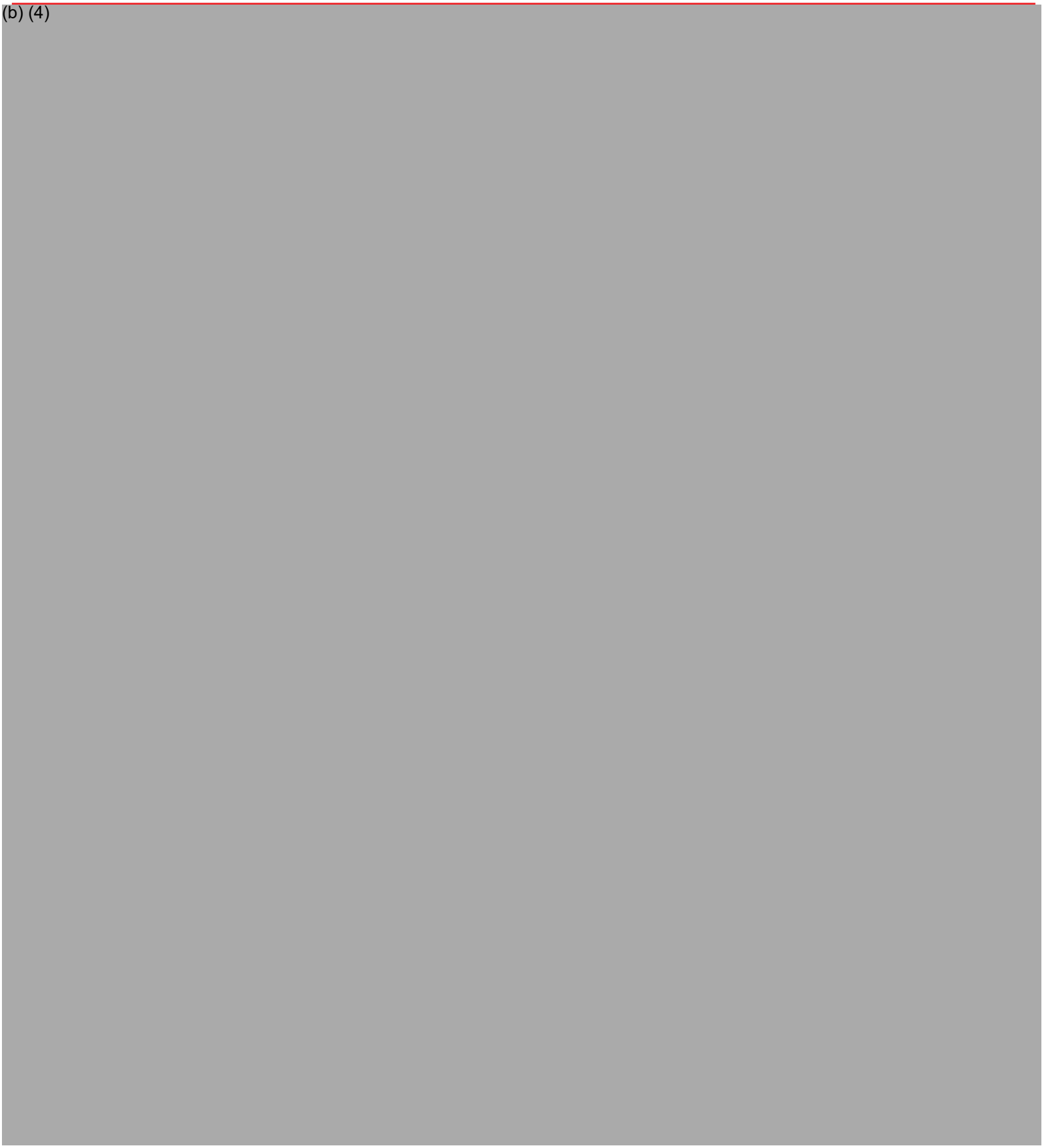

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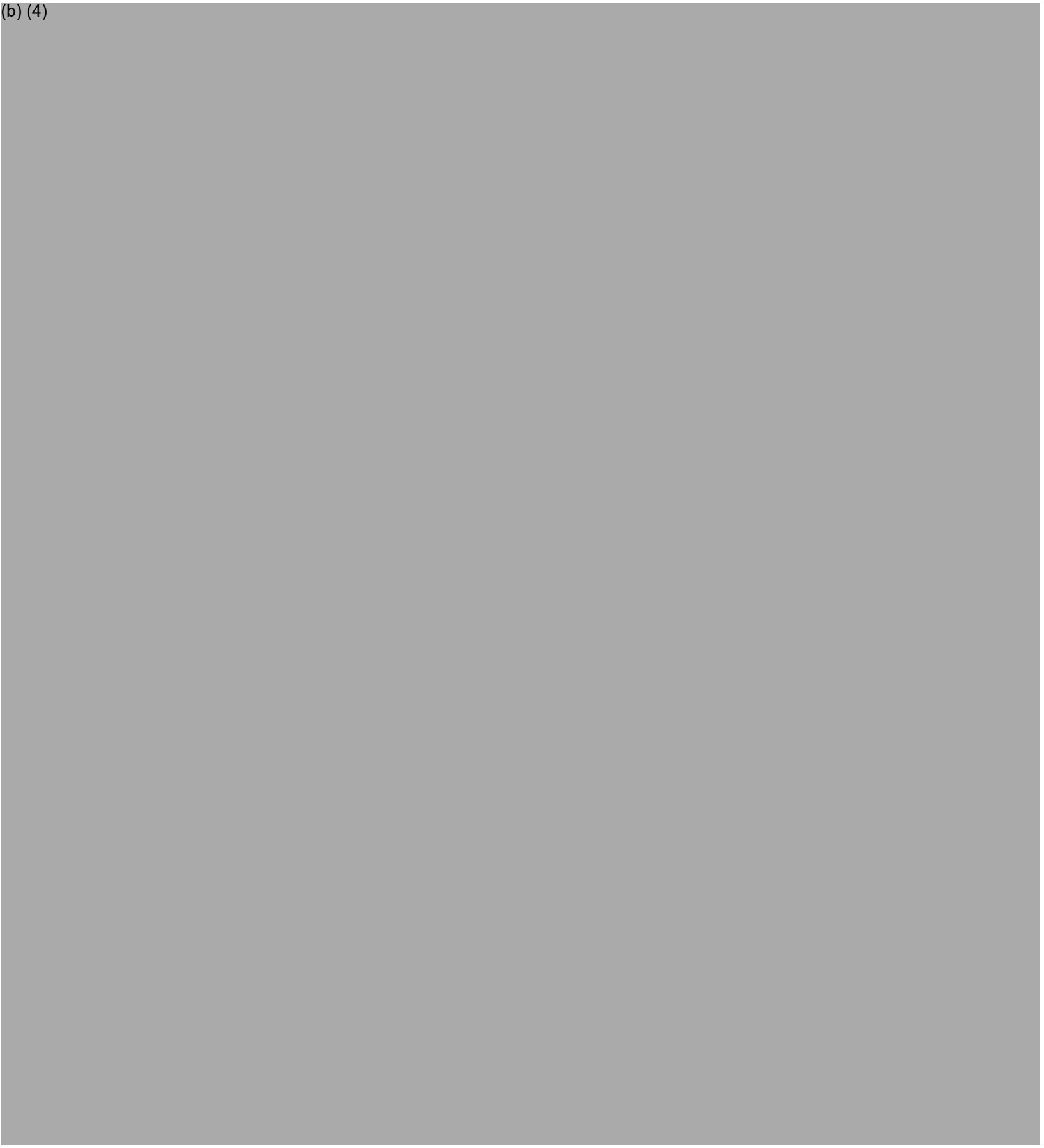

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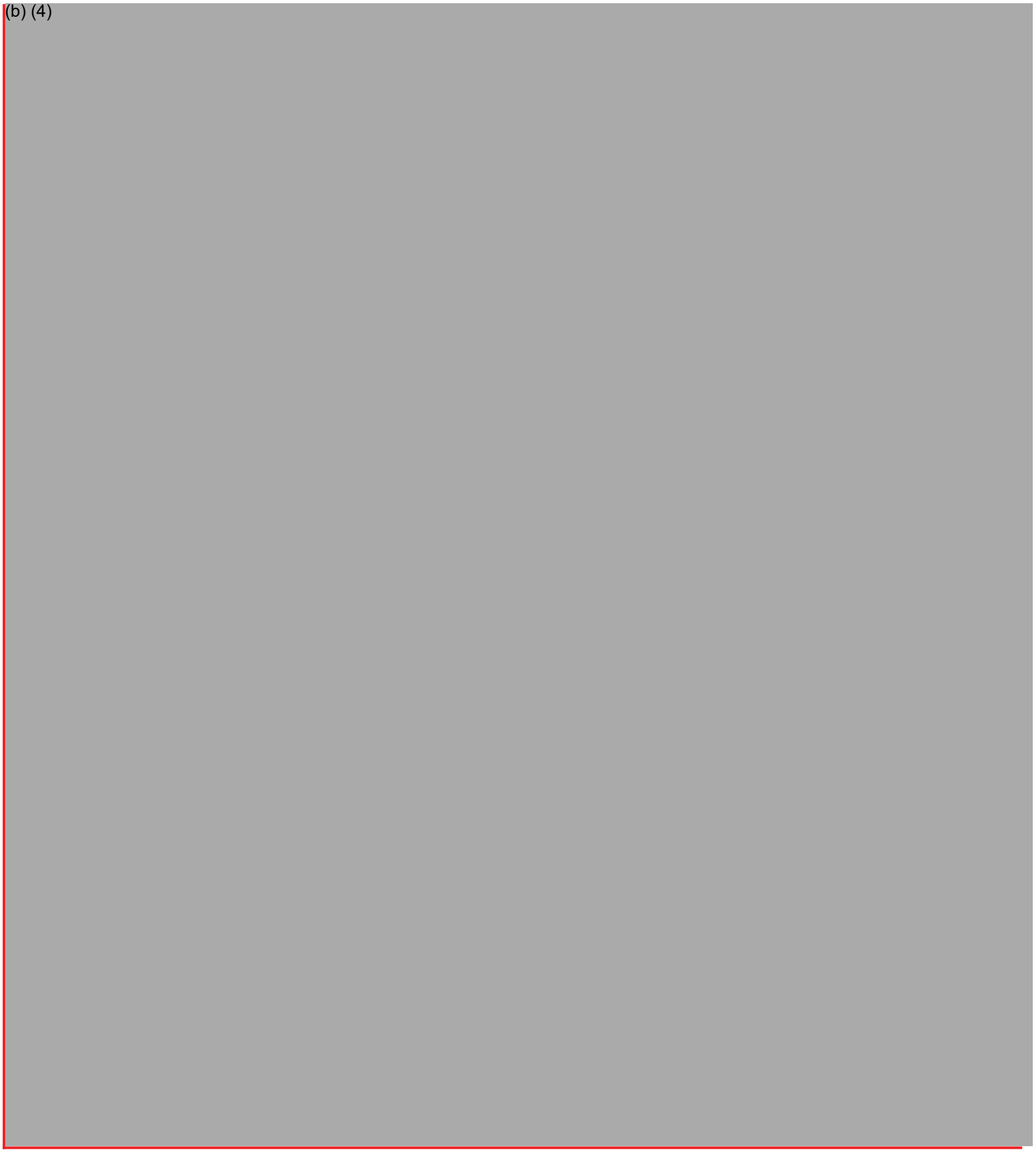

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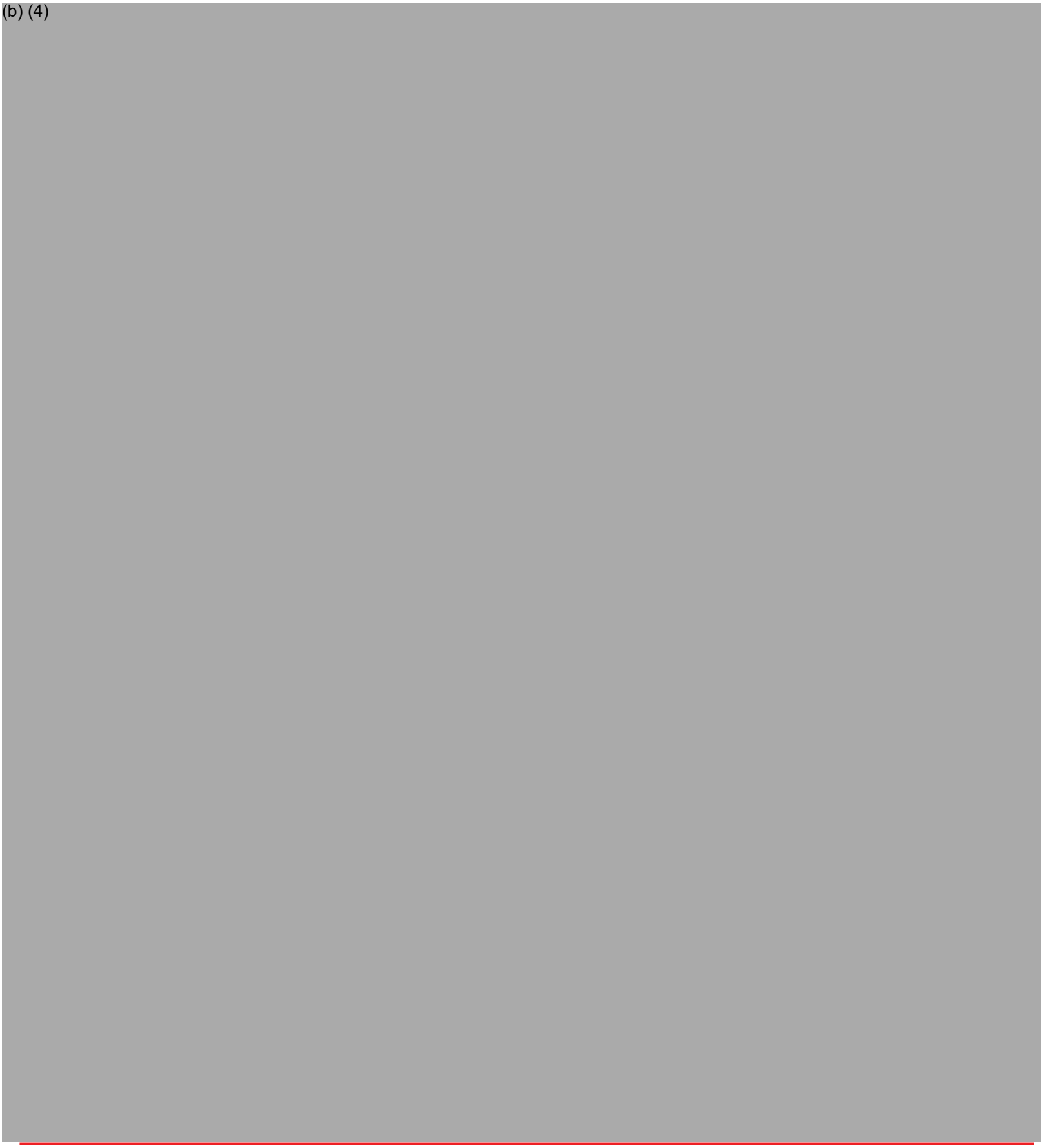

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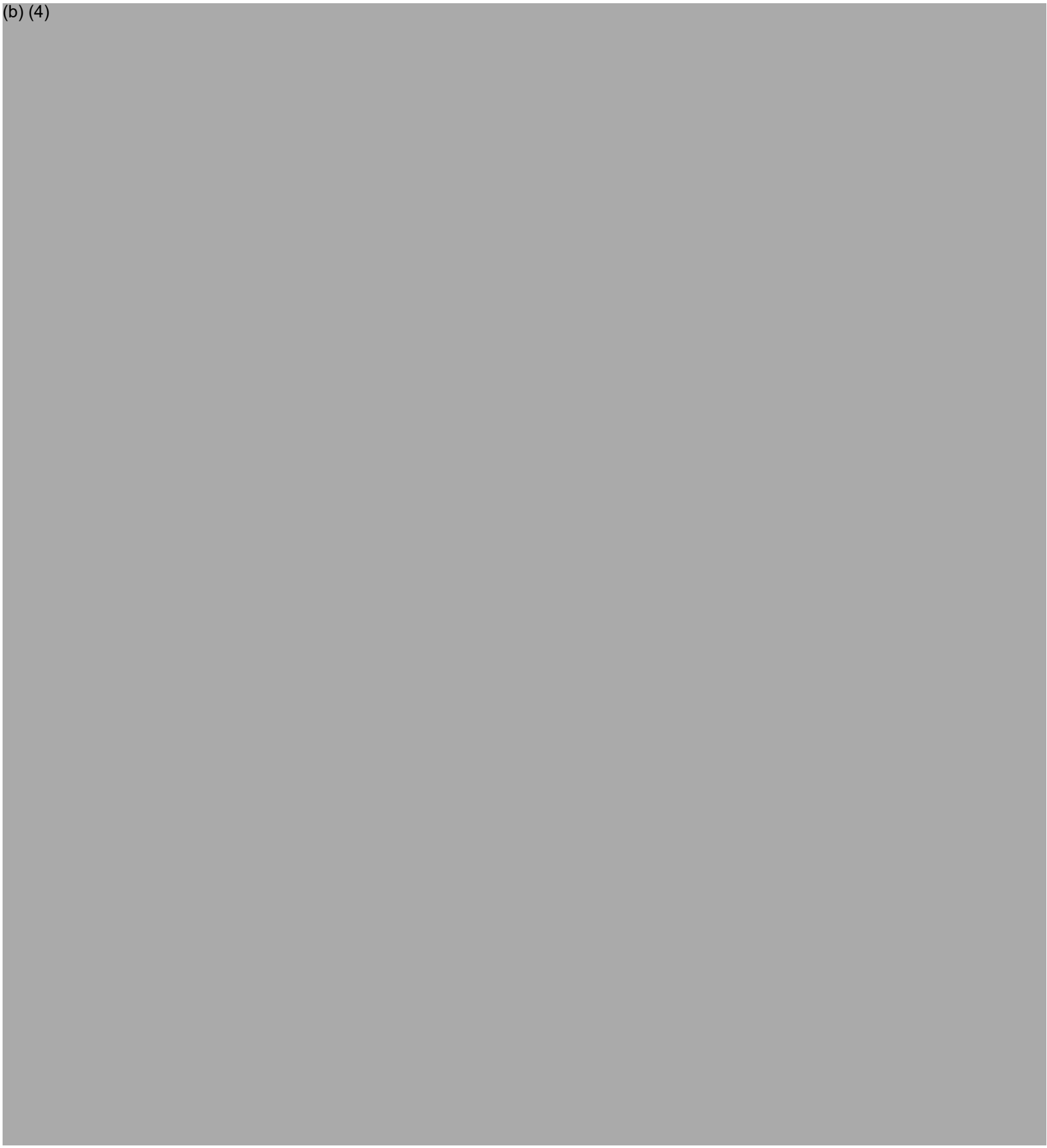

