Minority Health and Health Disparities

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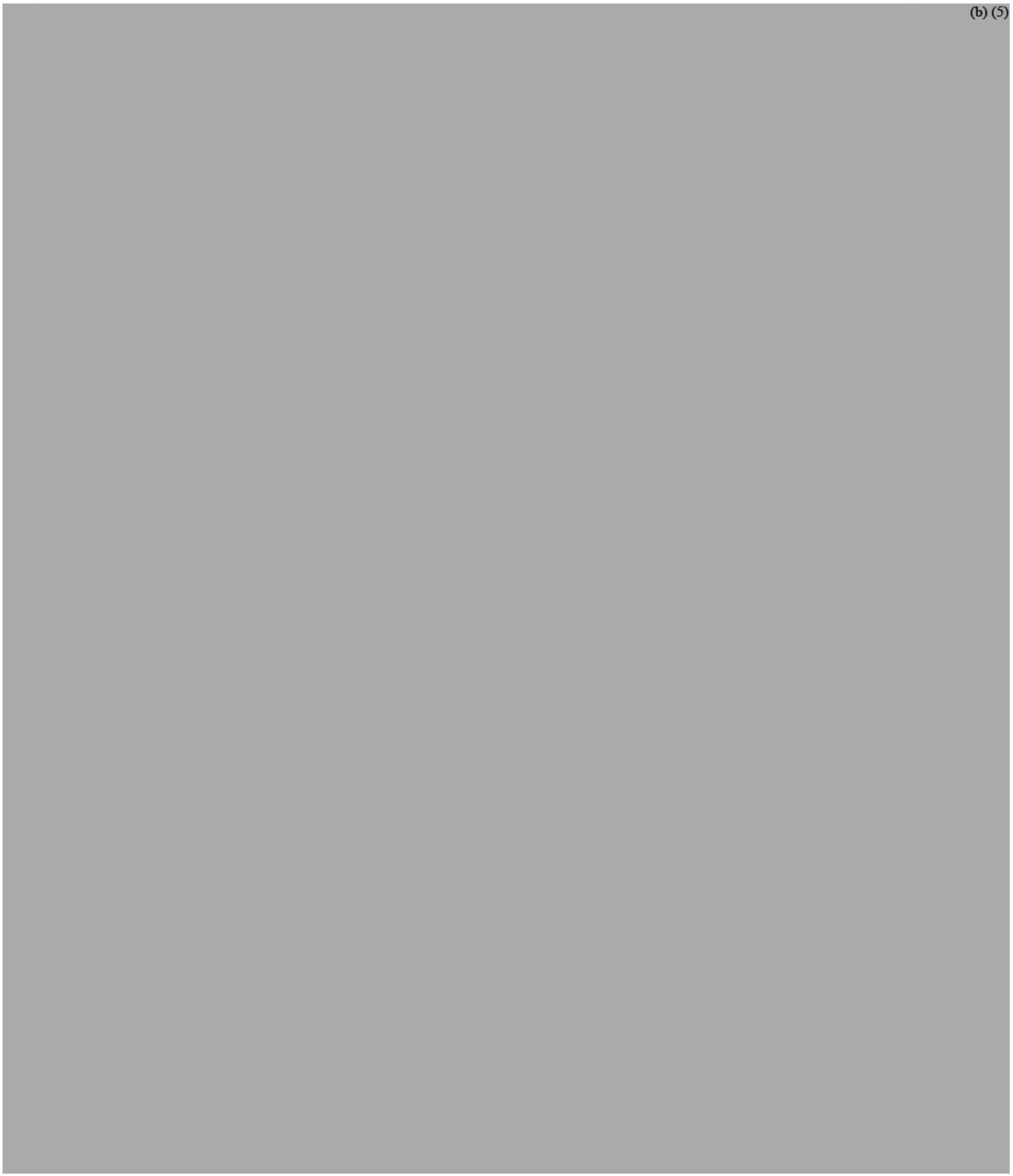

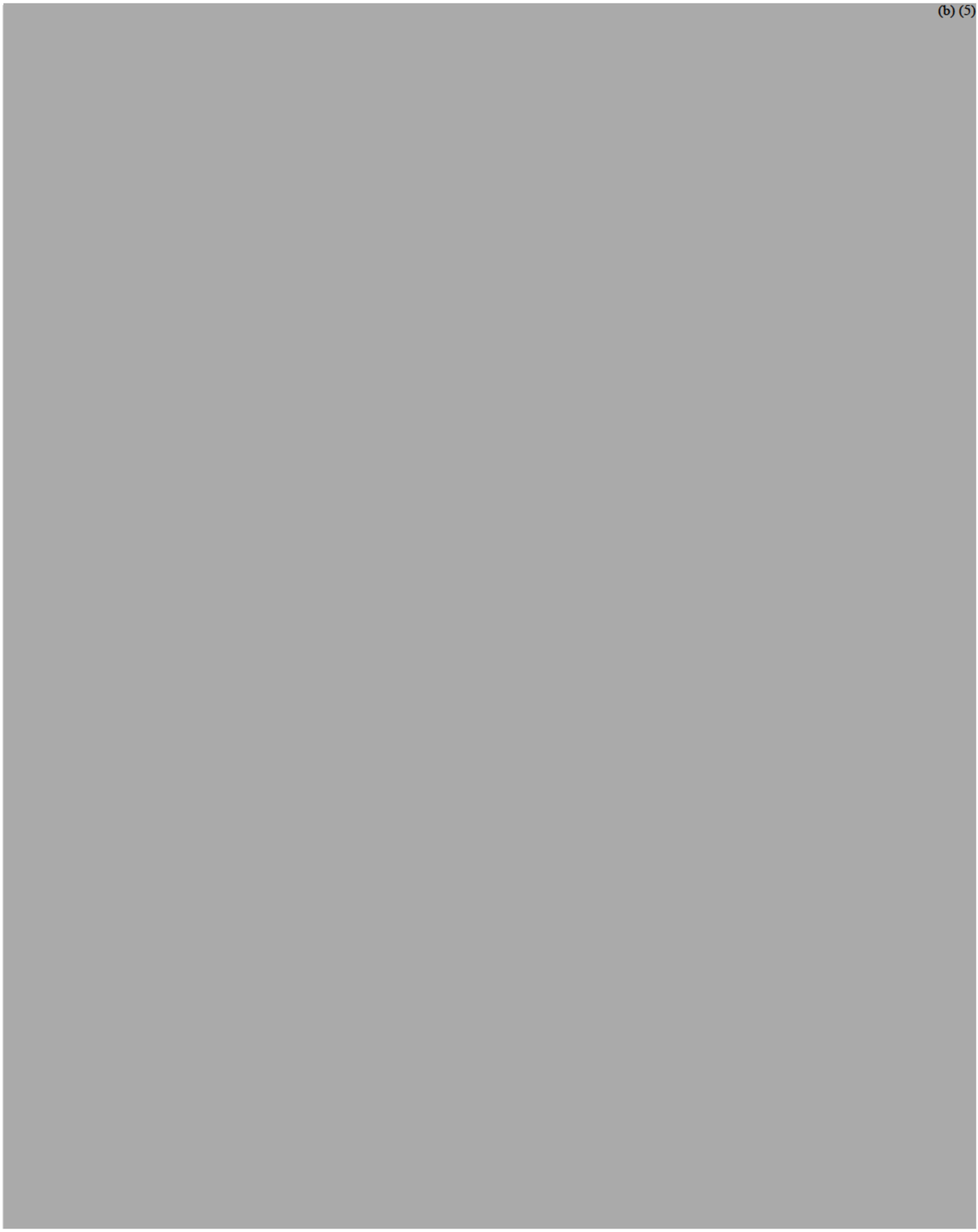
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