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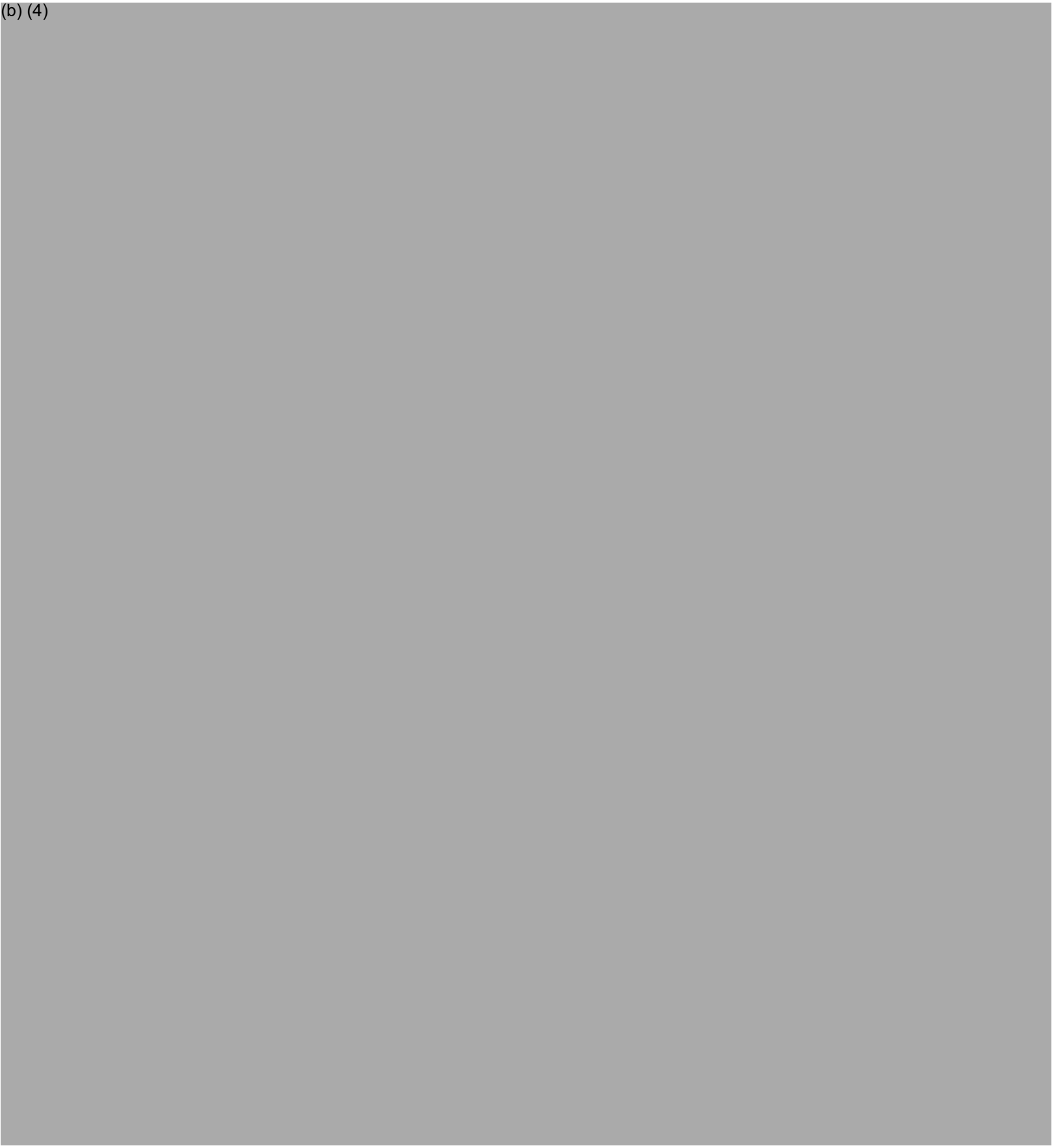

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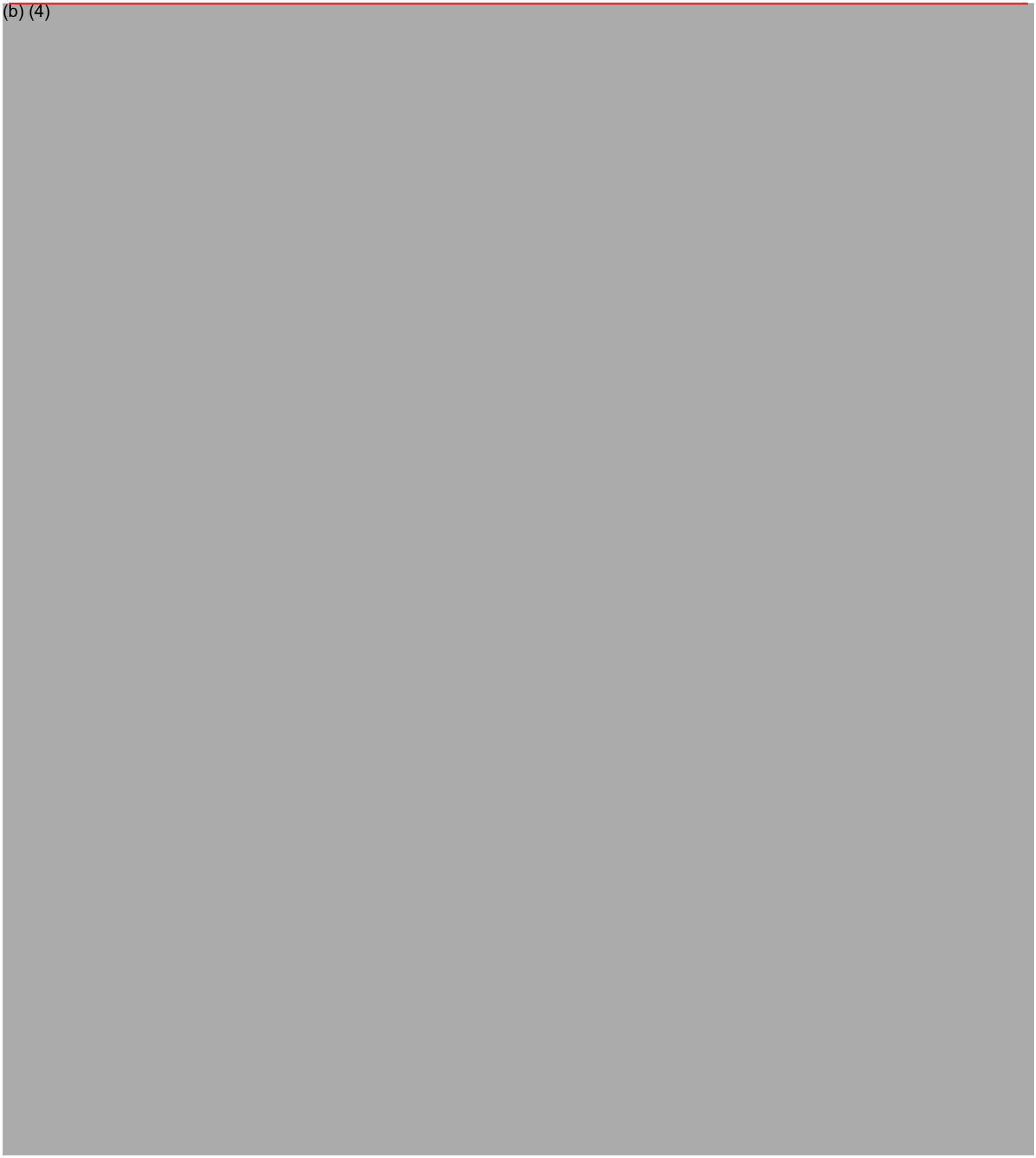

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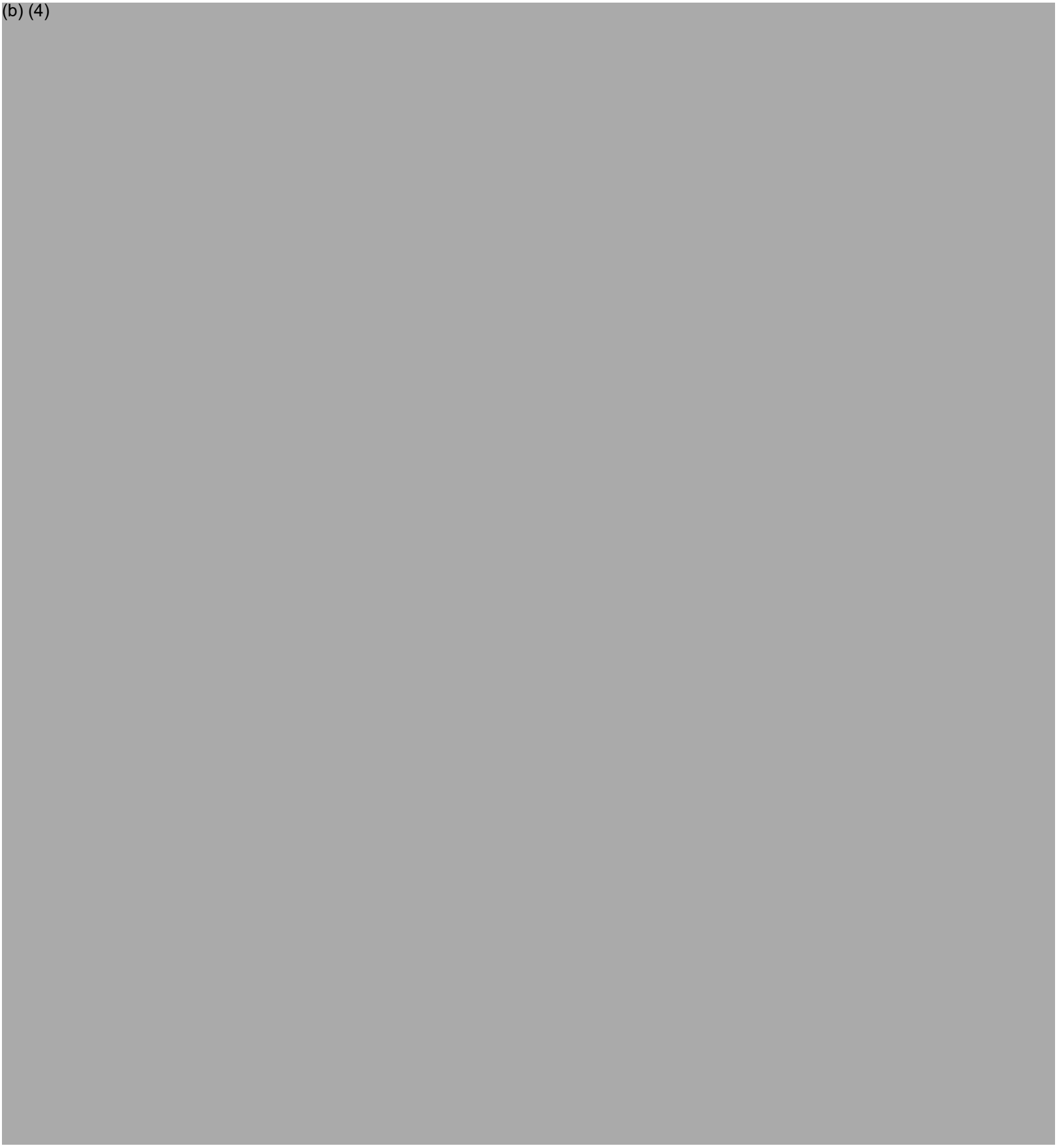

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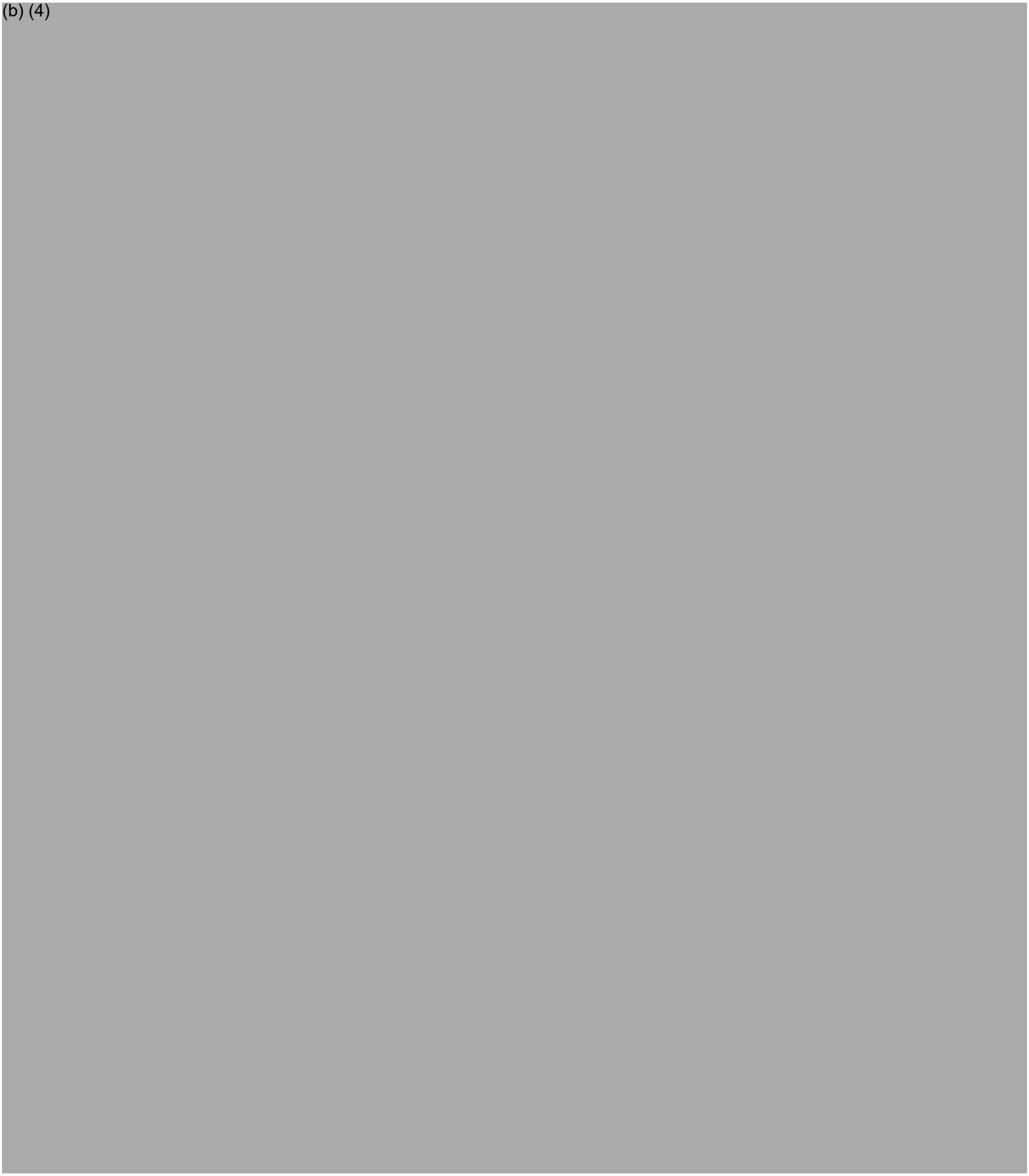

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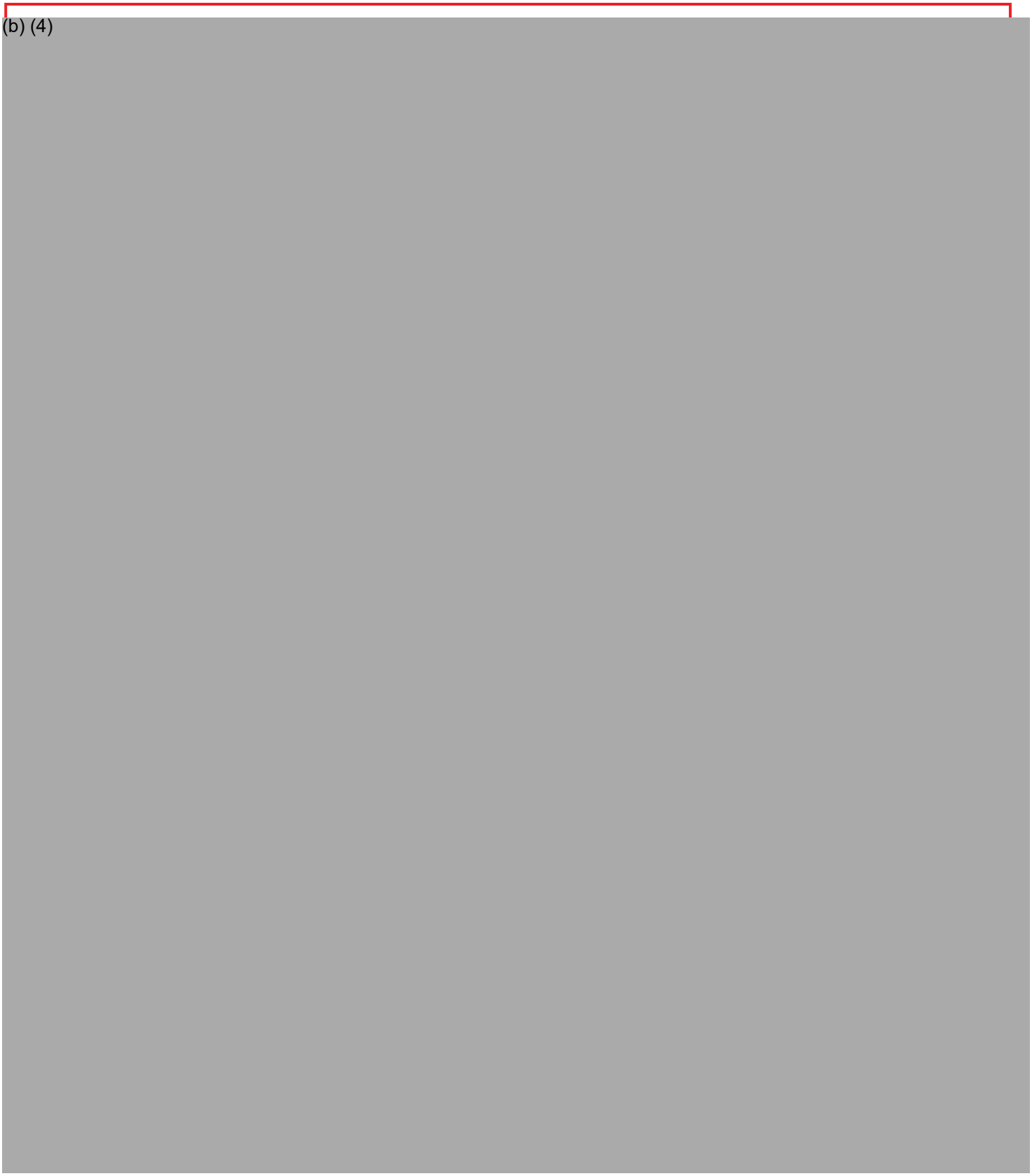

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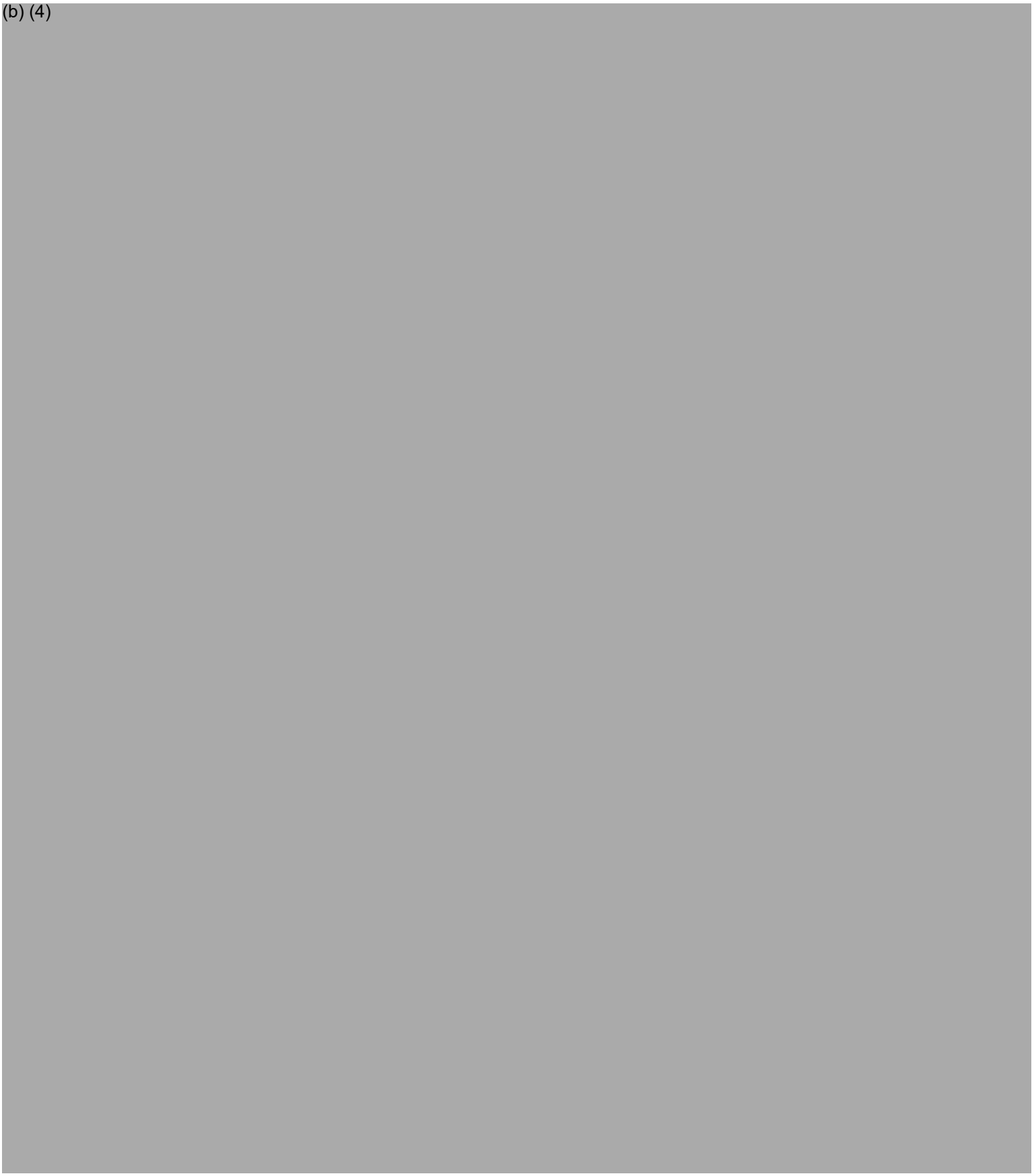

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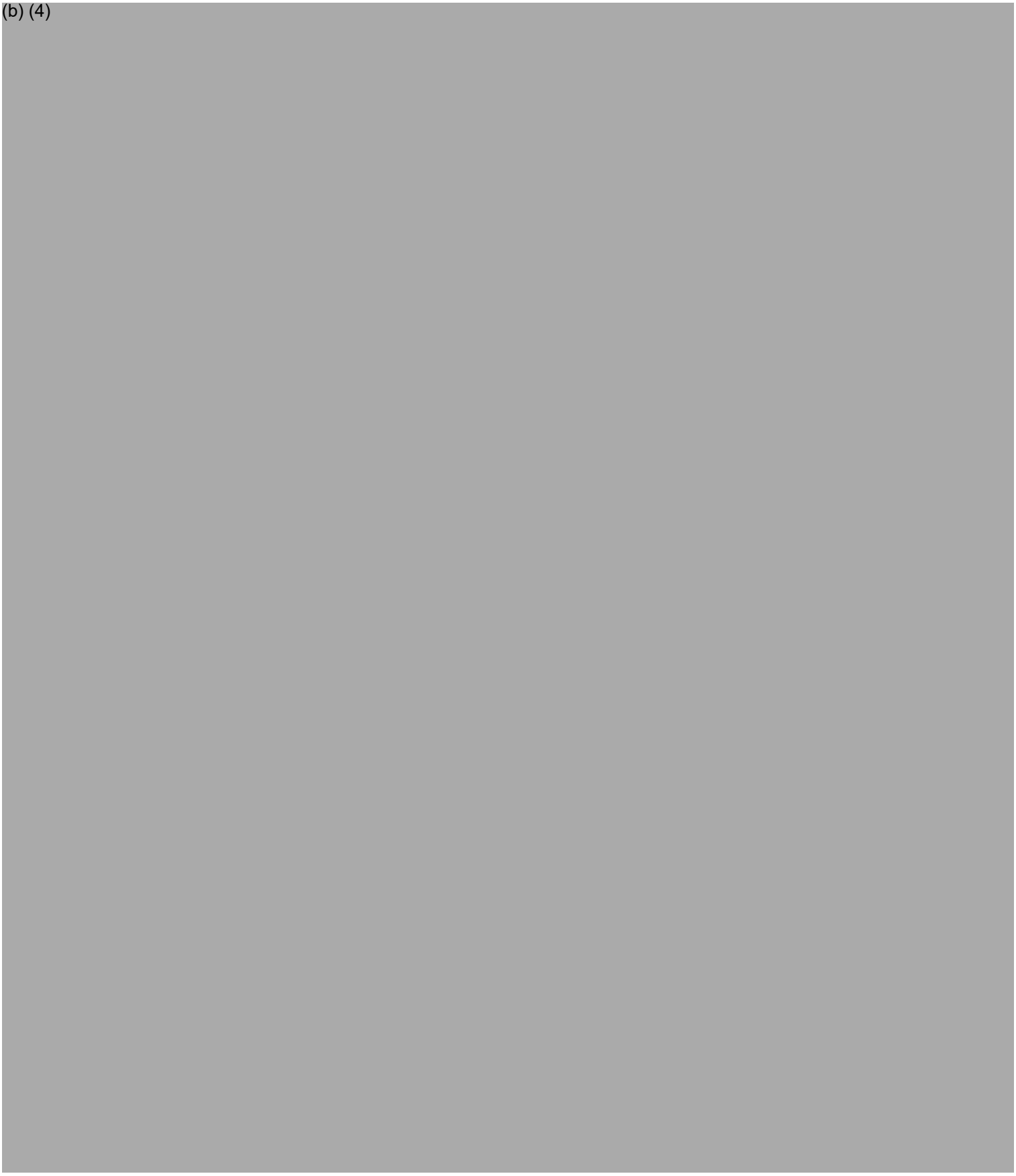

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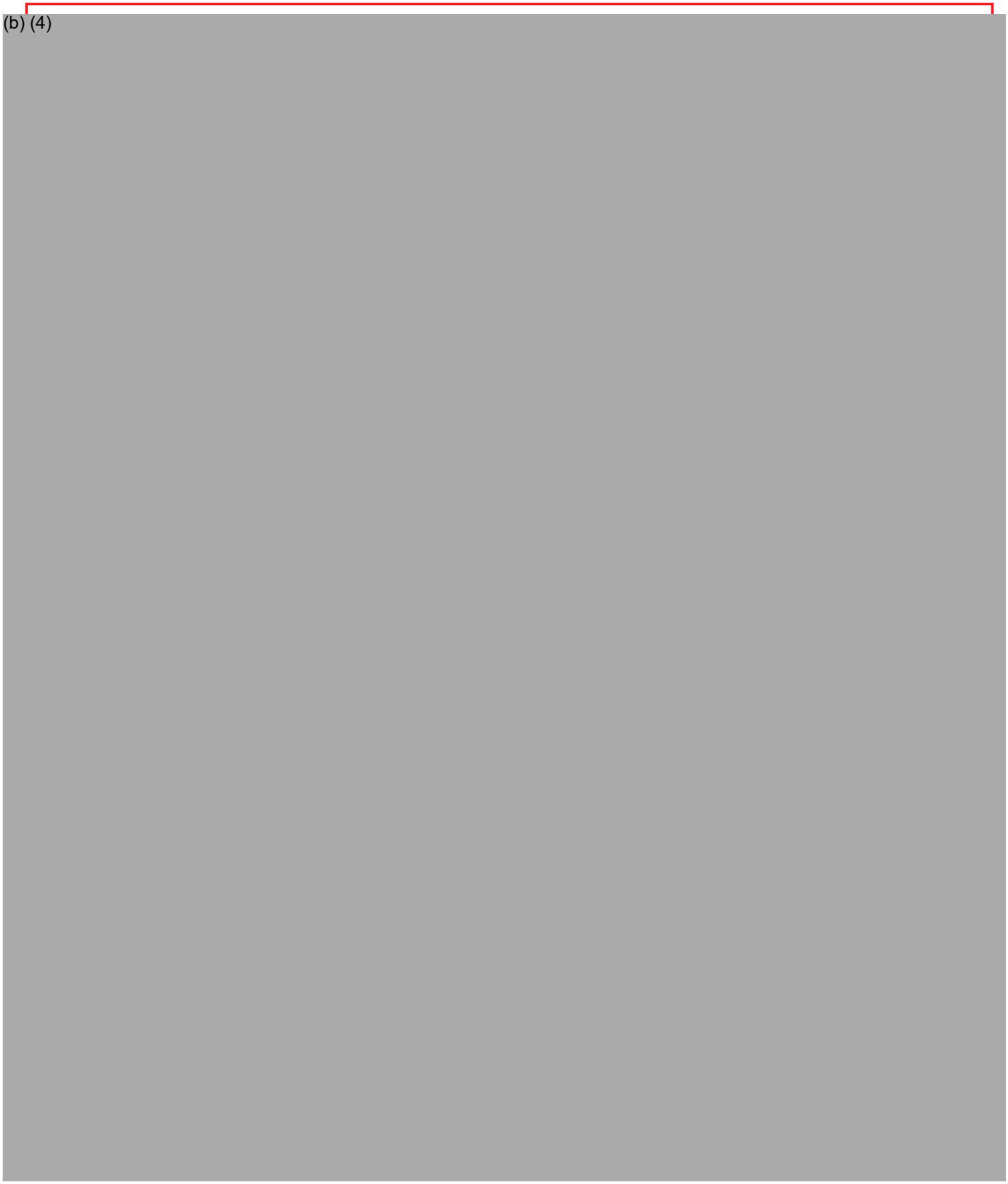

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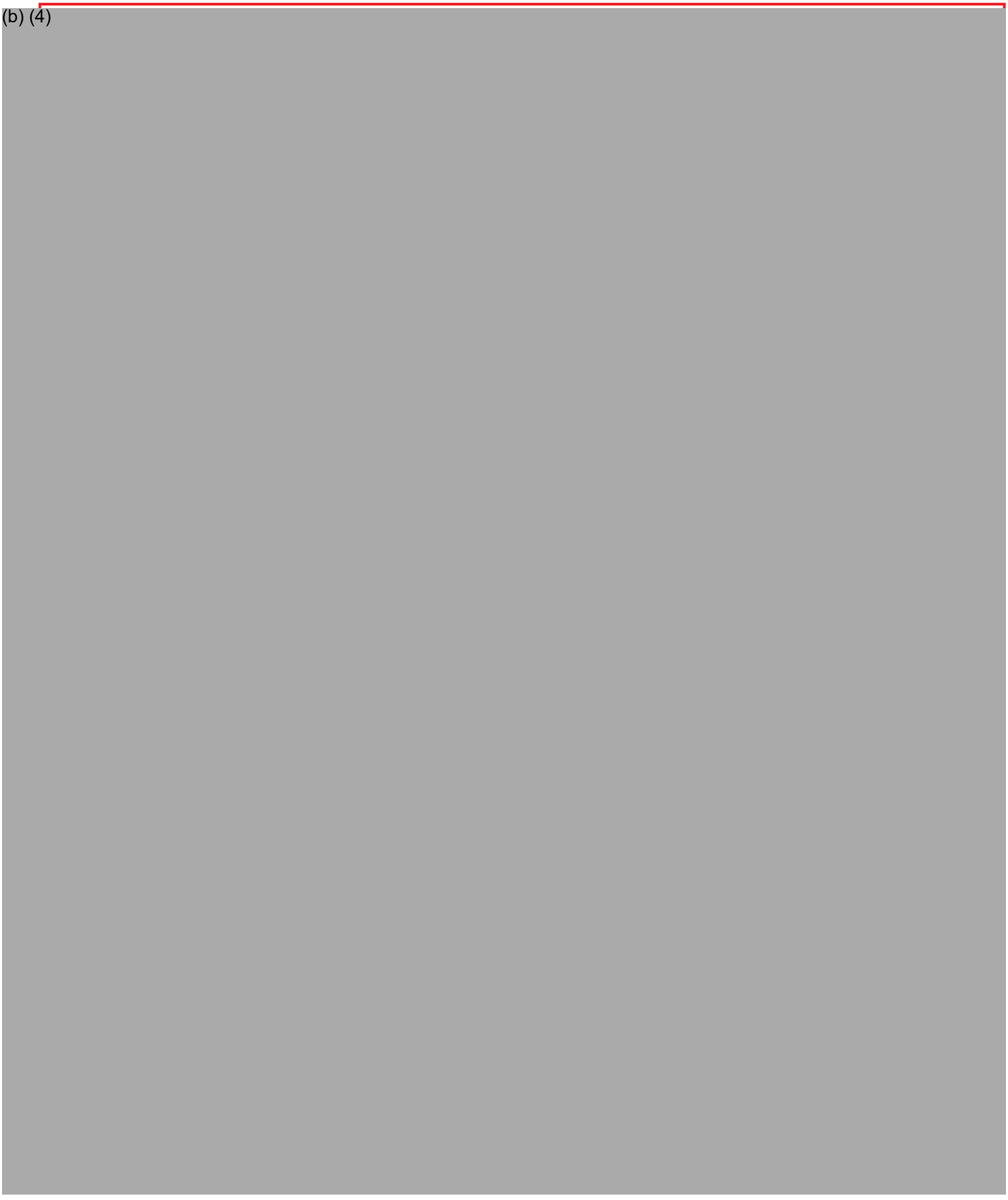