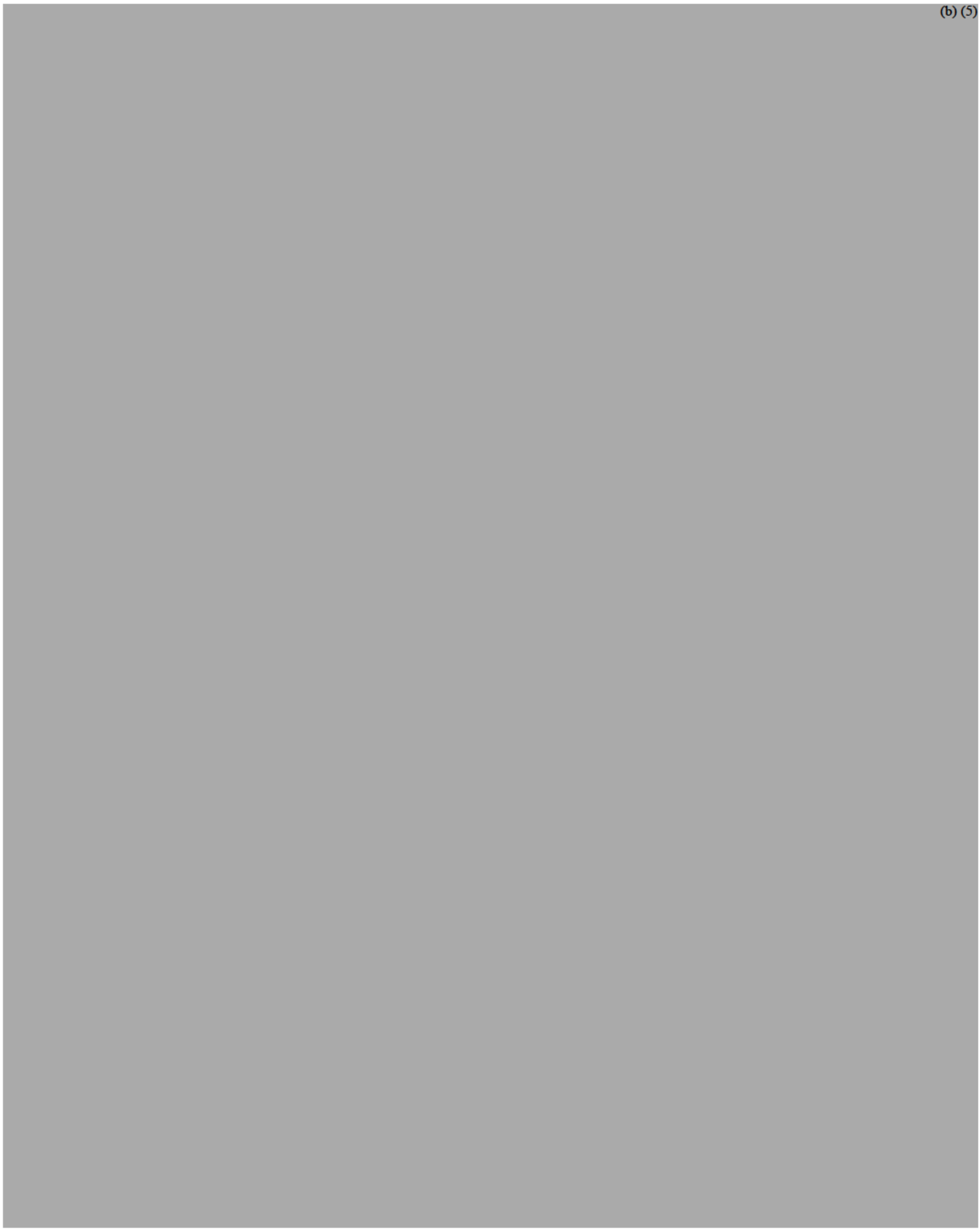
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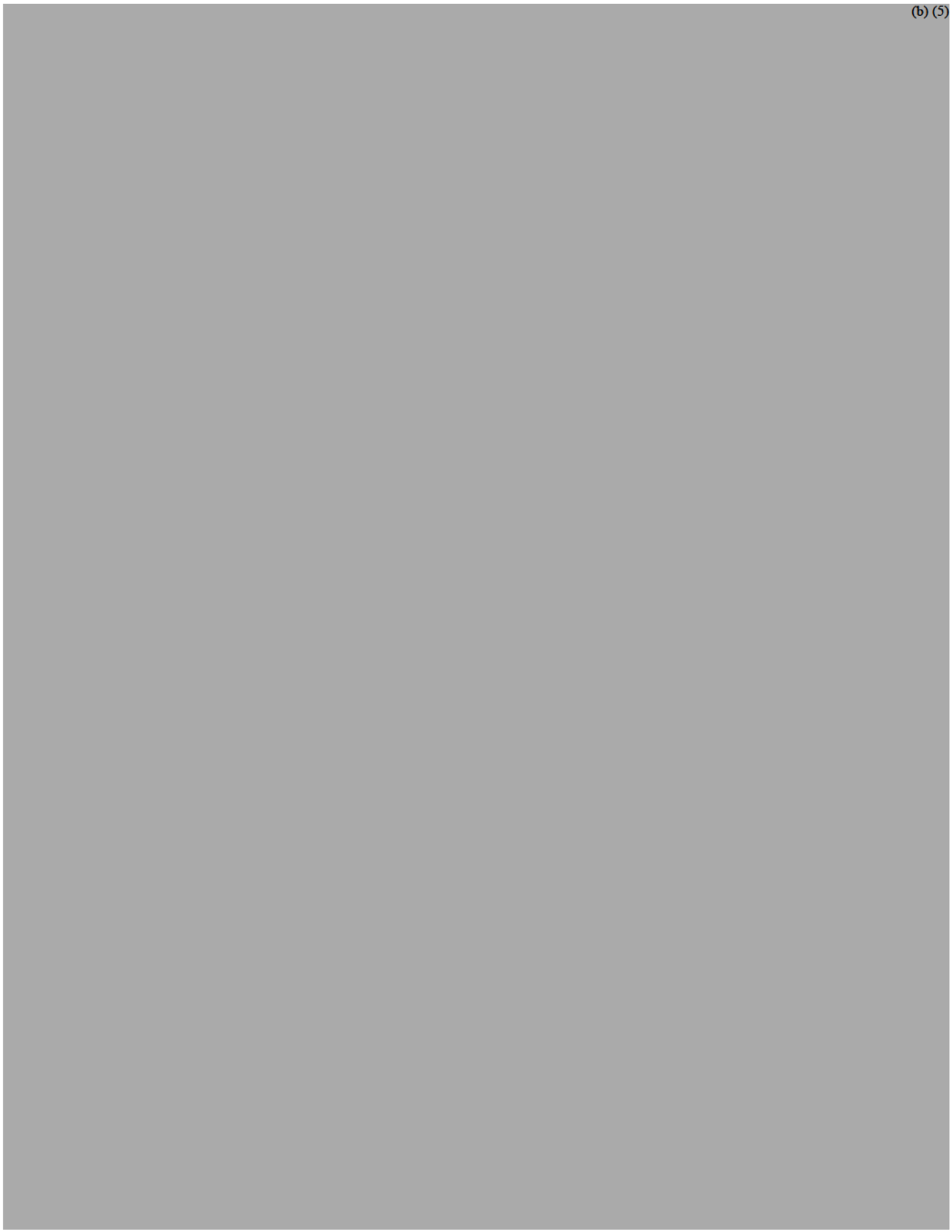
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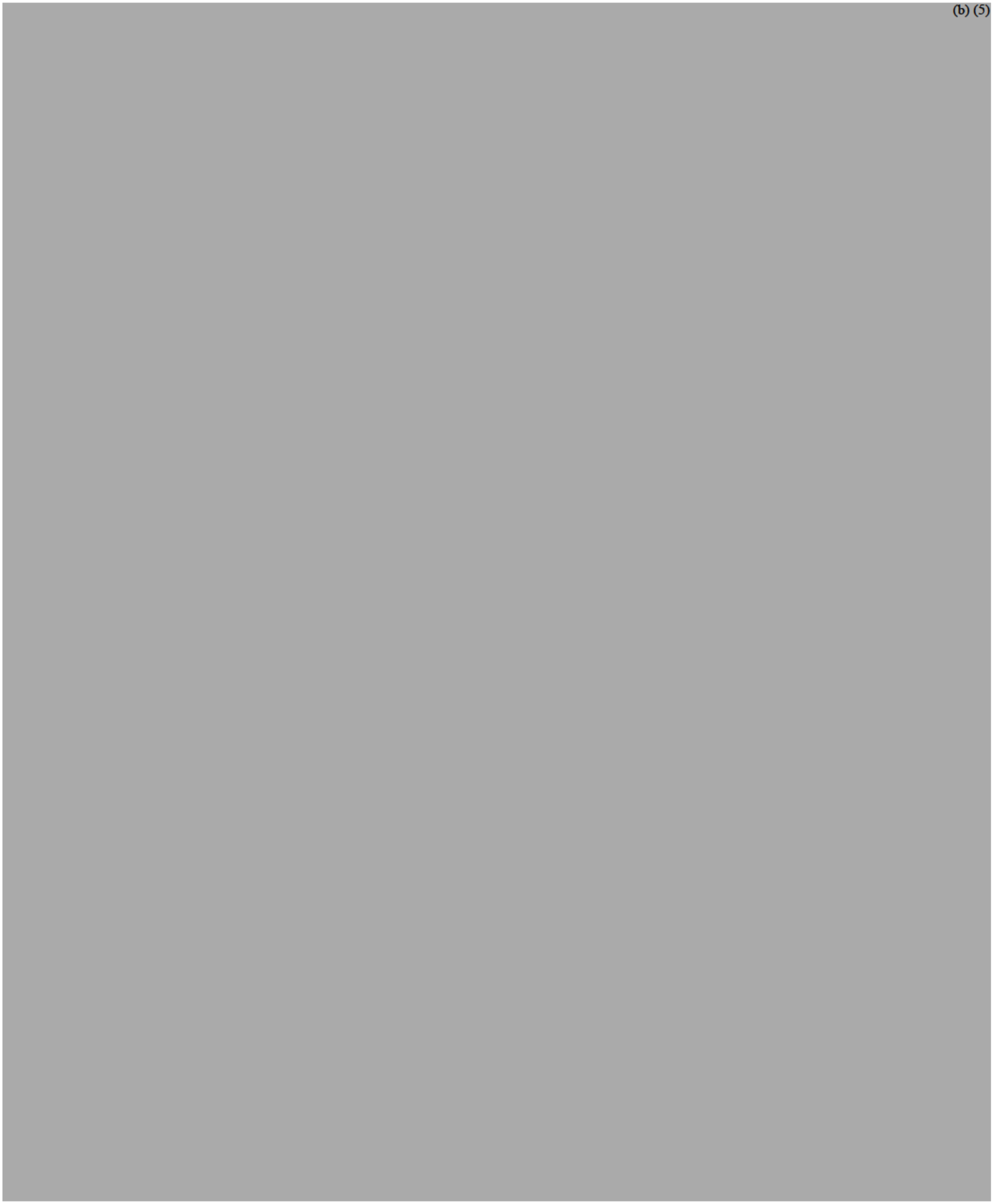
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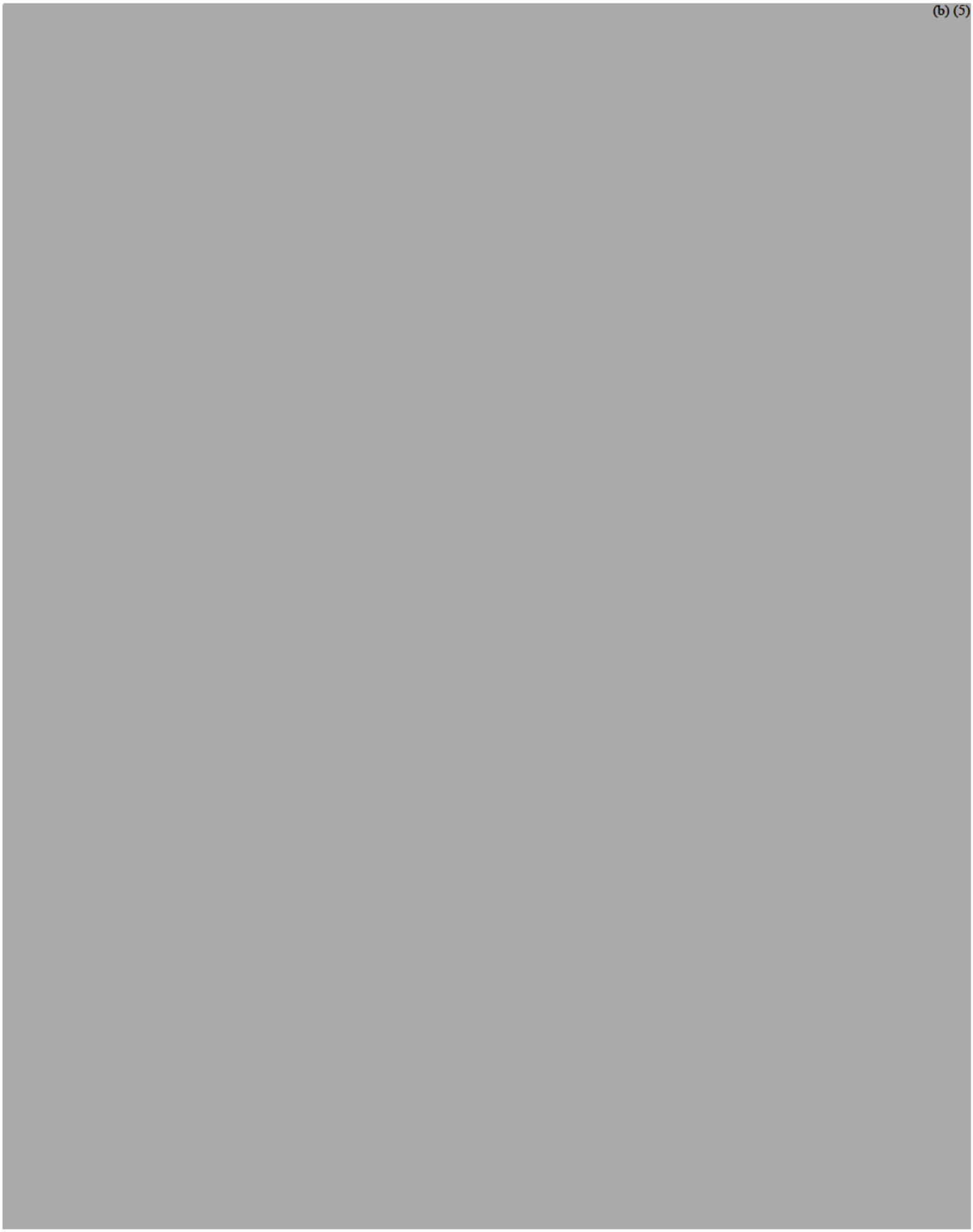
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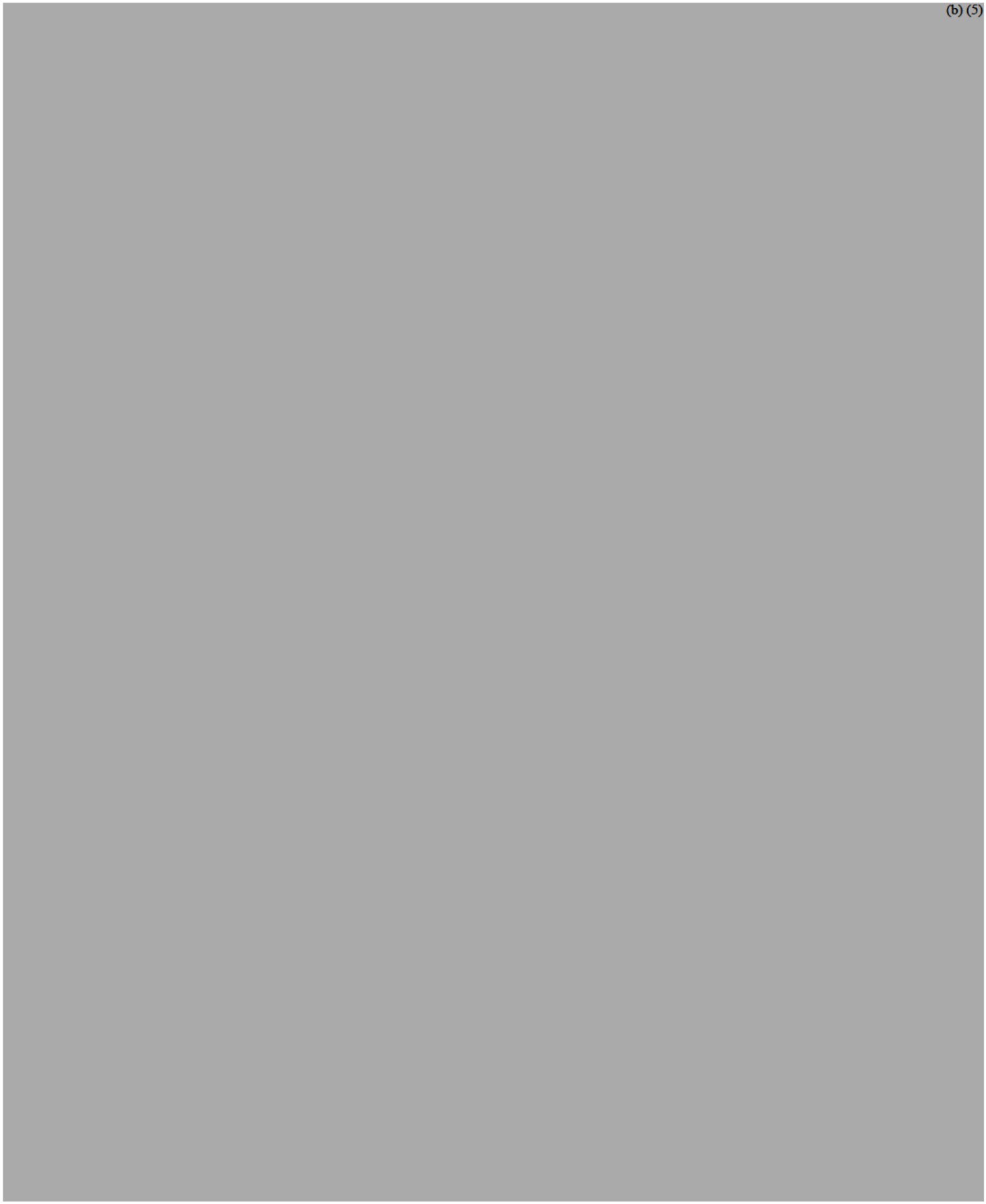