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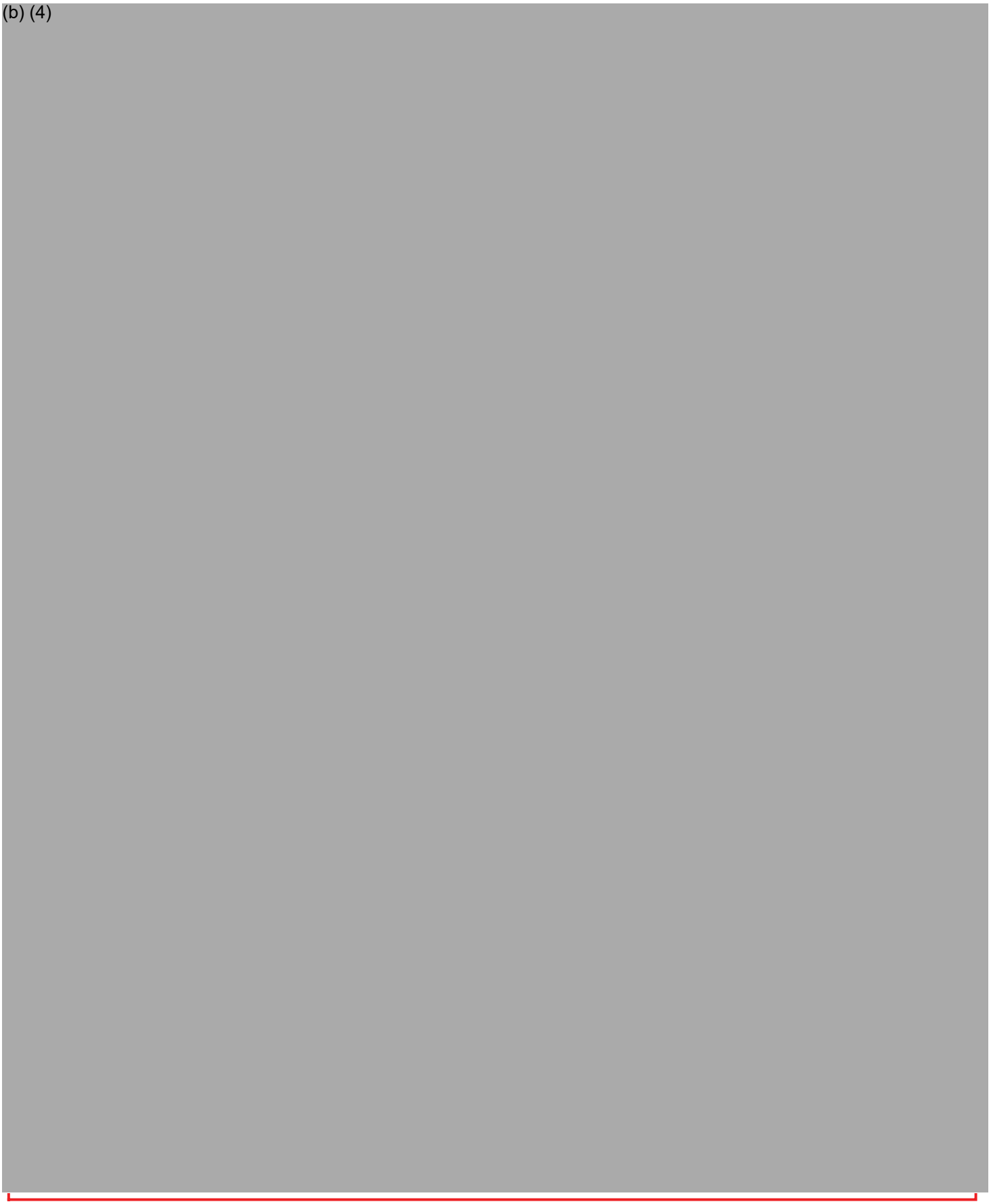
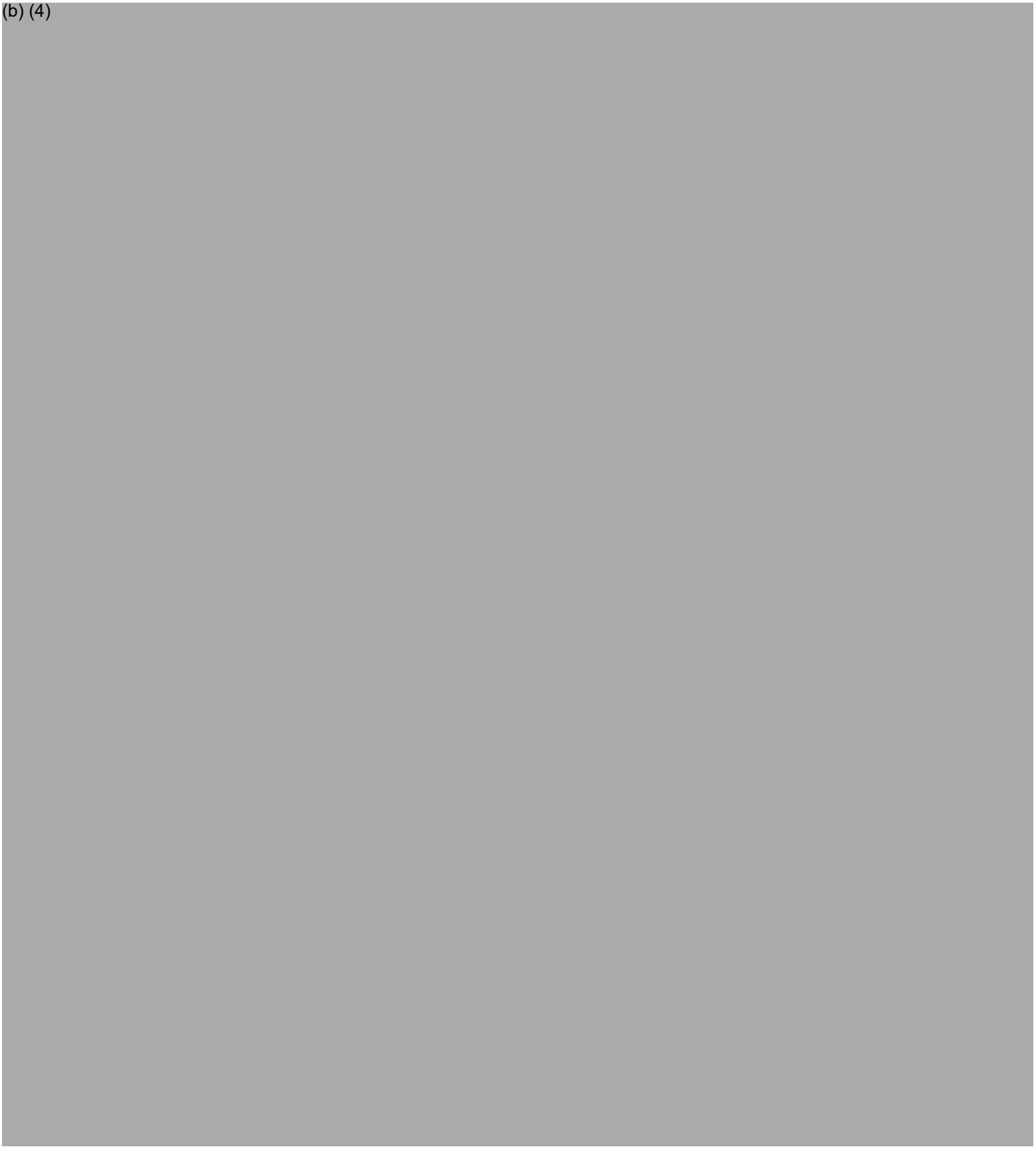


APPENDIX

Appendix 1 - (b) (4)

(b) (4)



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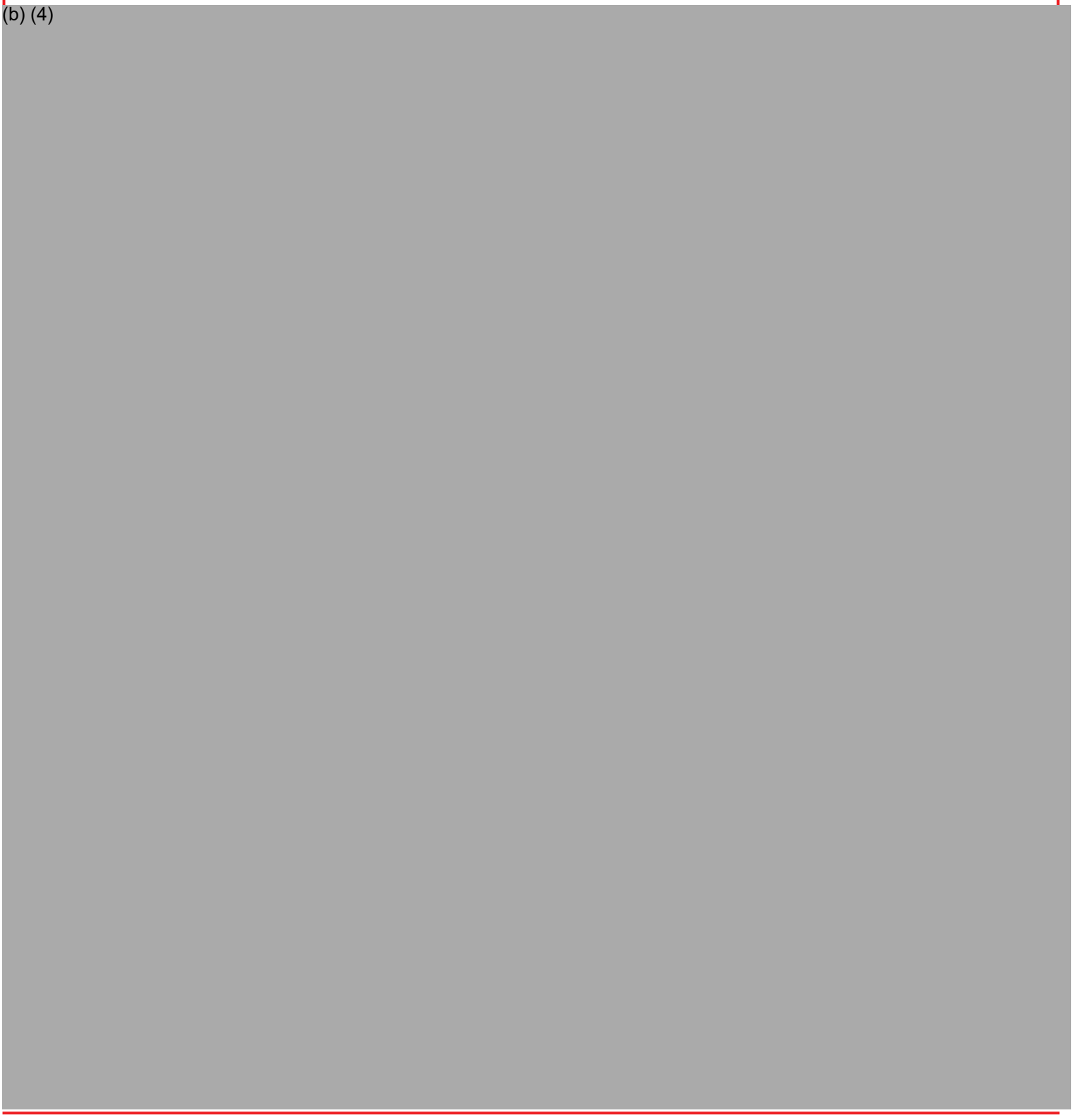

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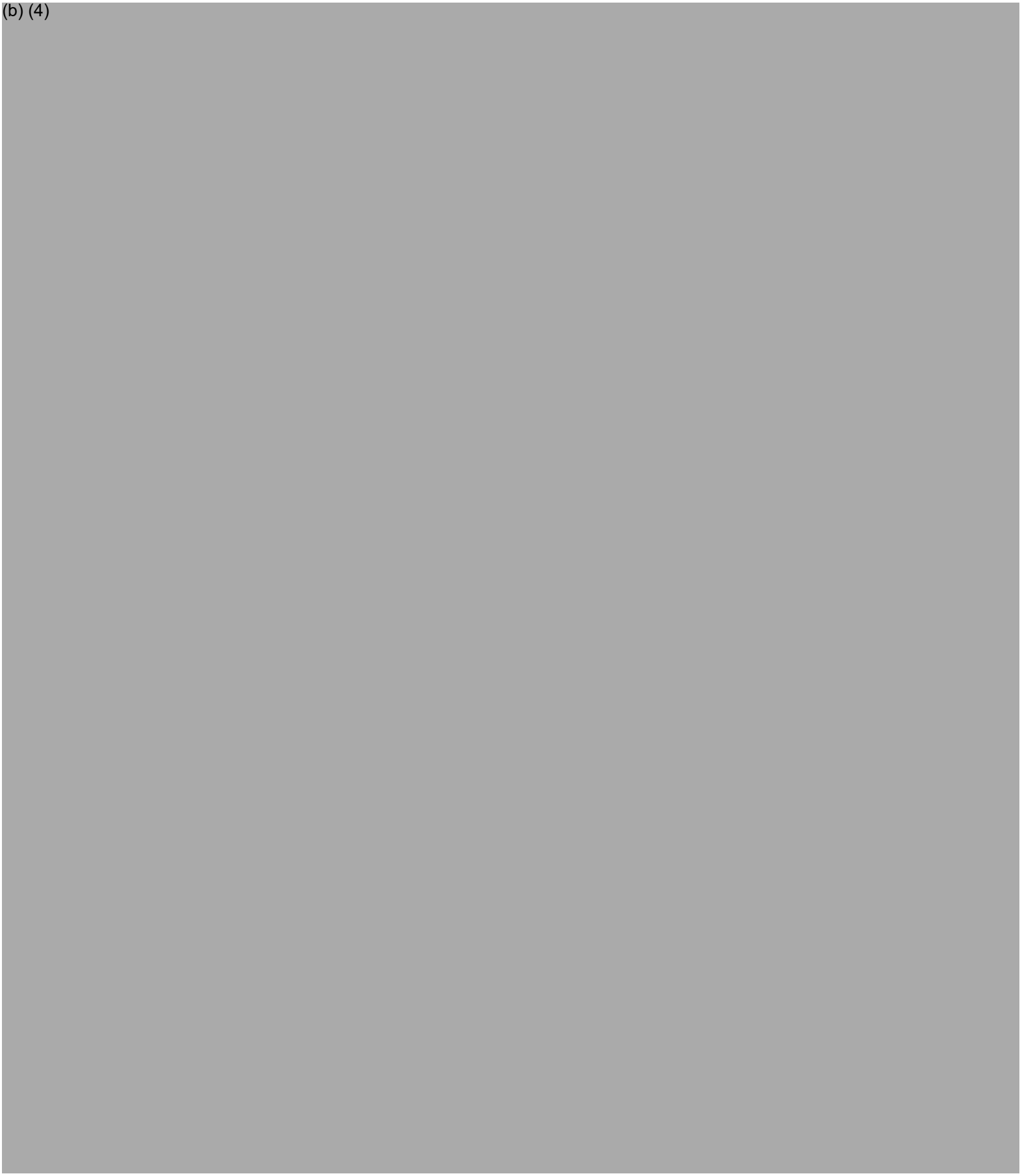

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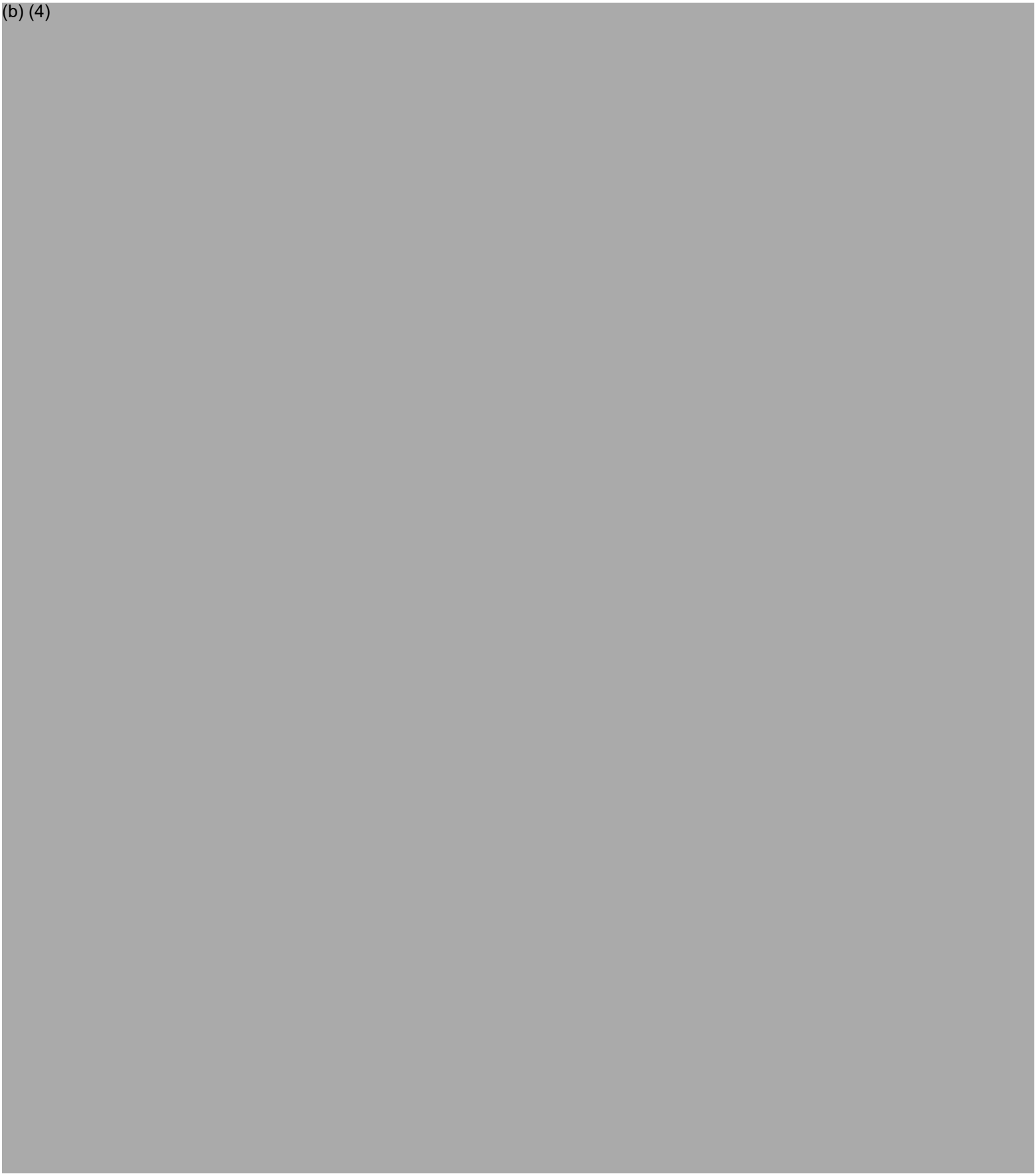

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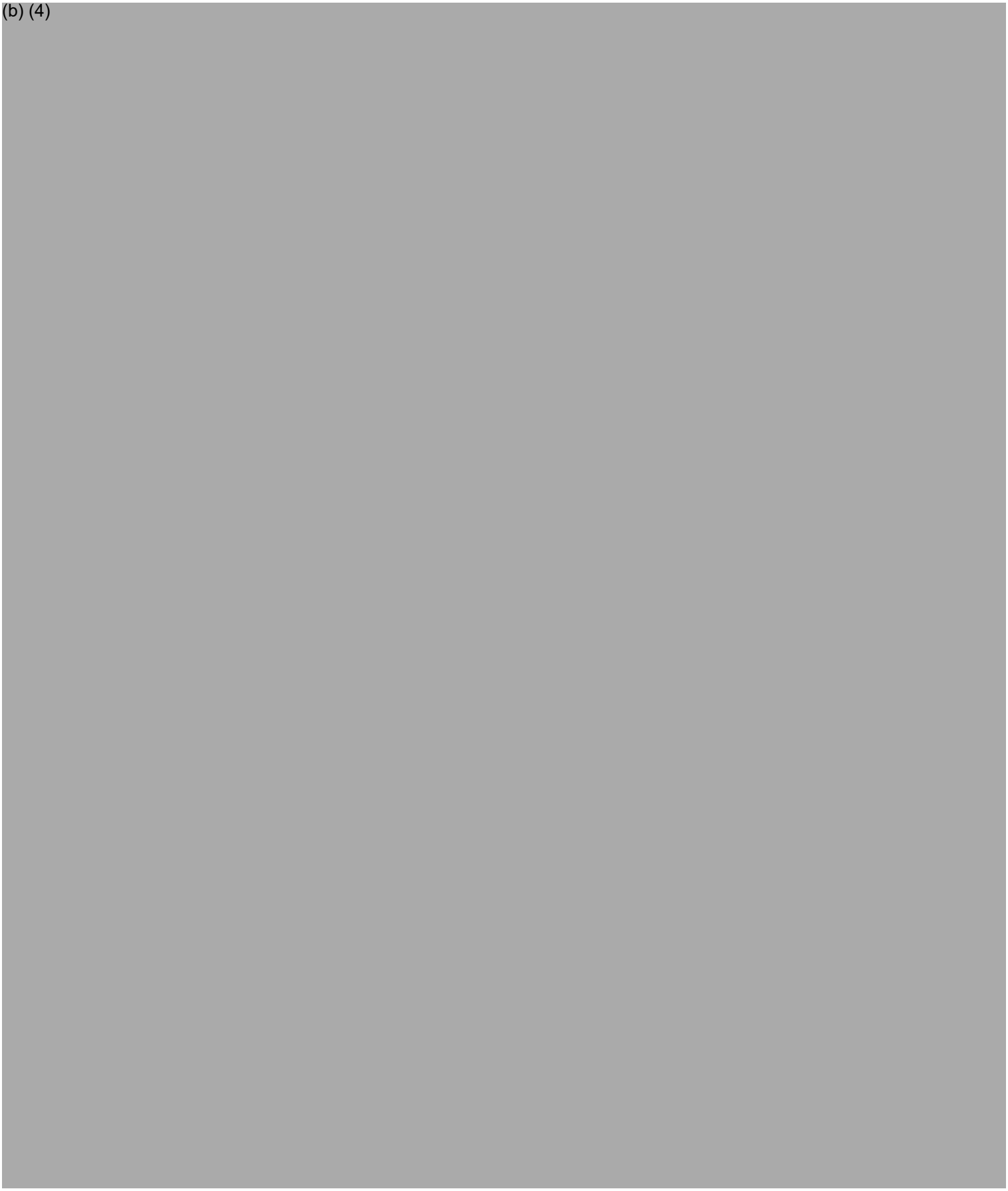

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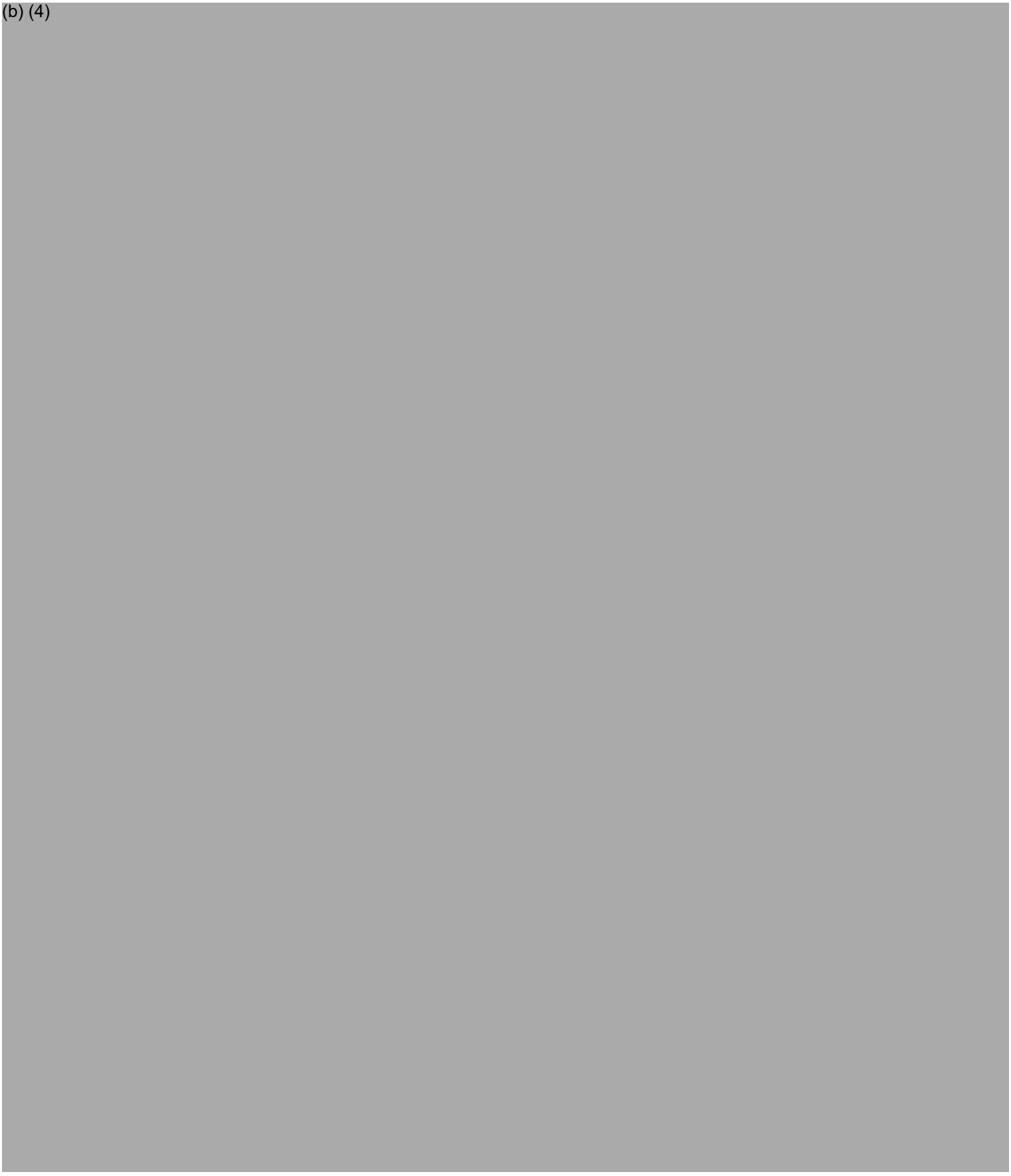

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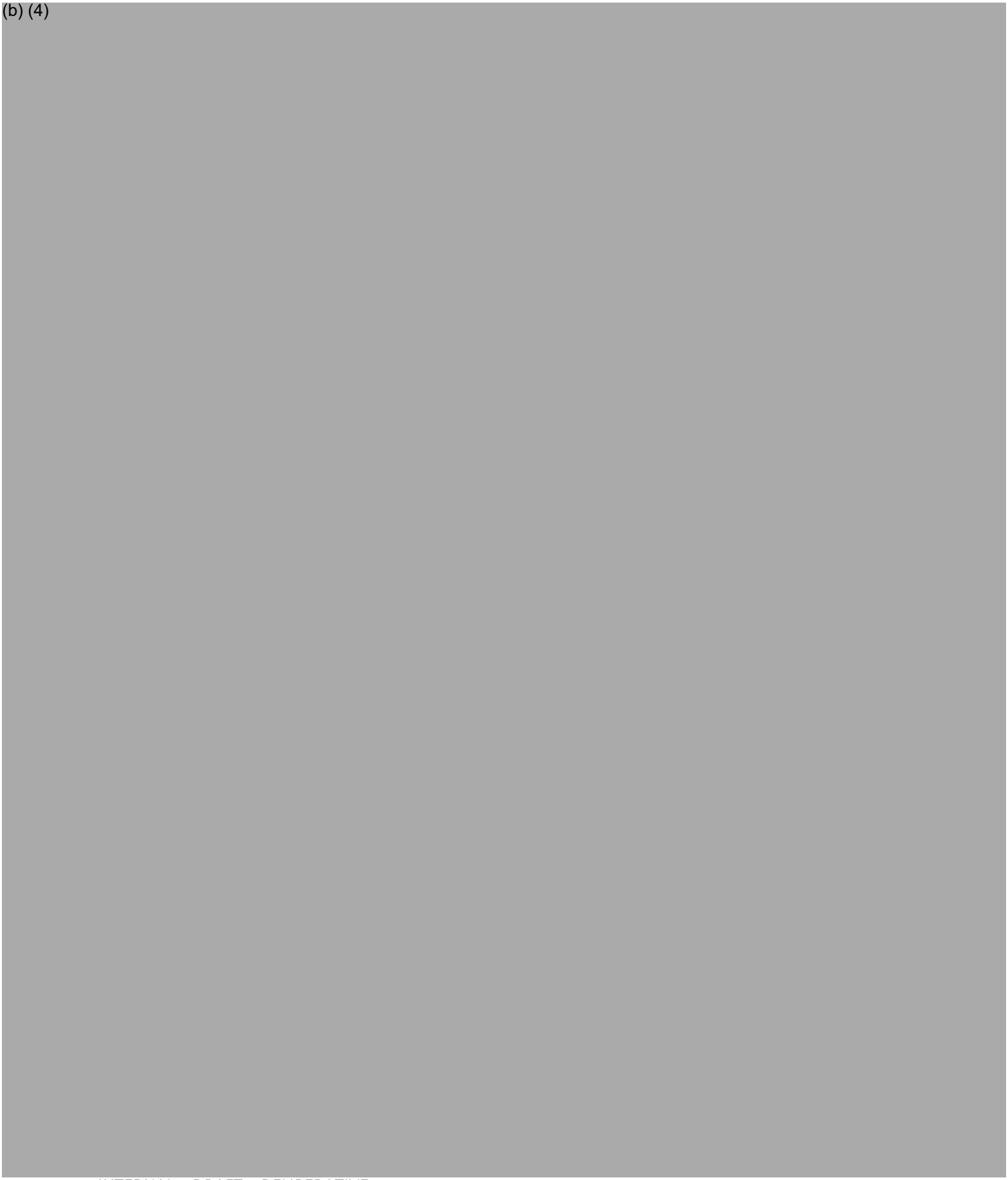

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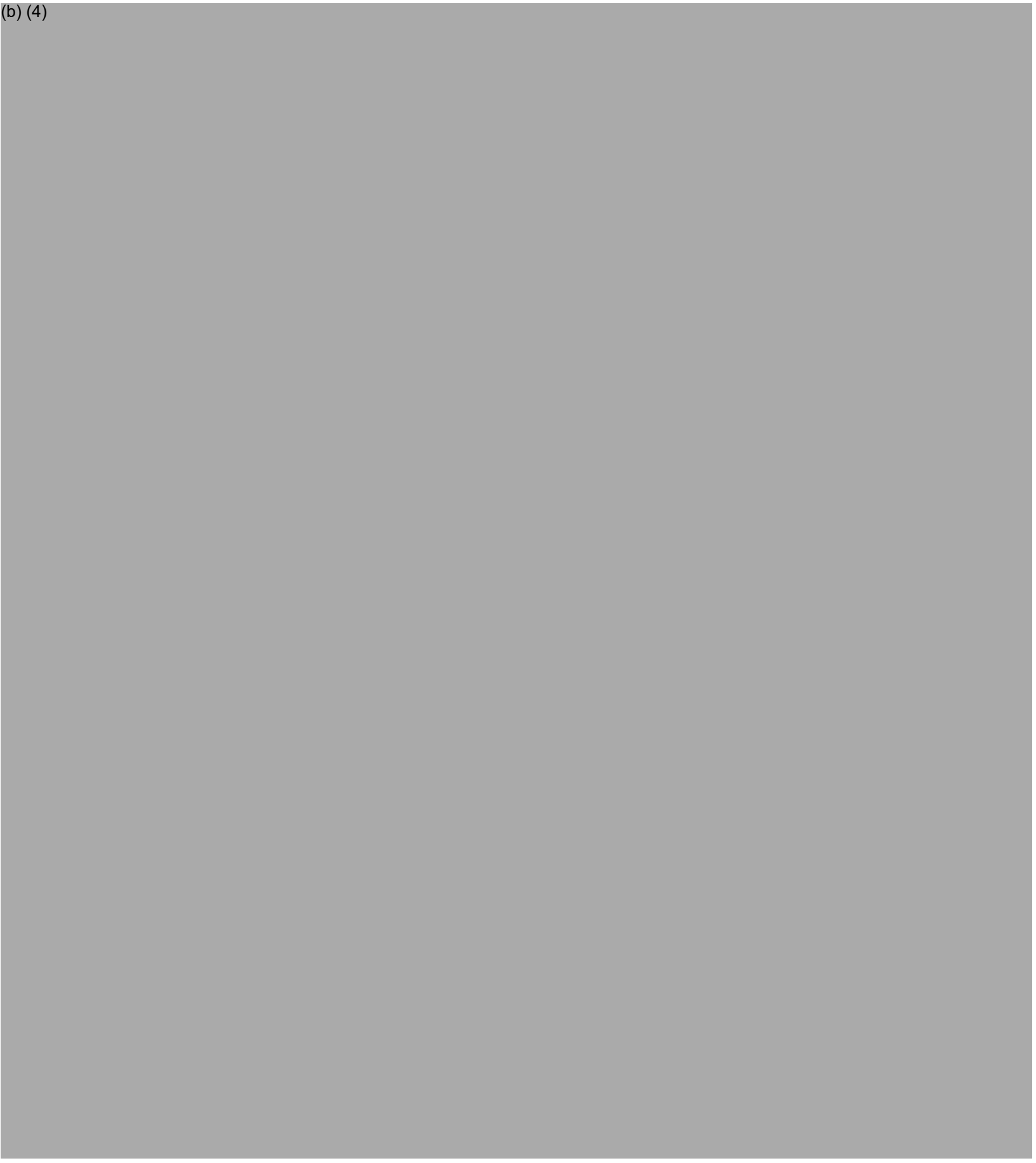

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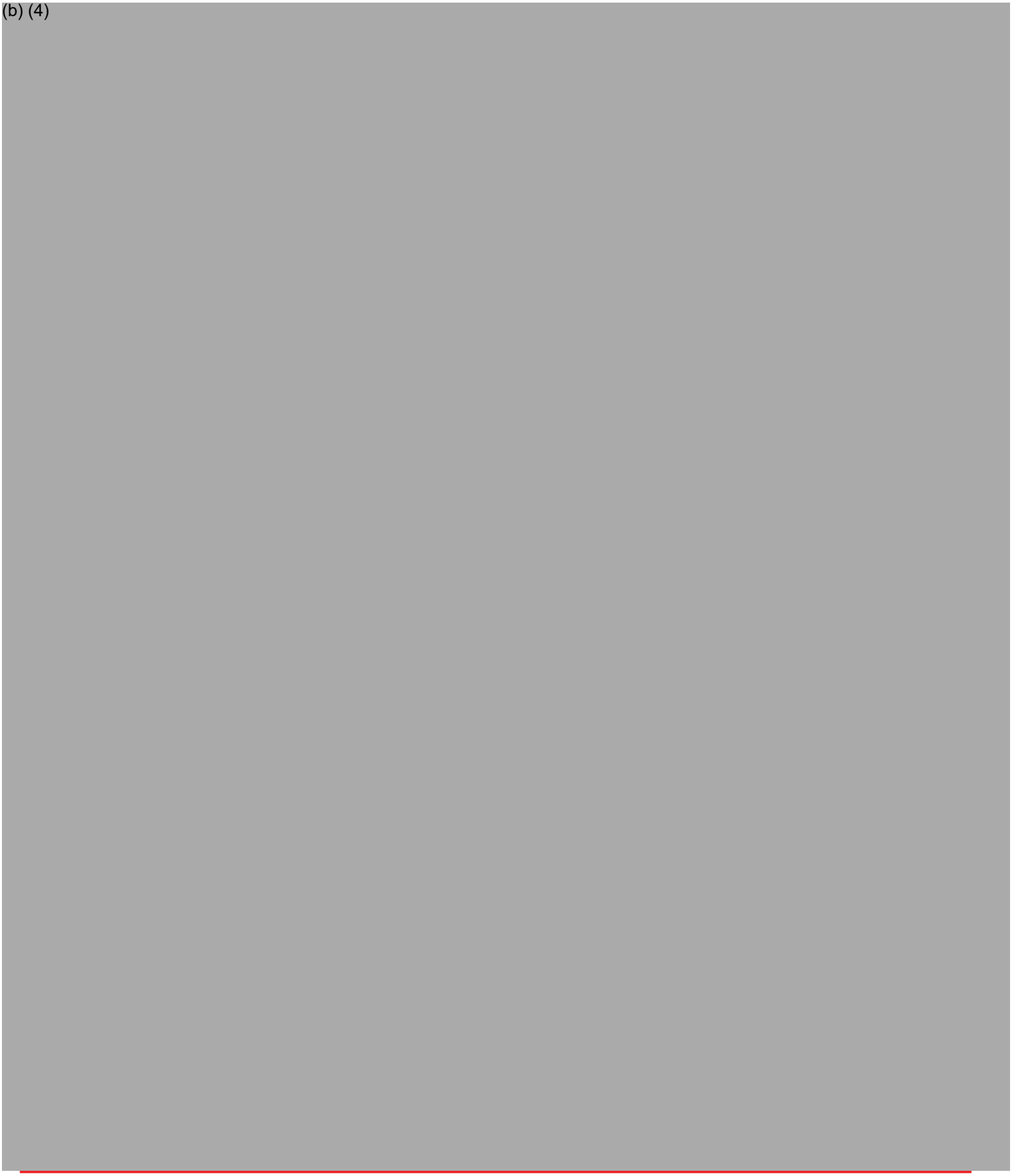

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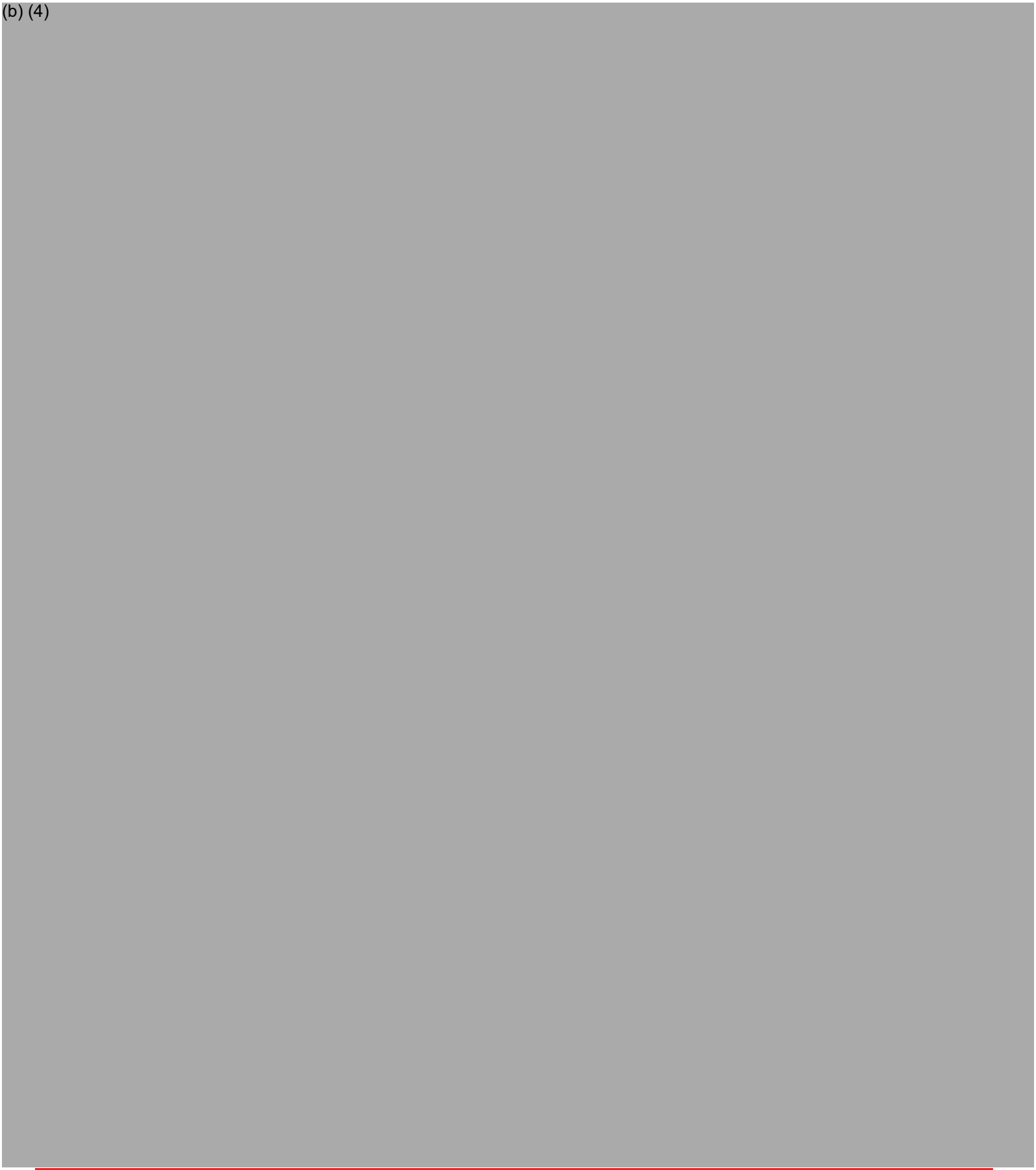