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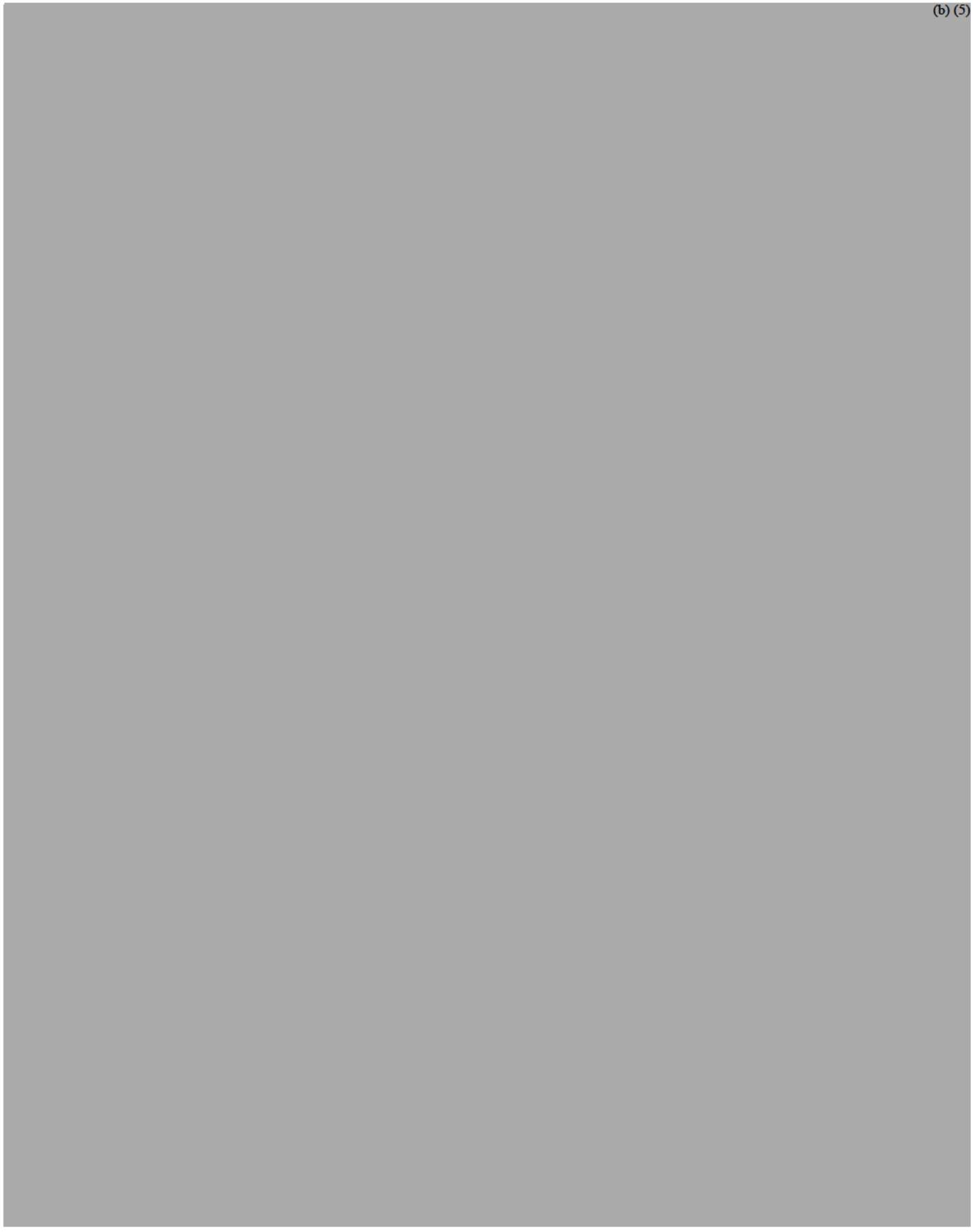
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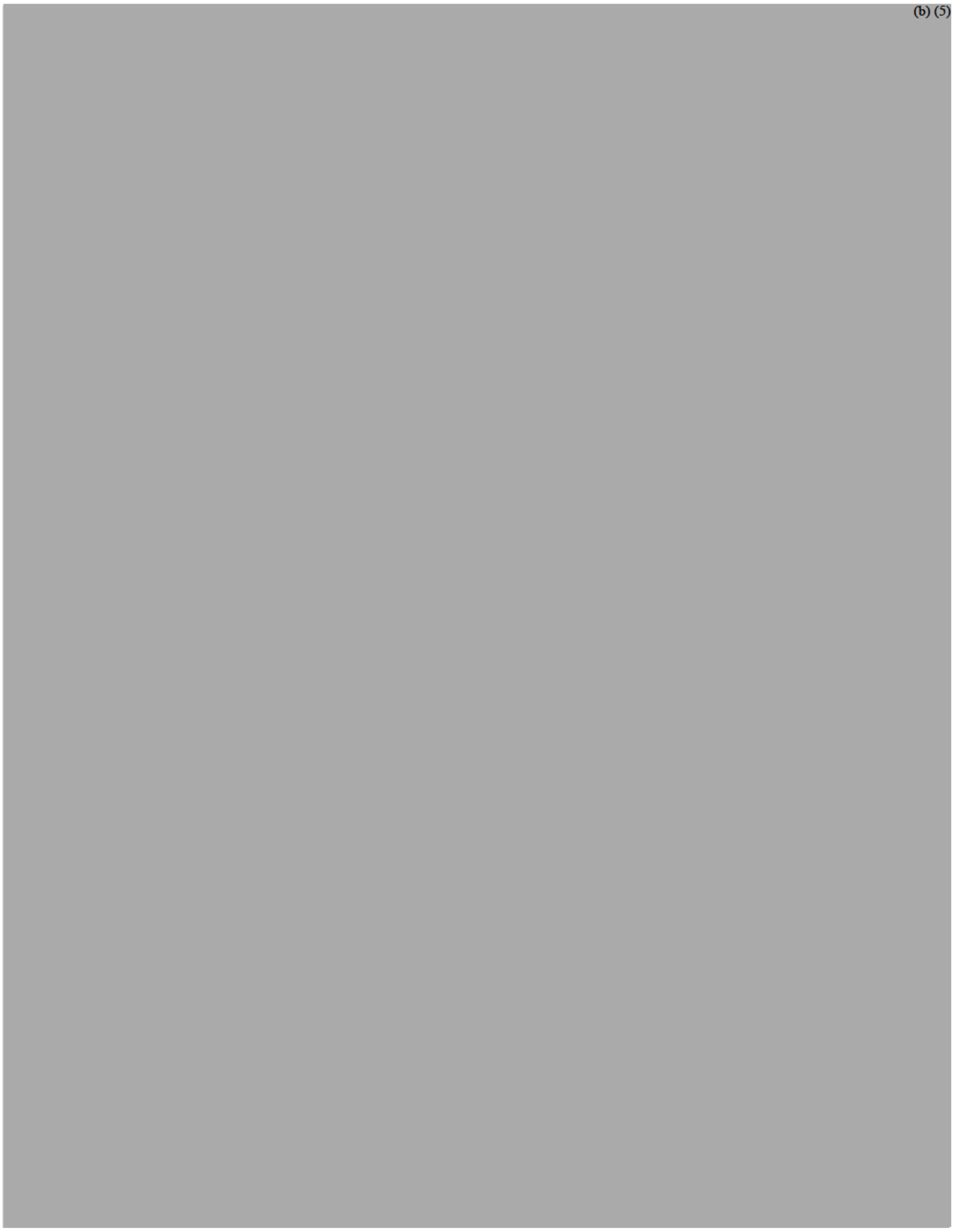
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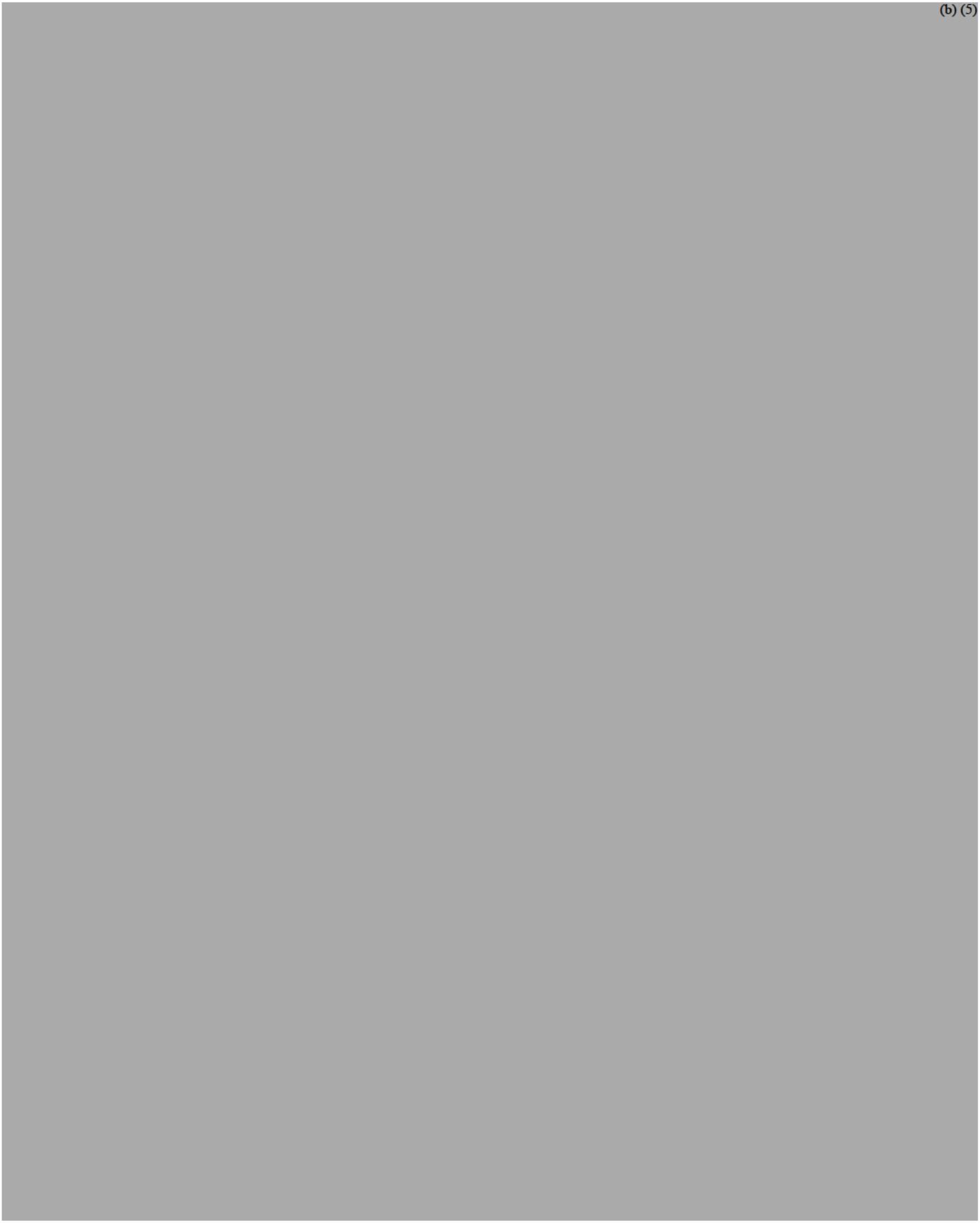
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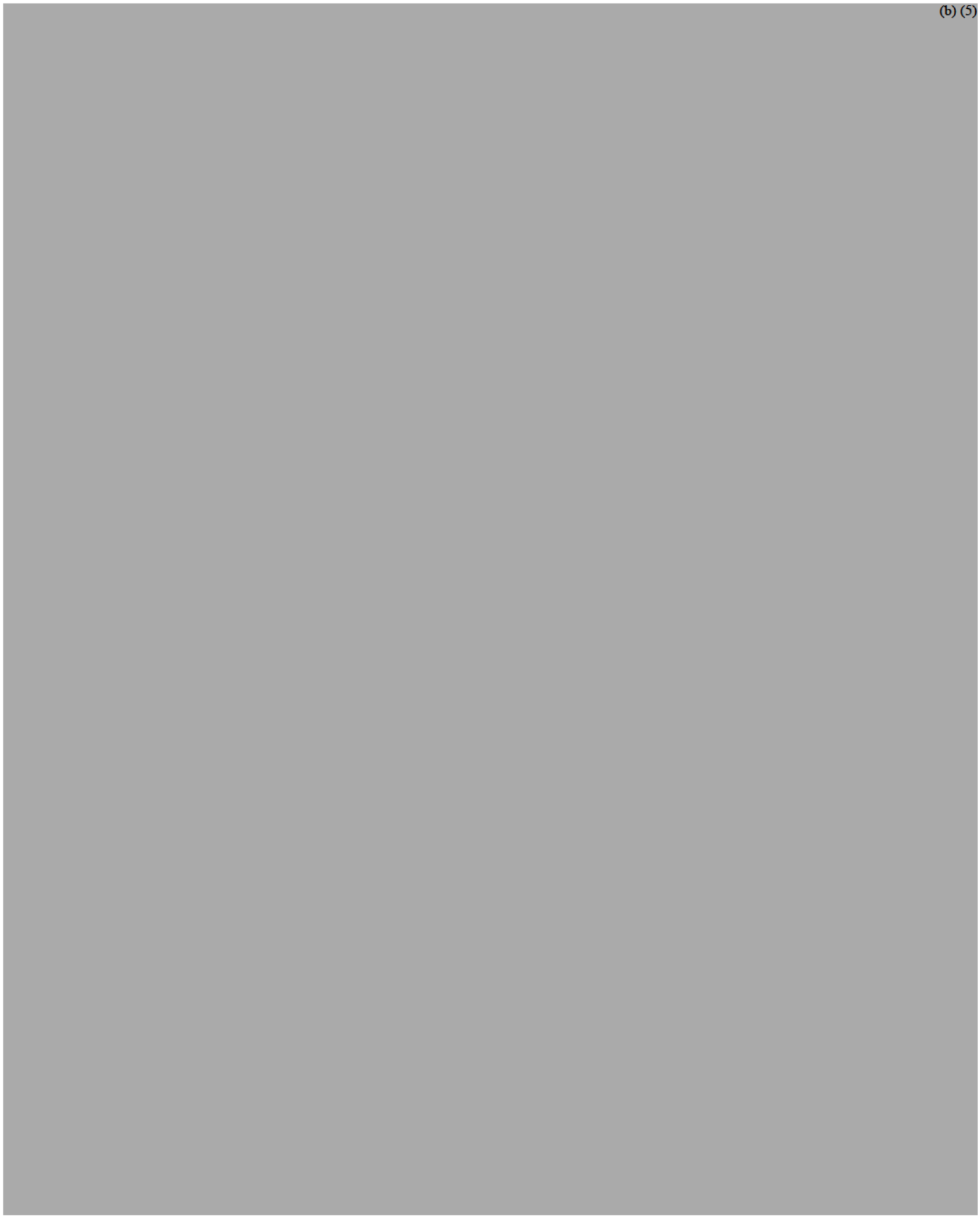
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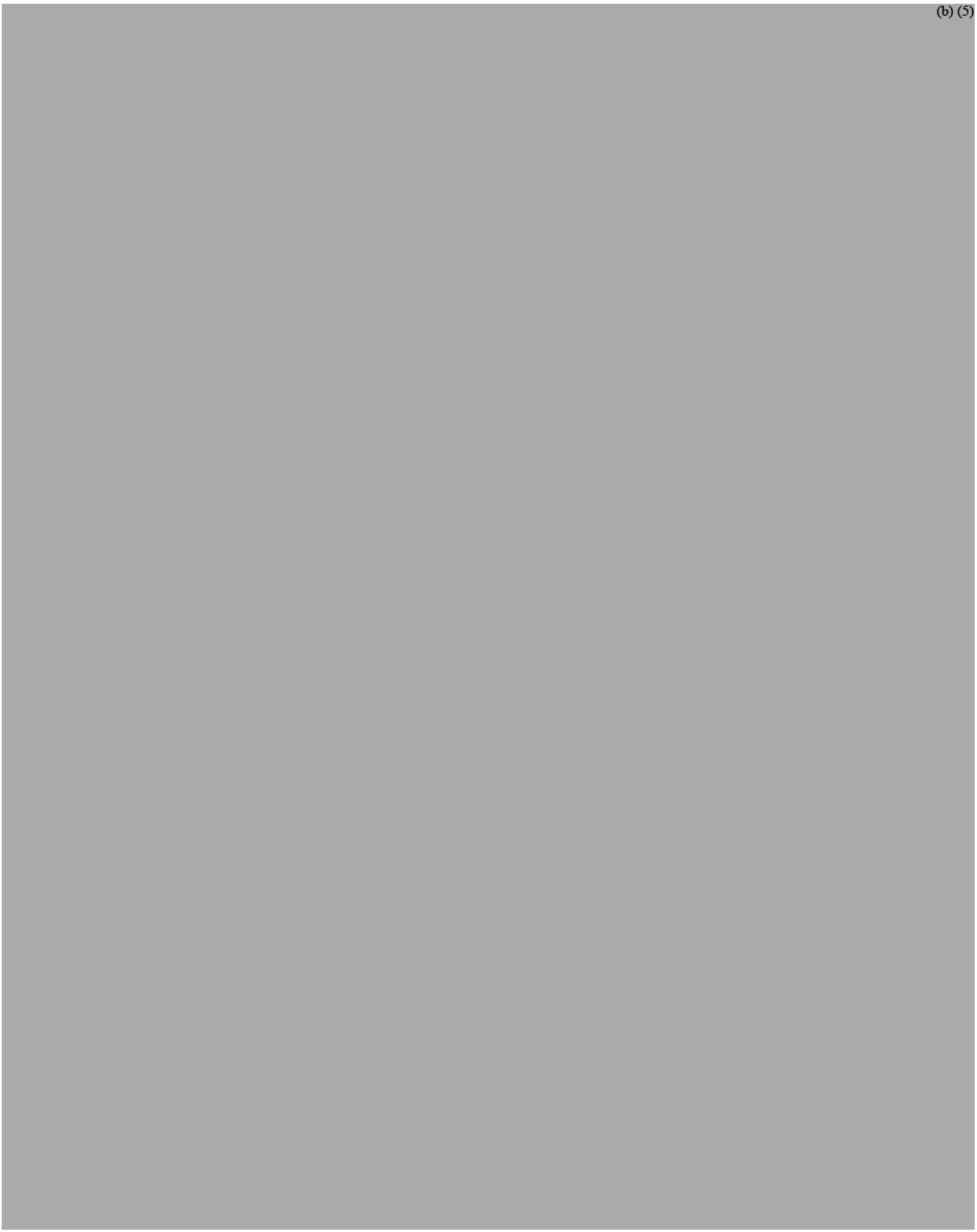