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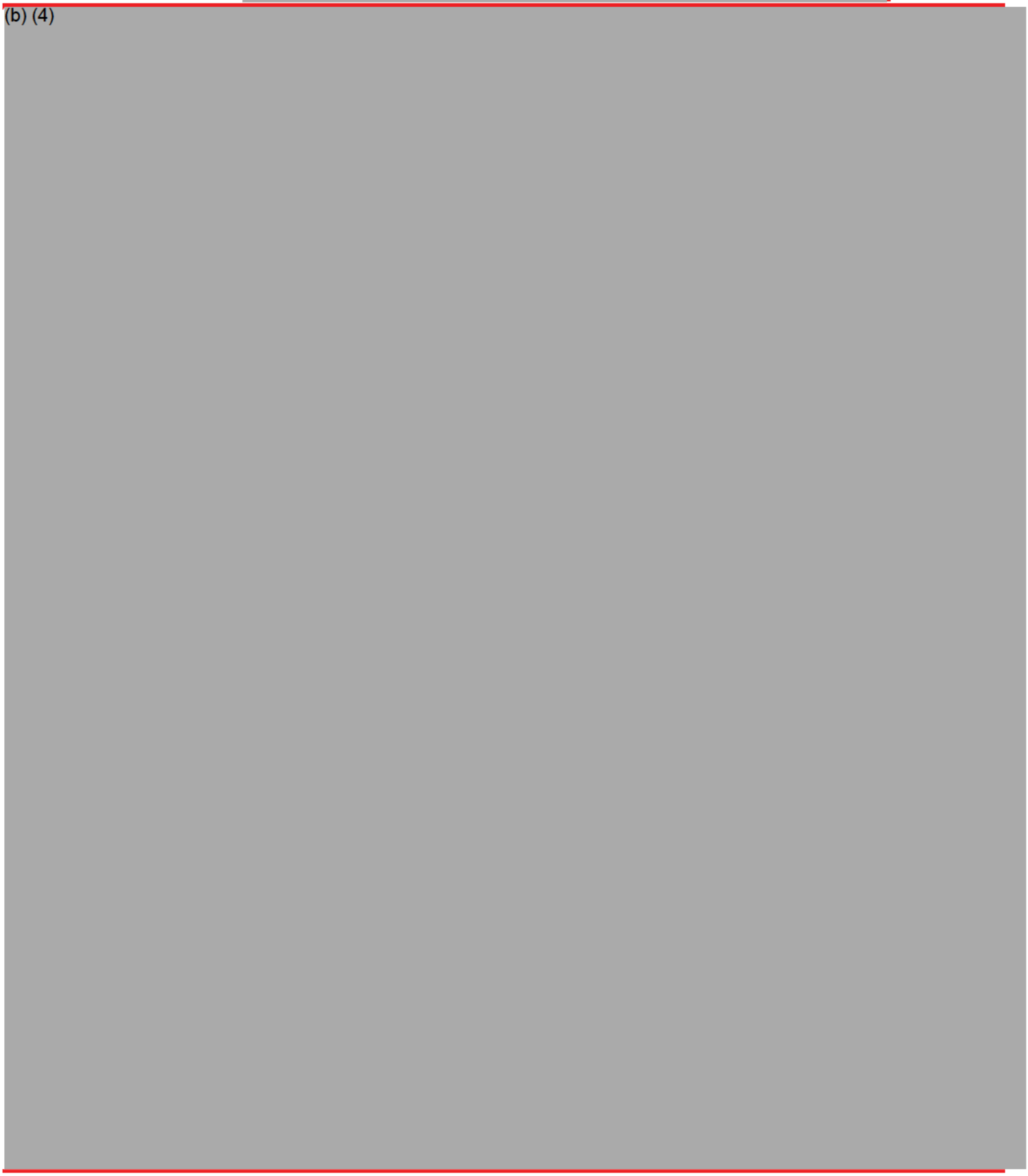

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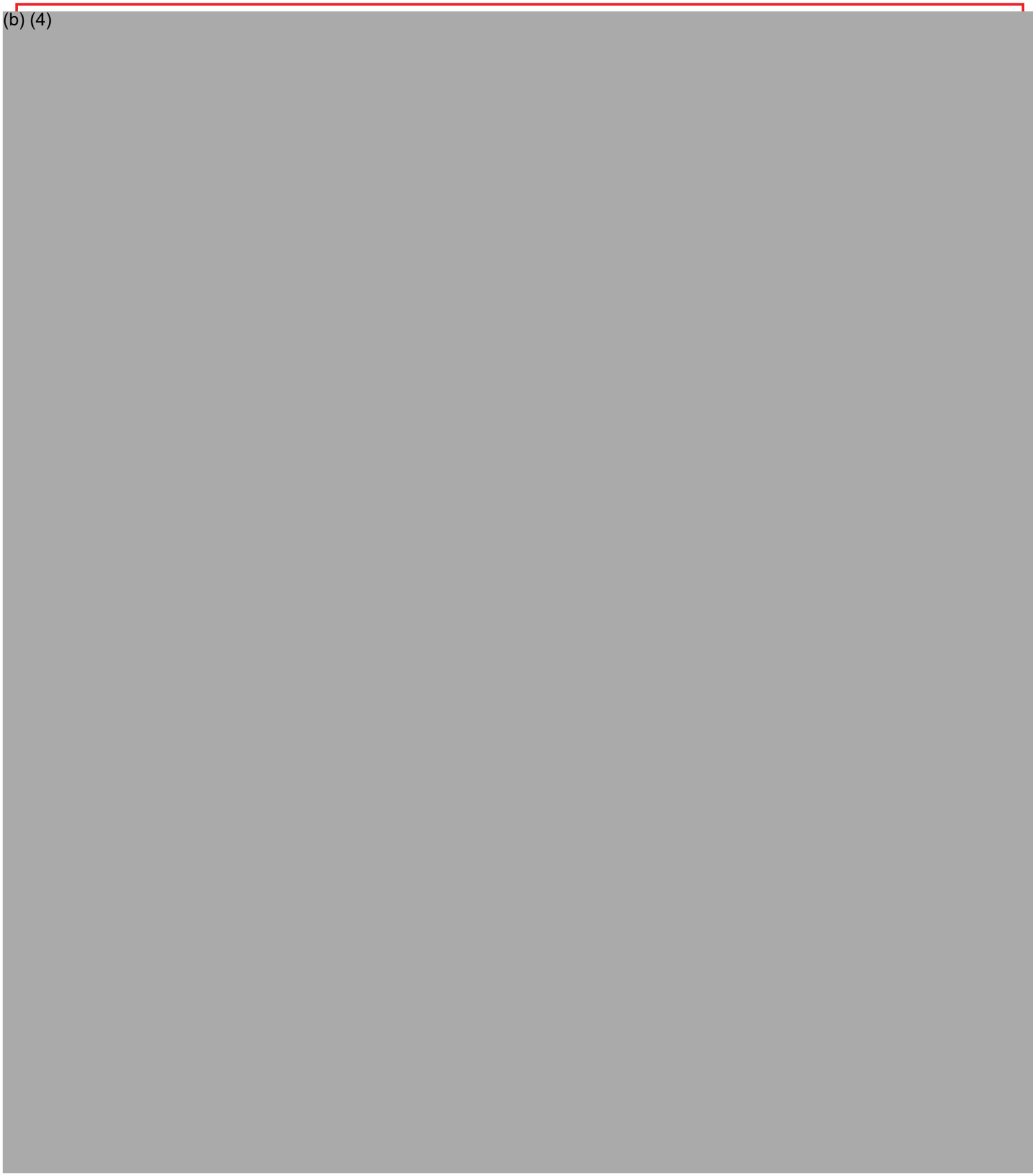

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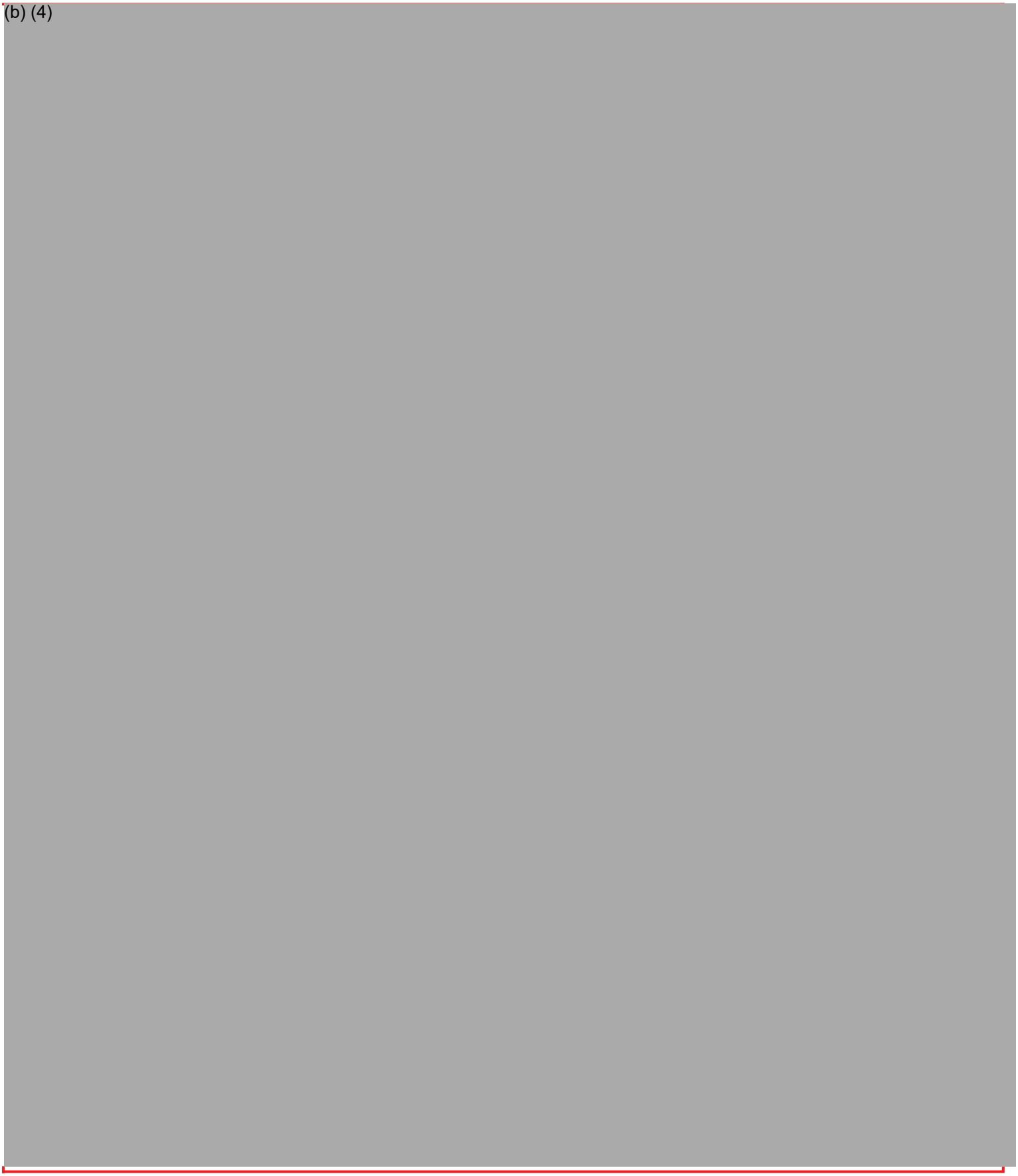

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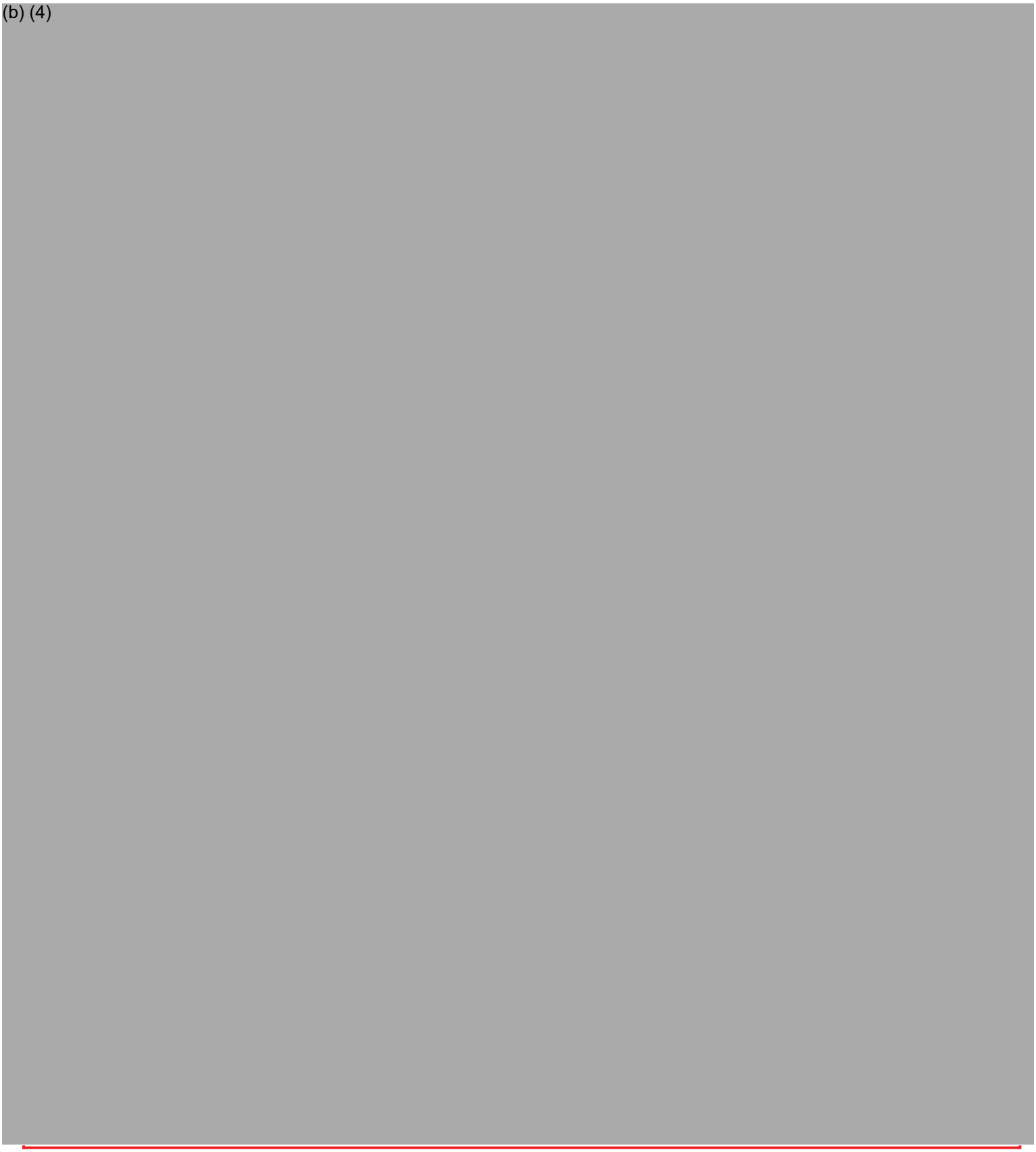

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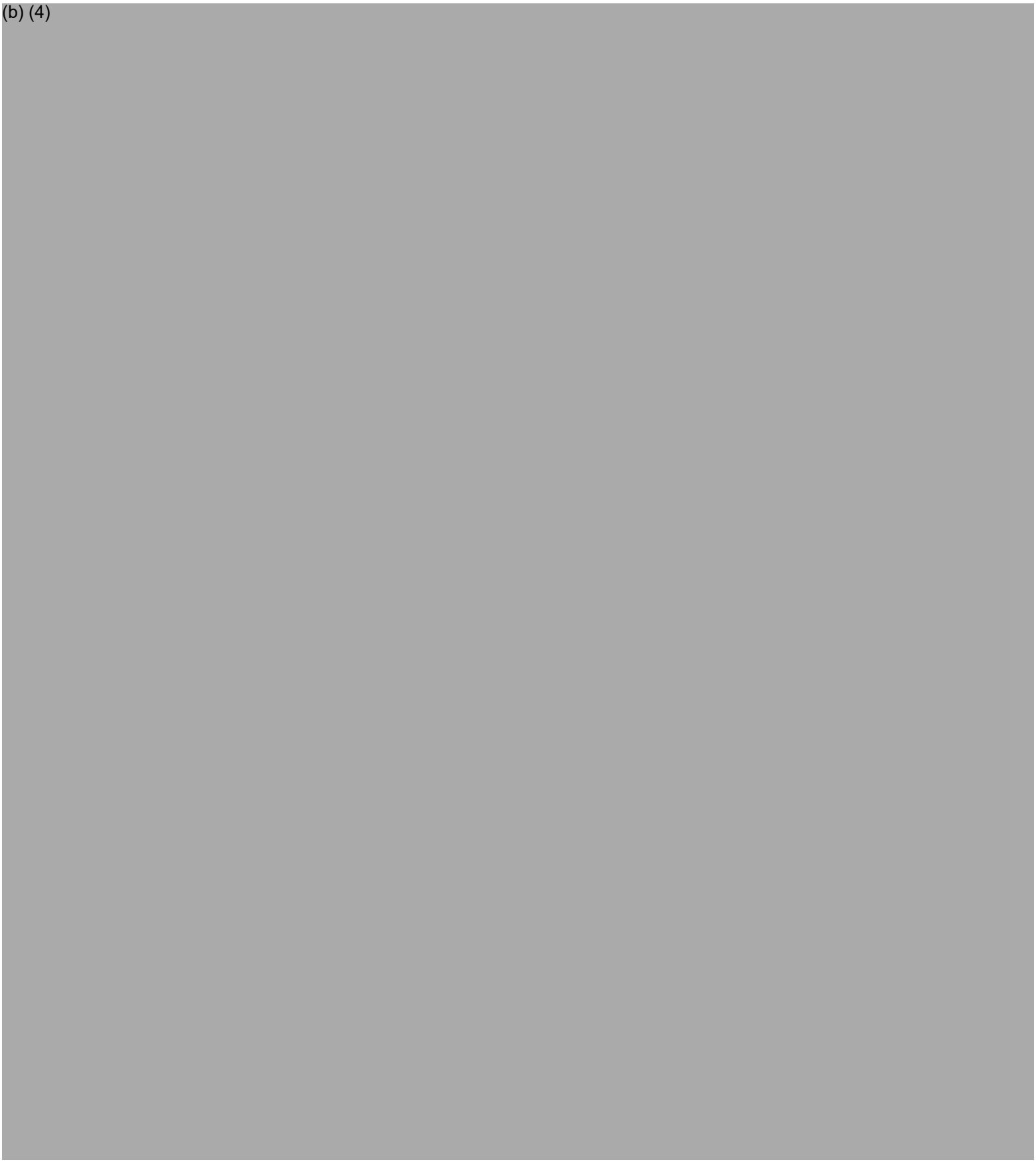