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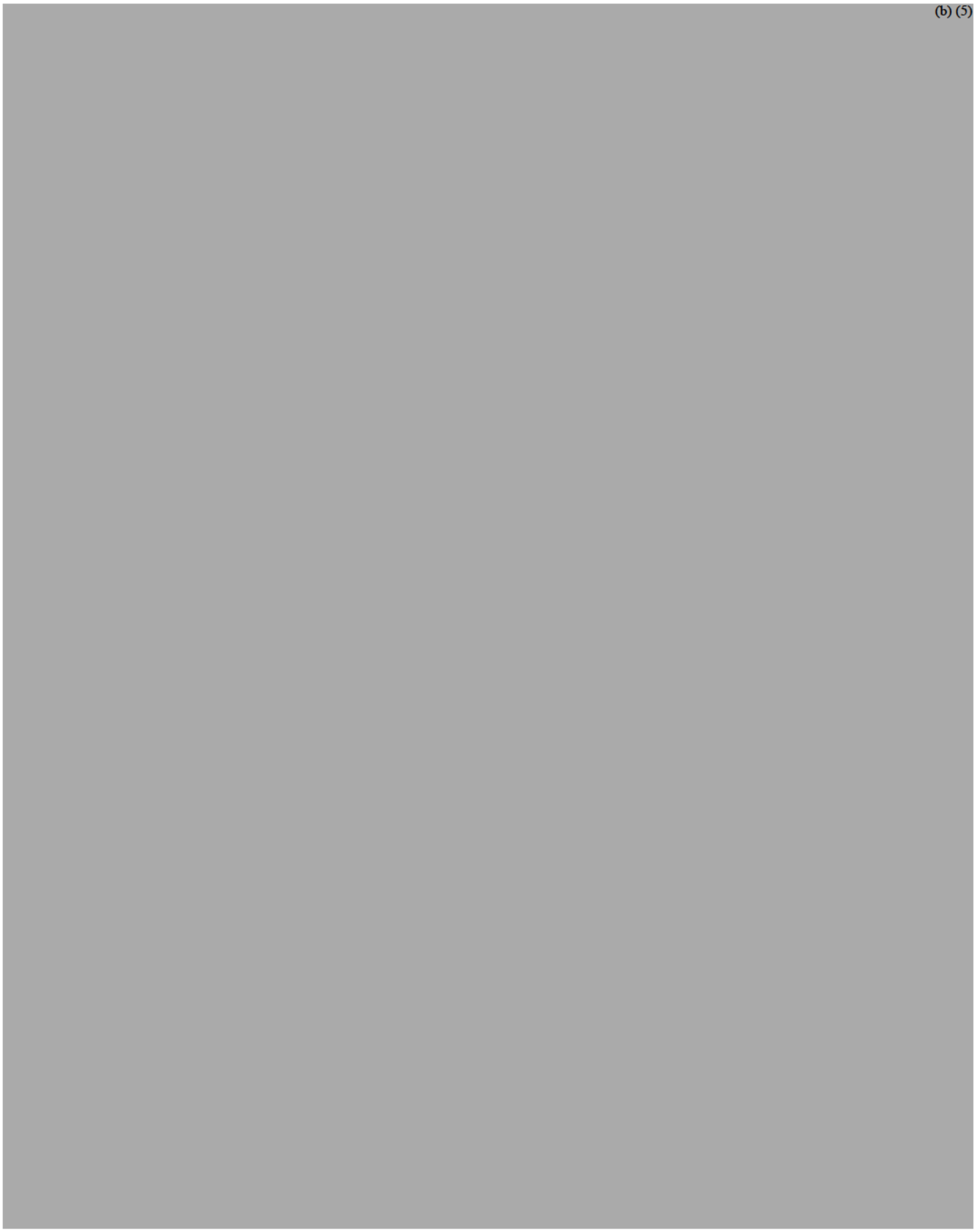
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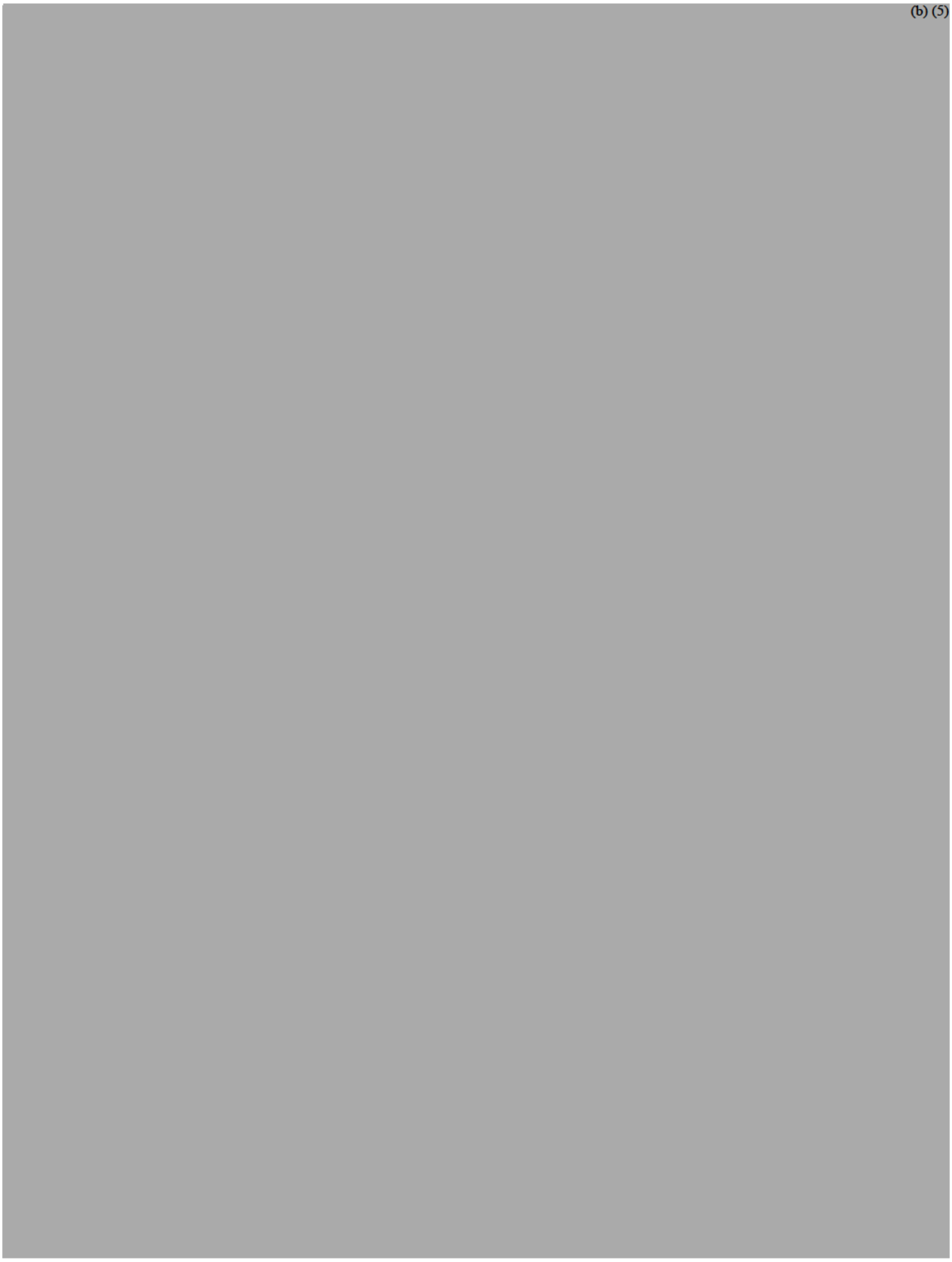
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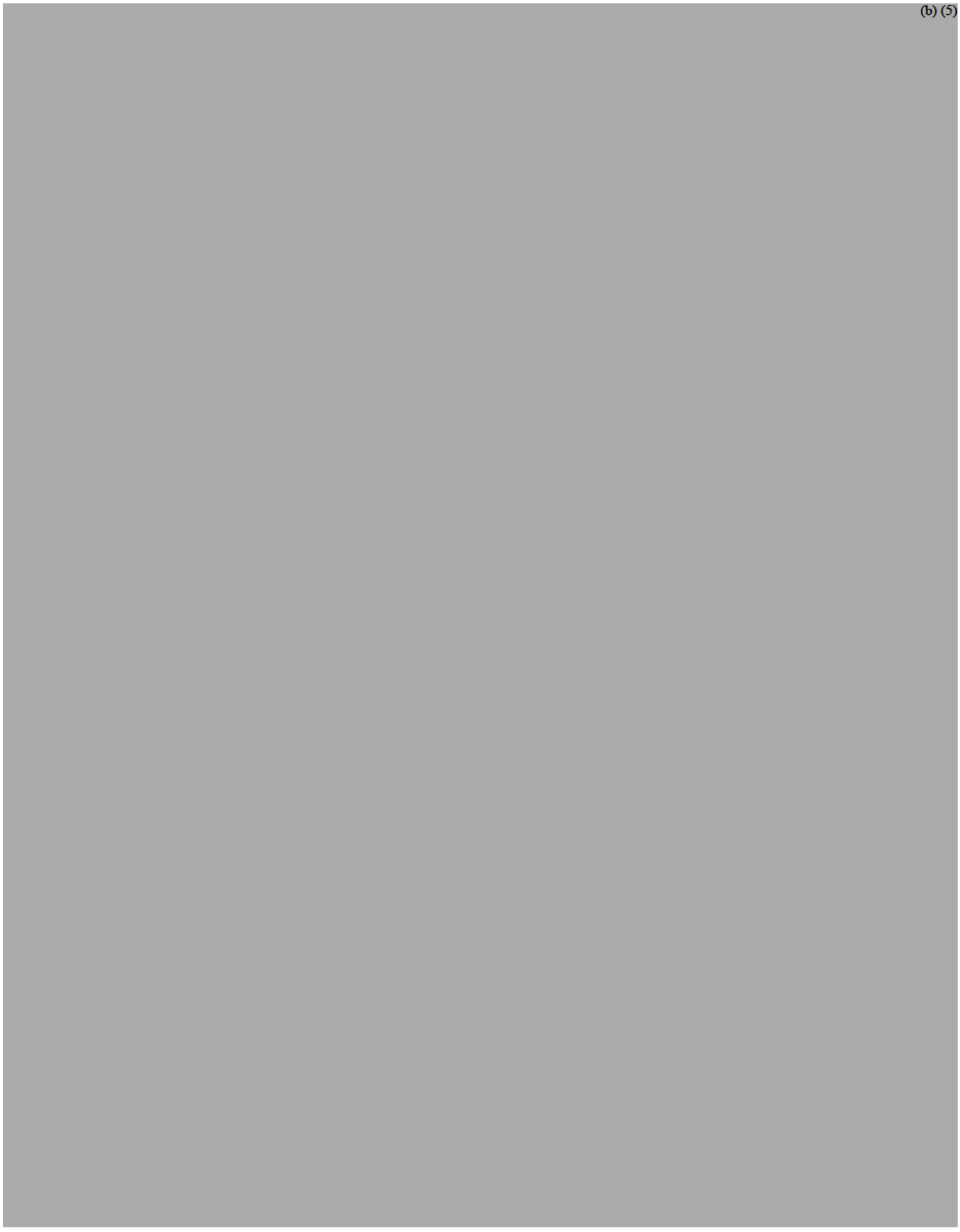
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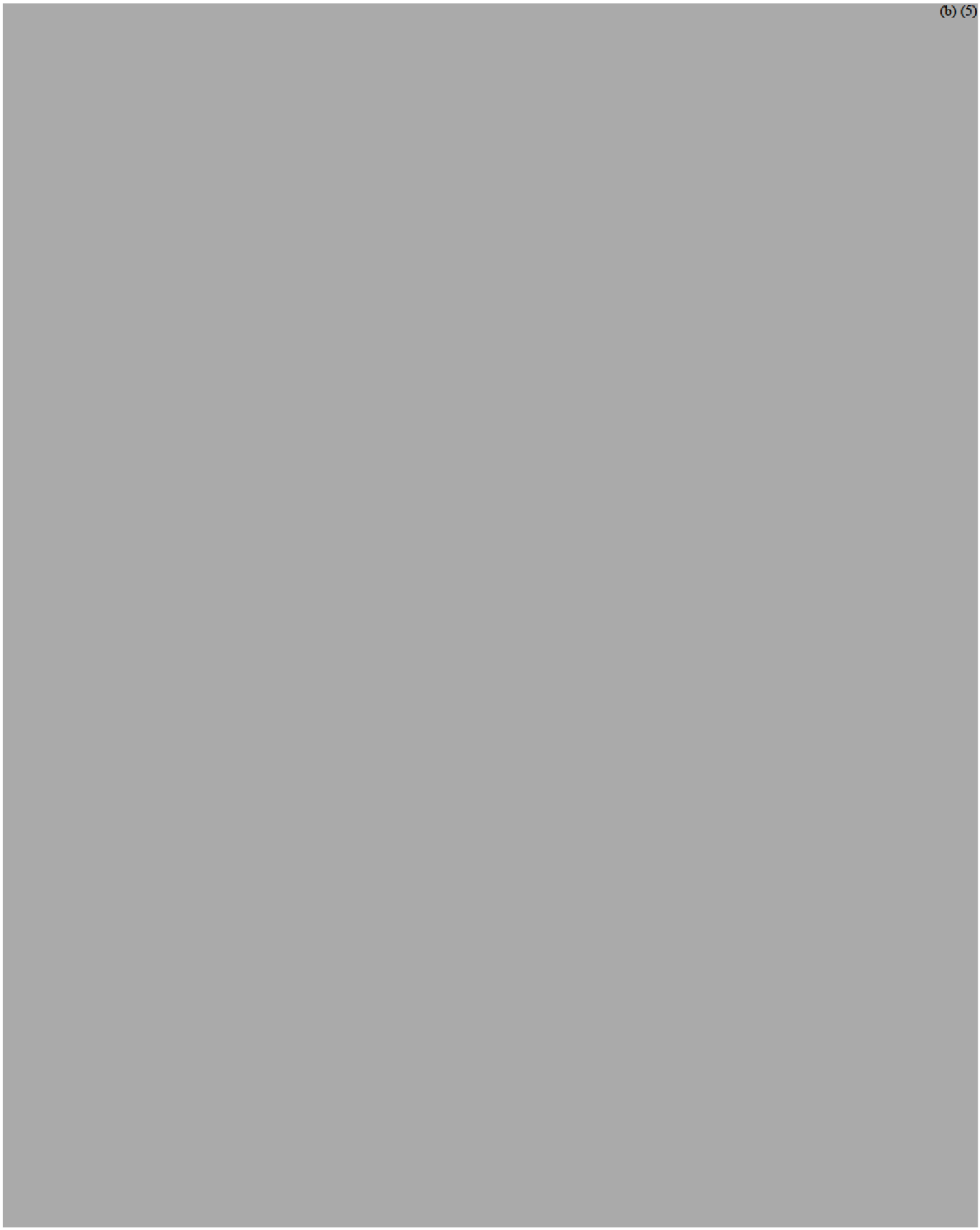
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