Appendix 3a - (b) (4)

(b) (4)

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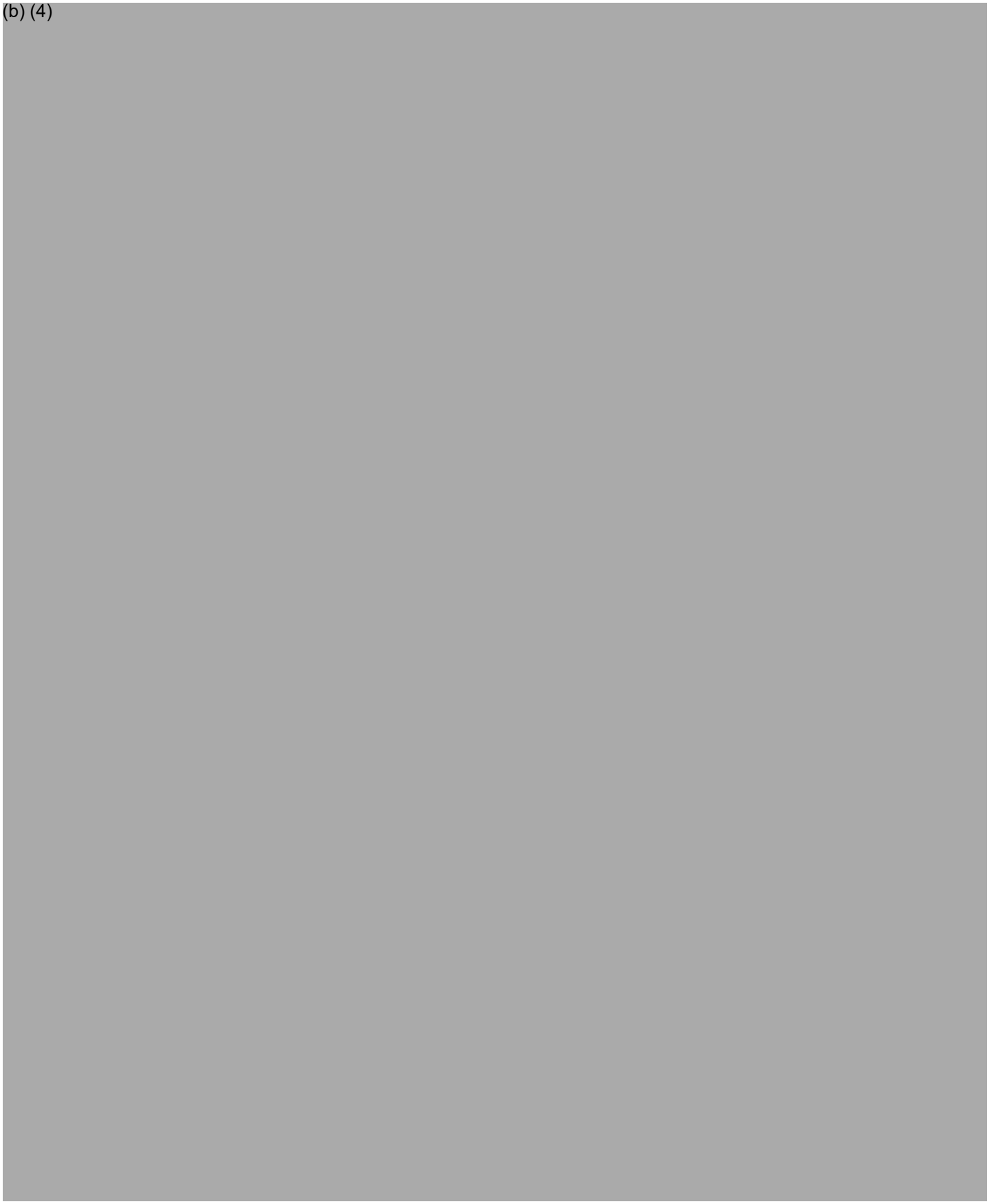

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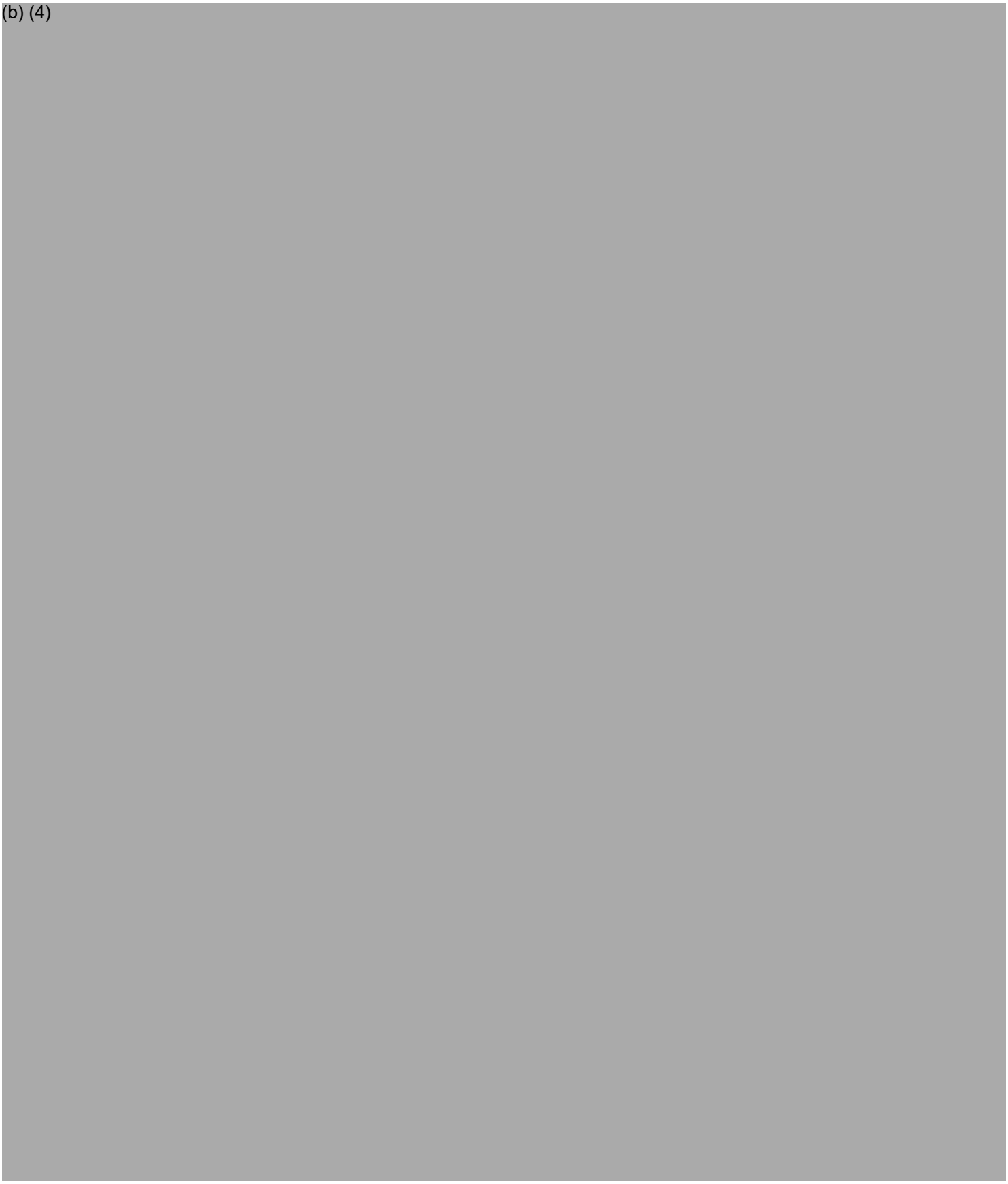

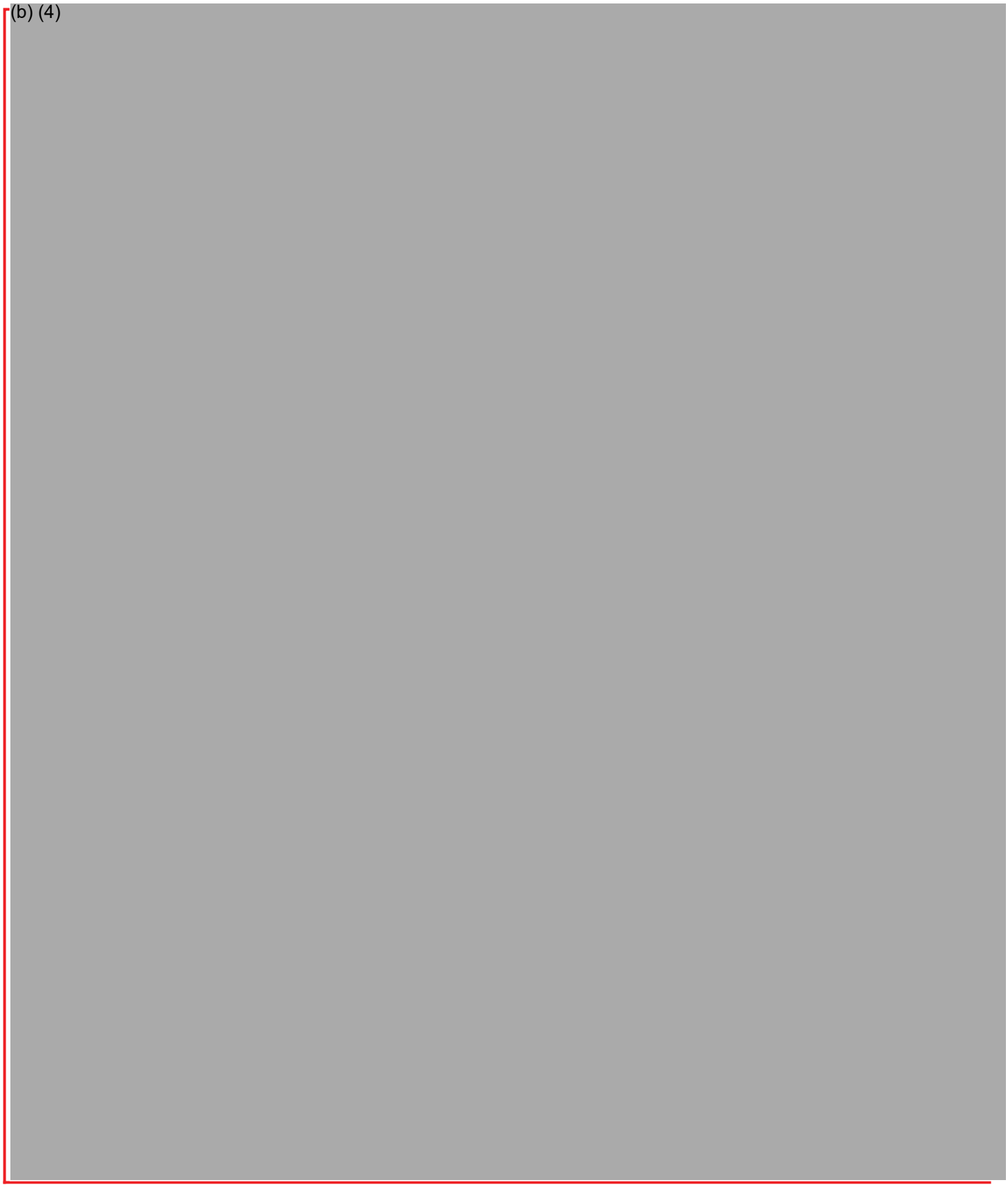
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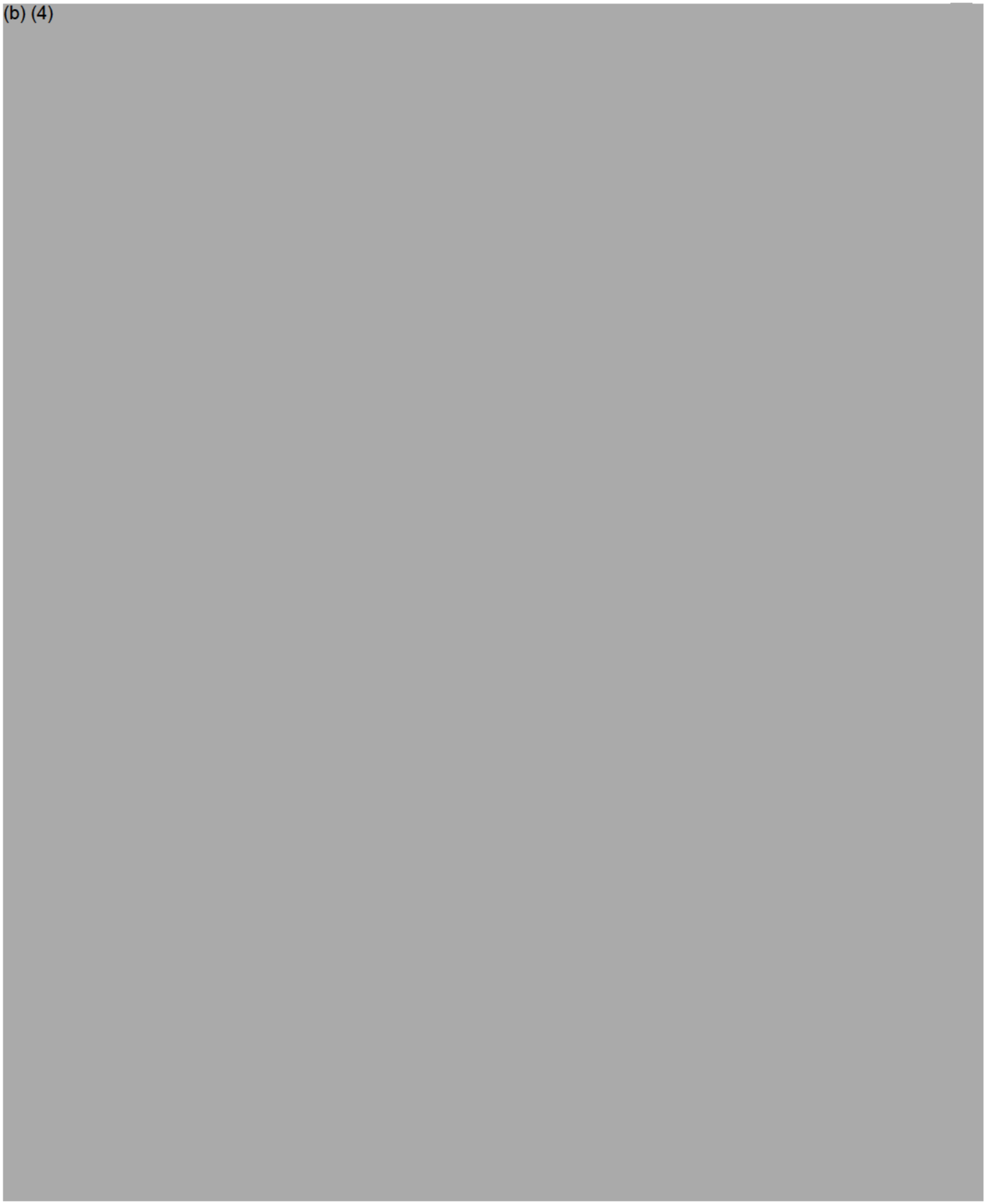

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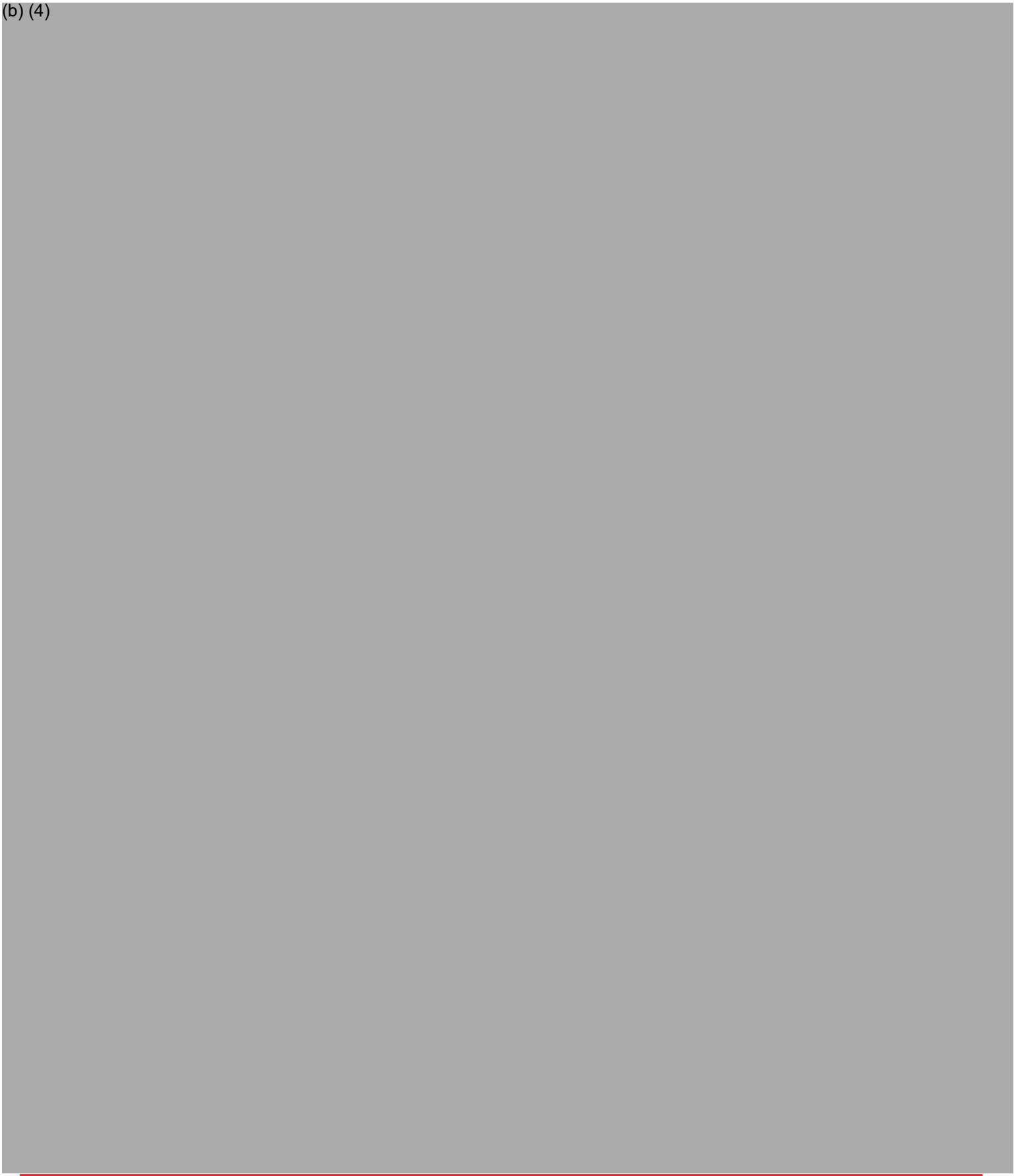

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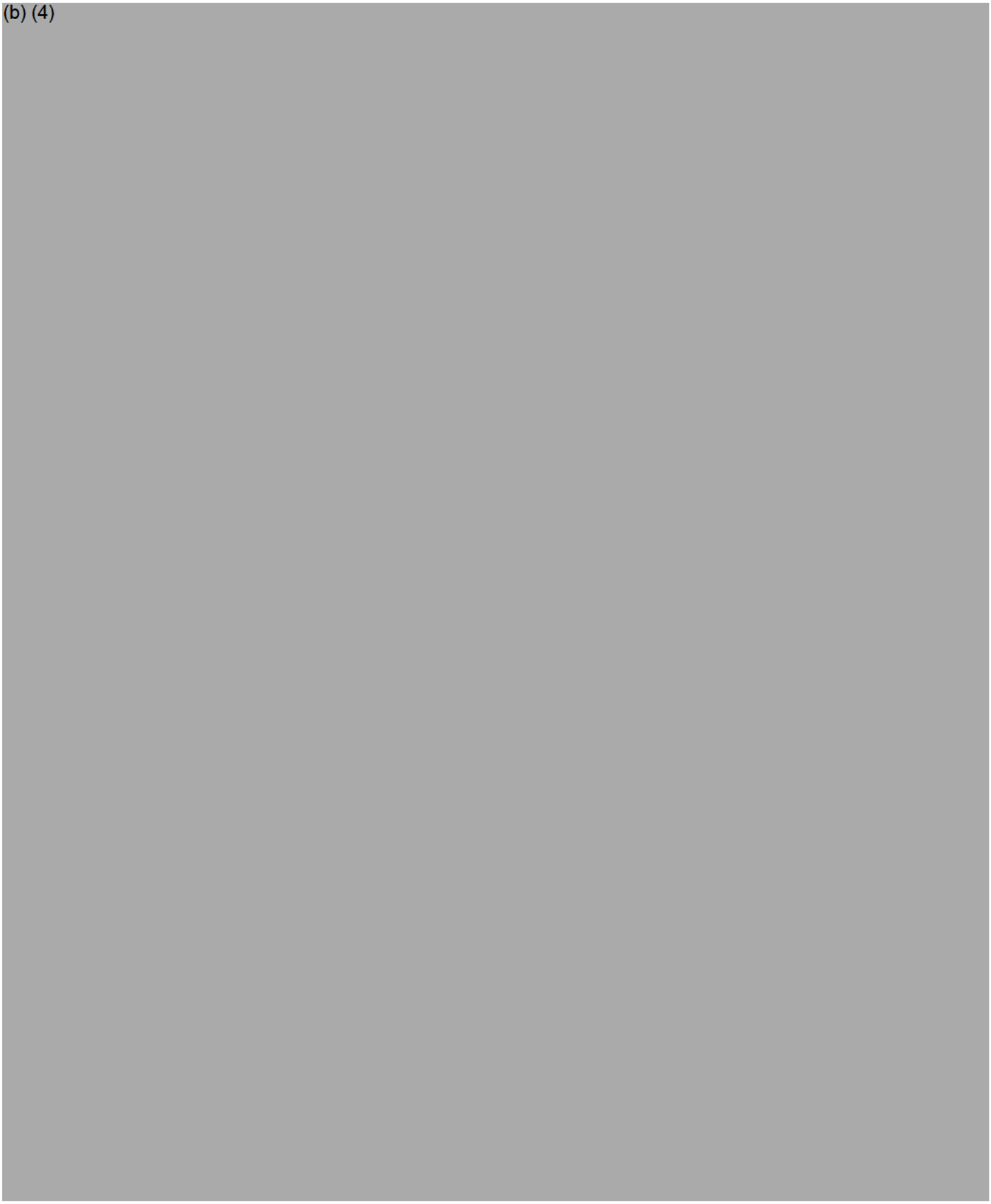

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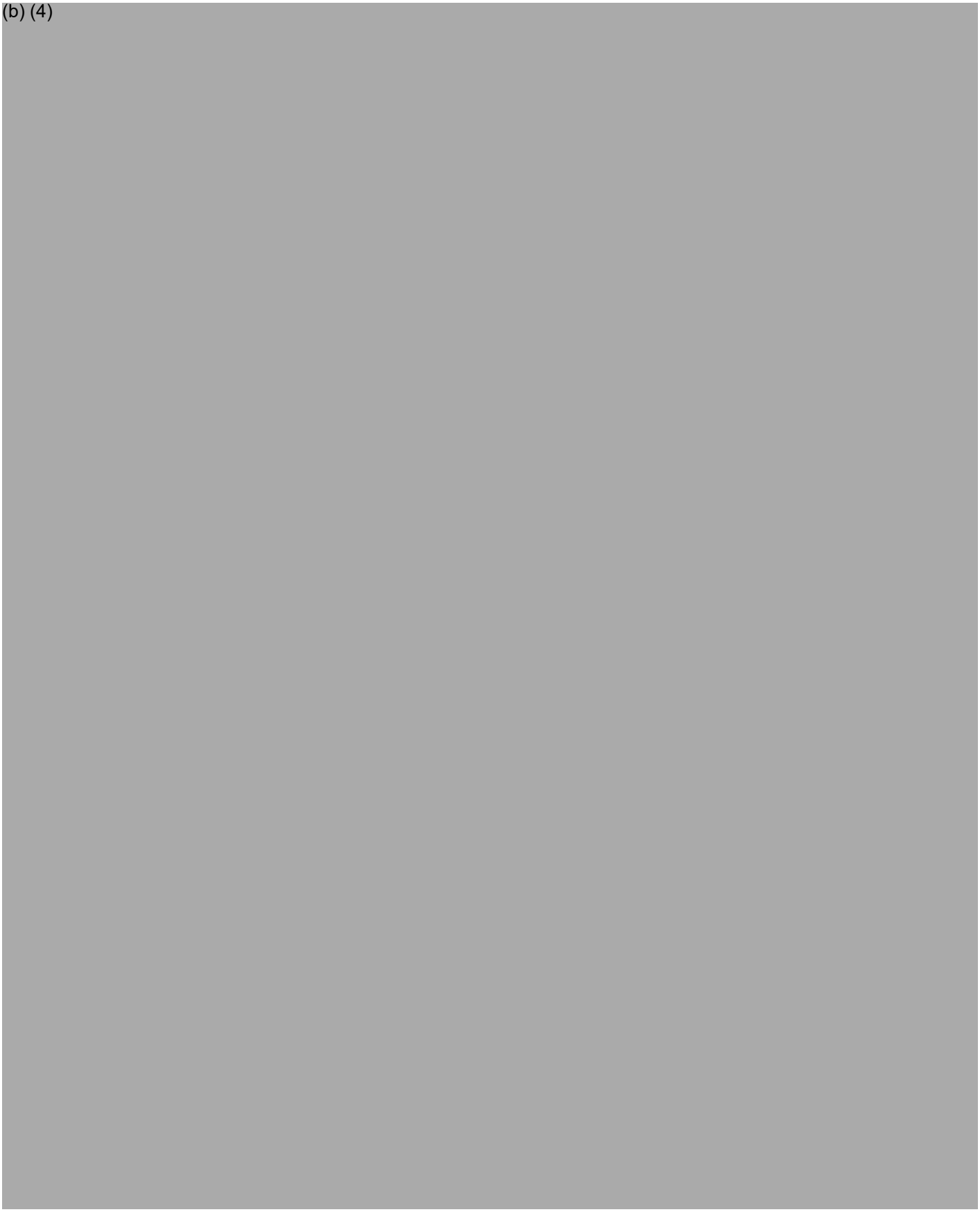

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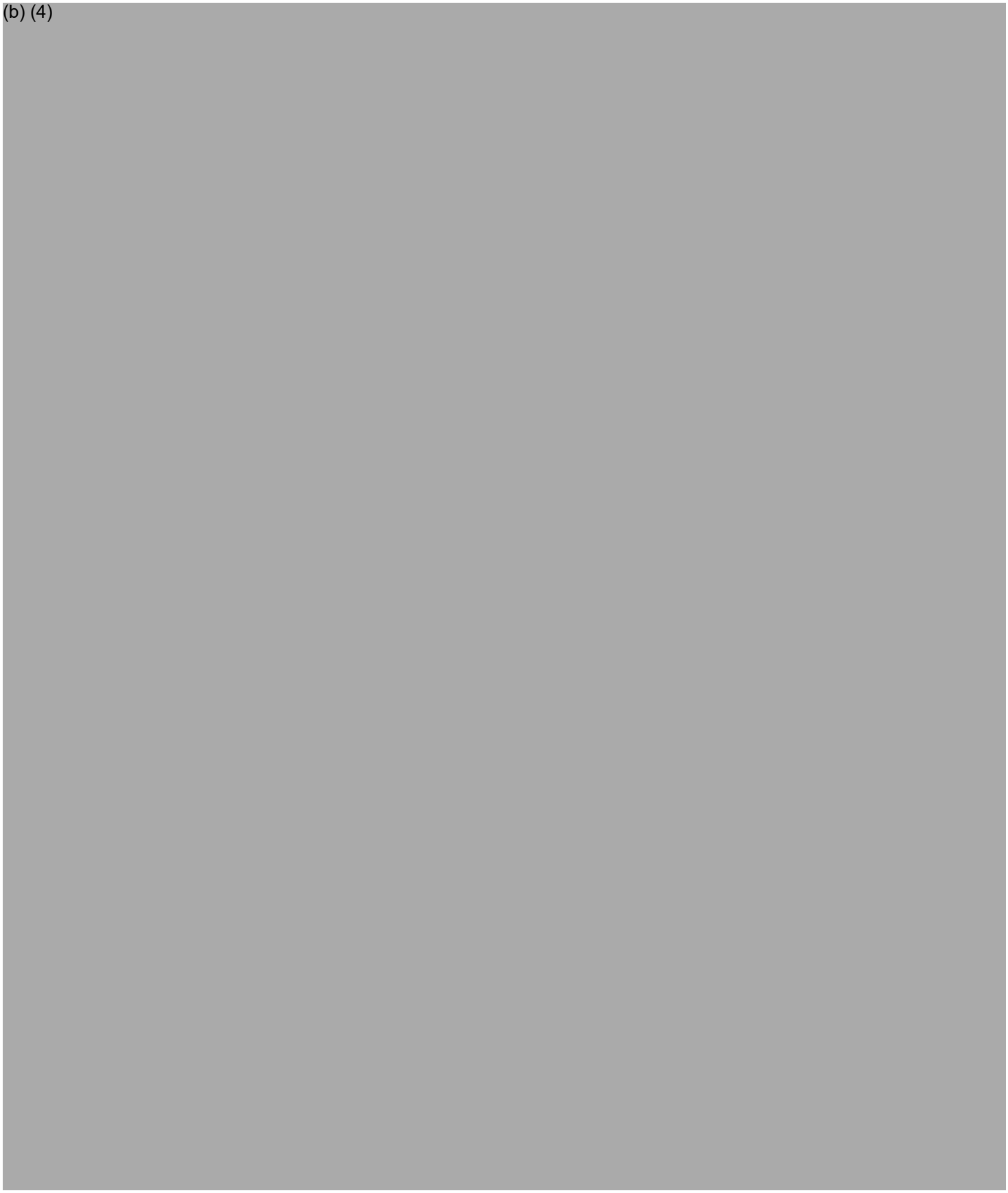

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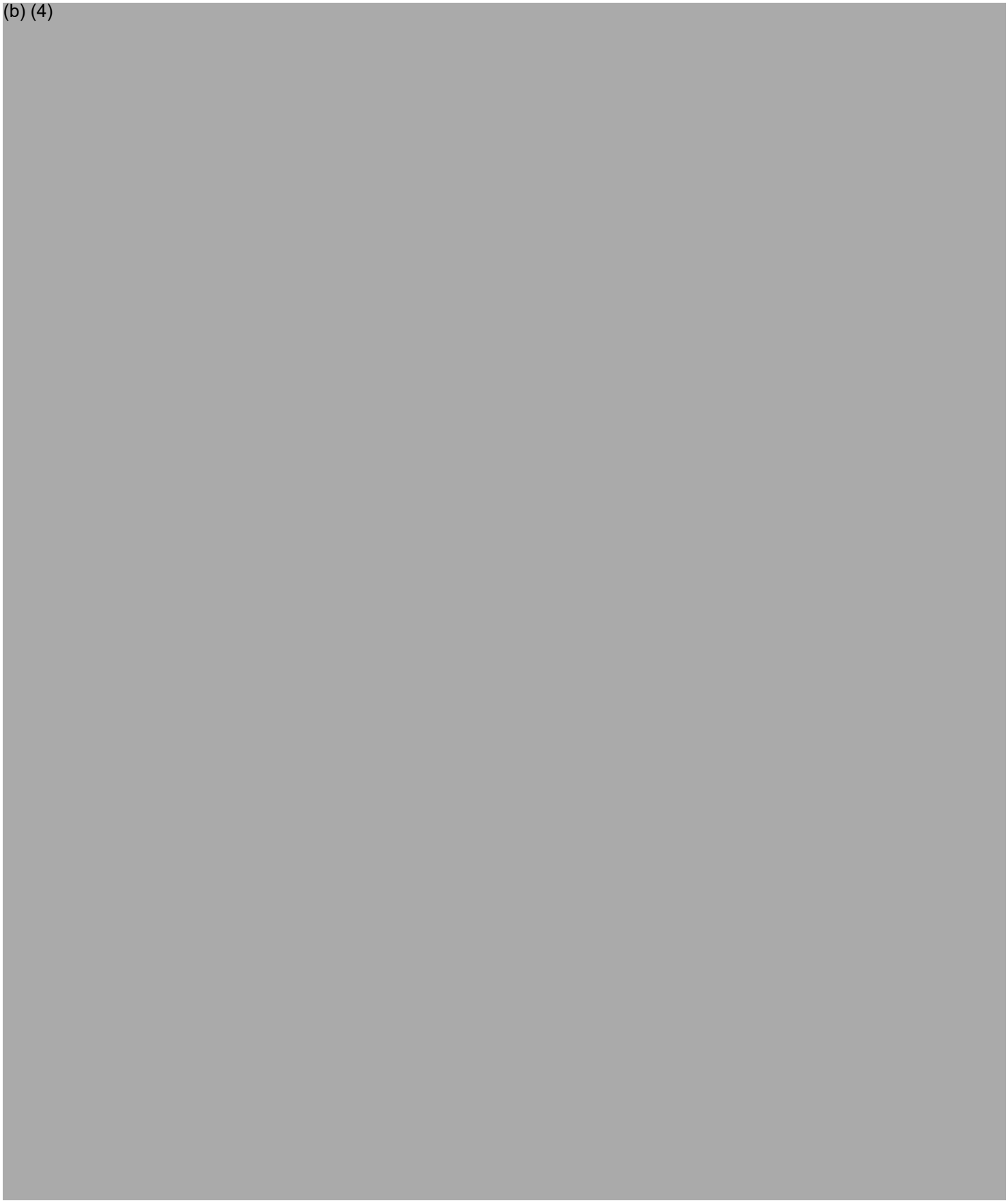

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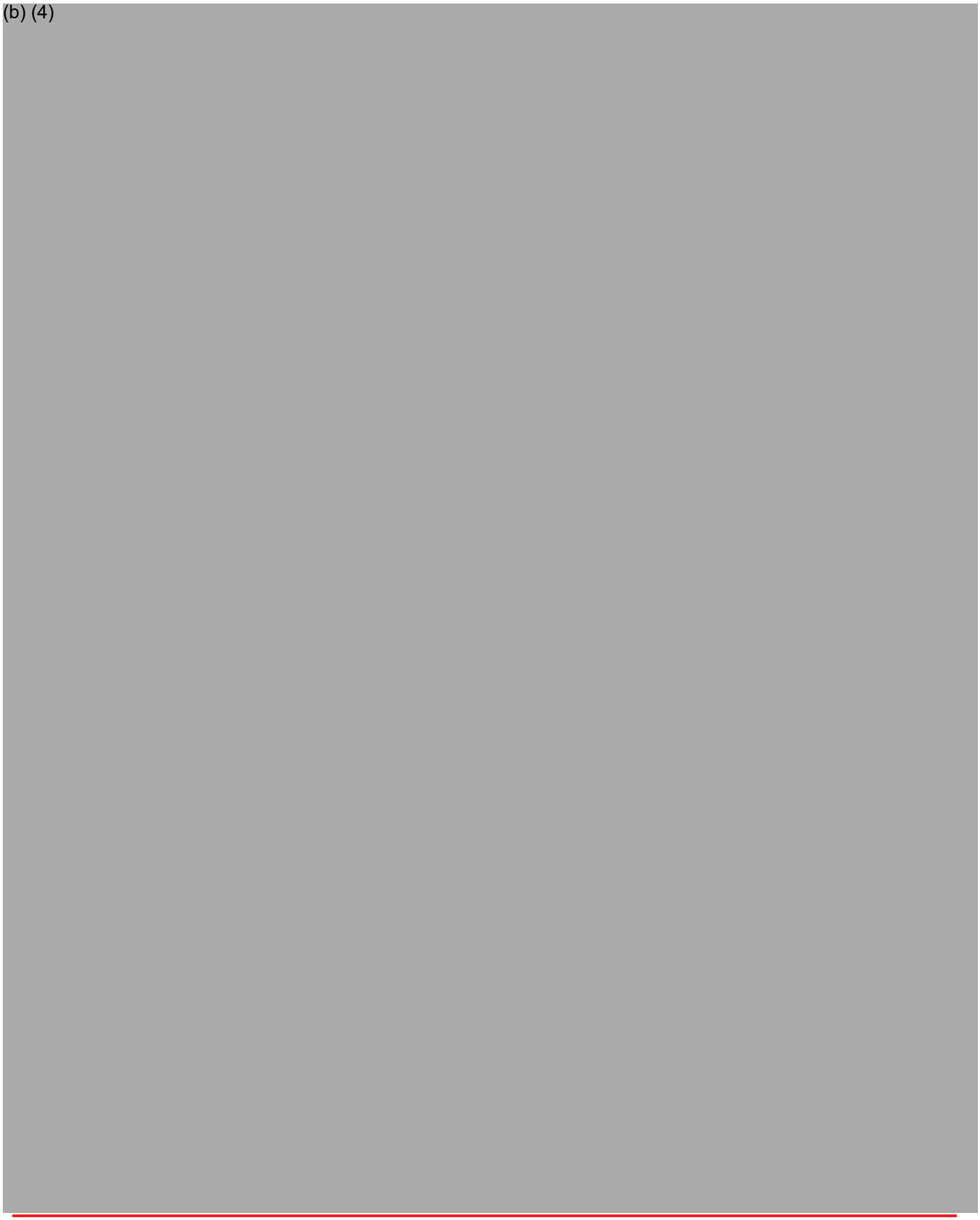

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