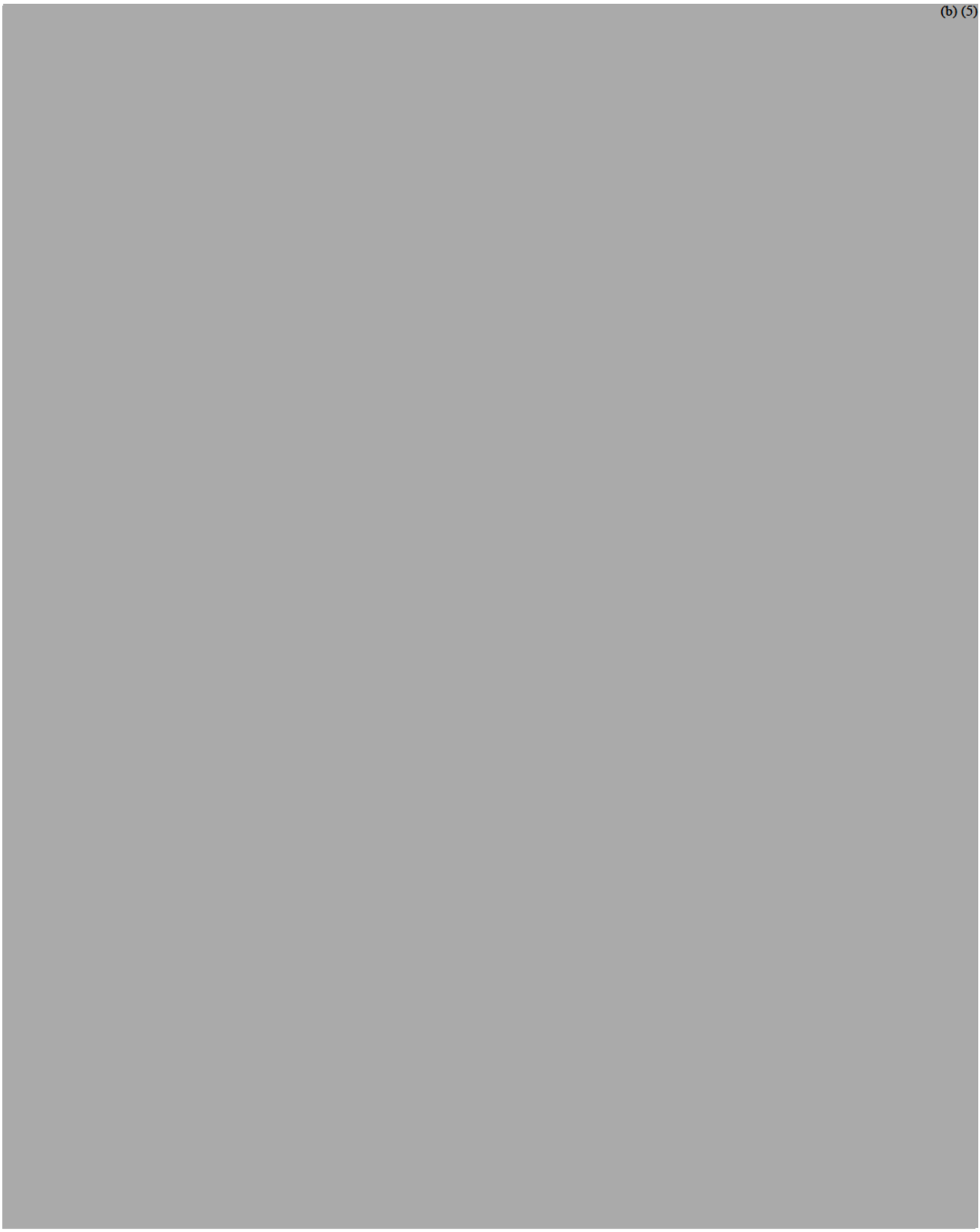

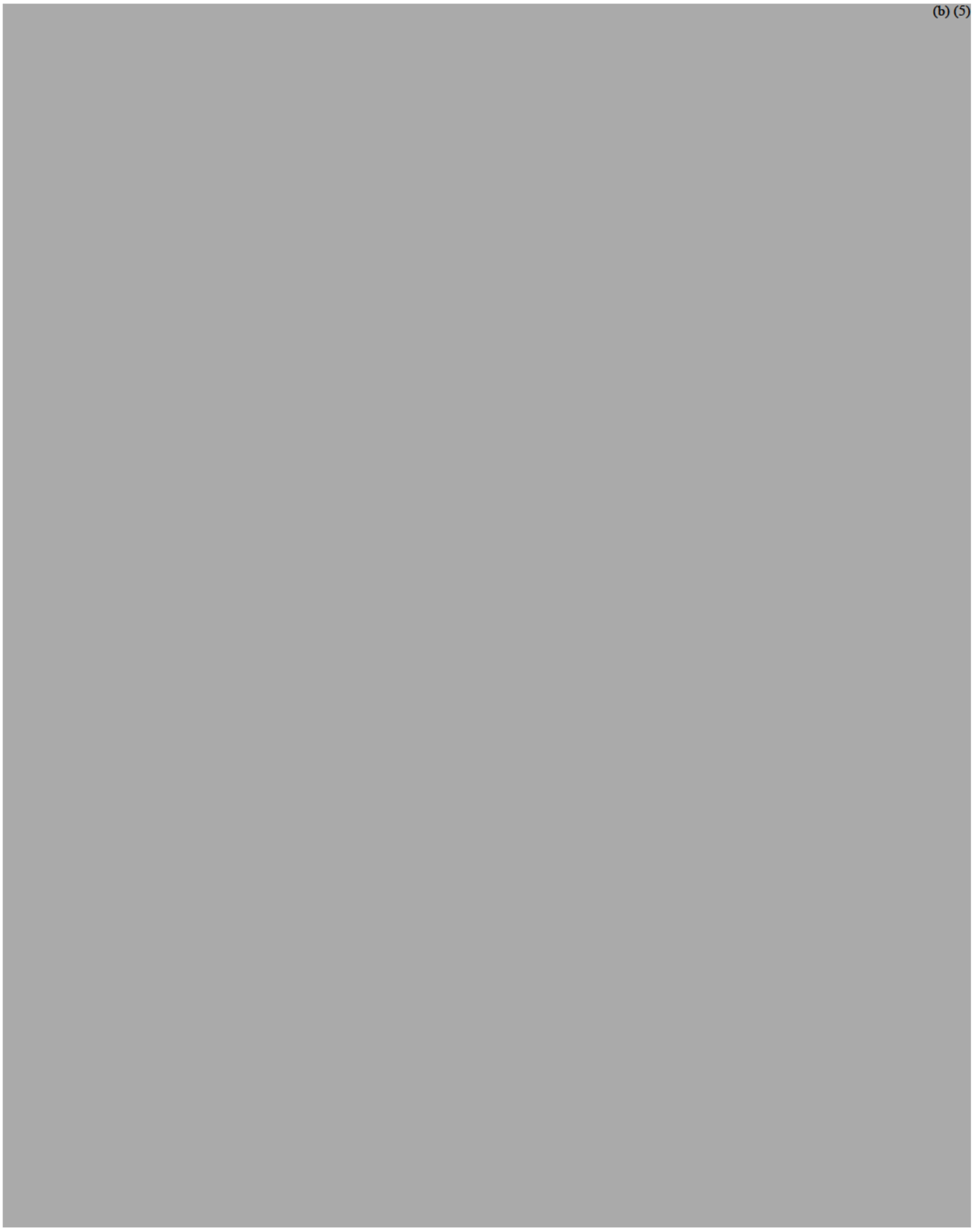
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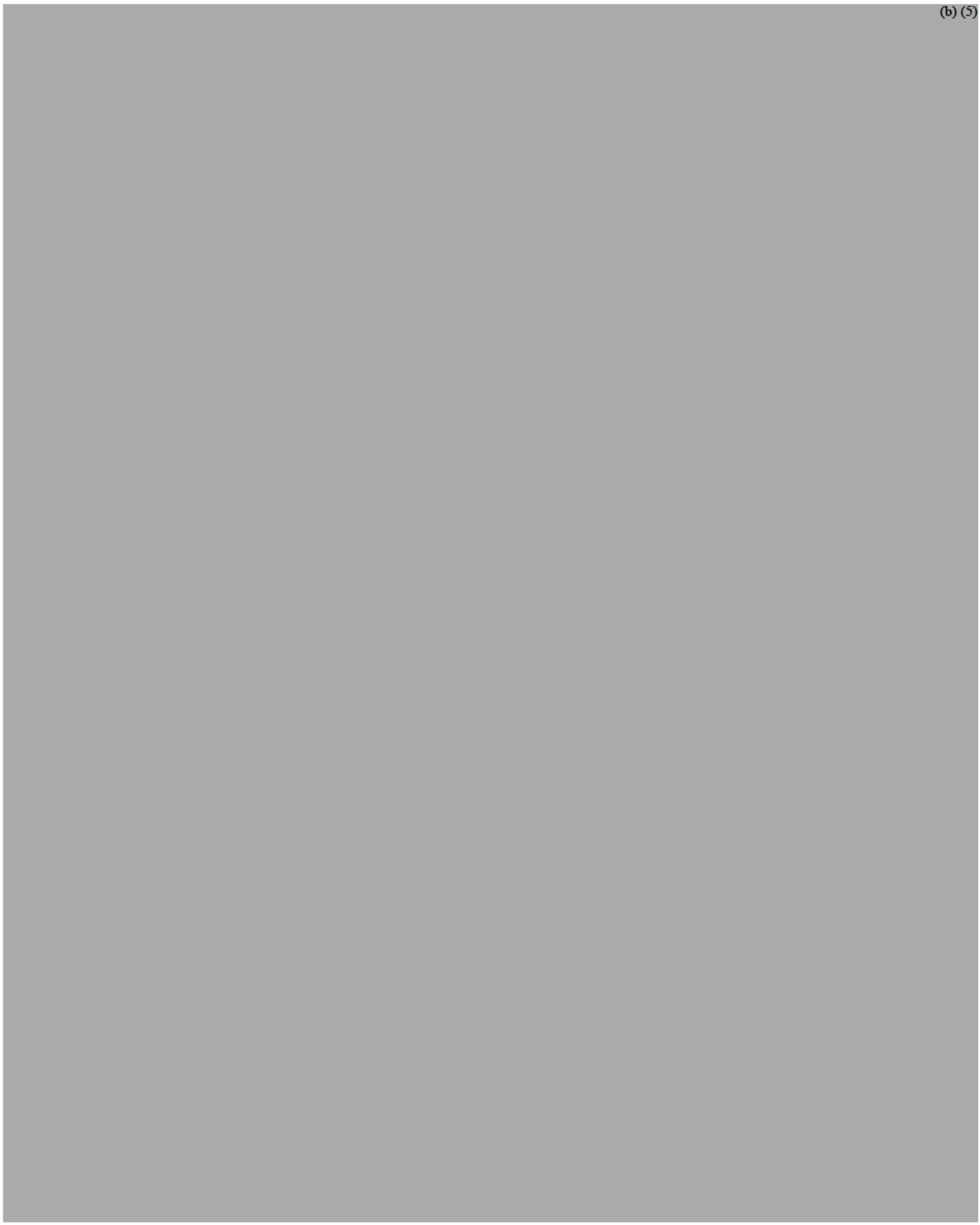
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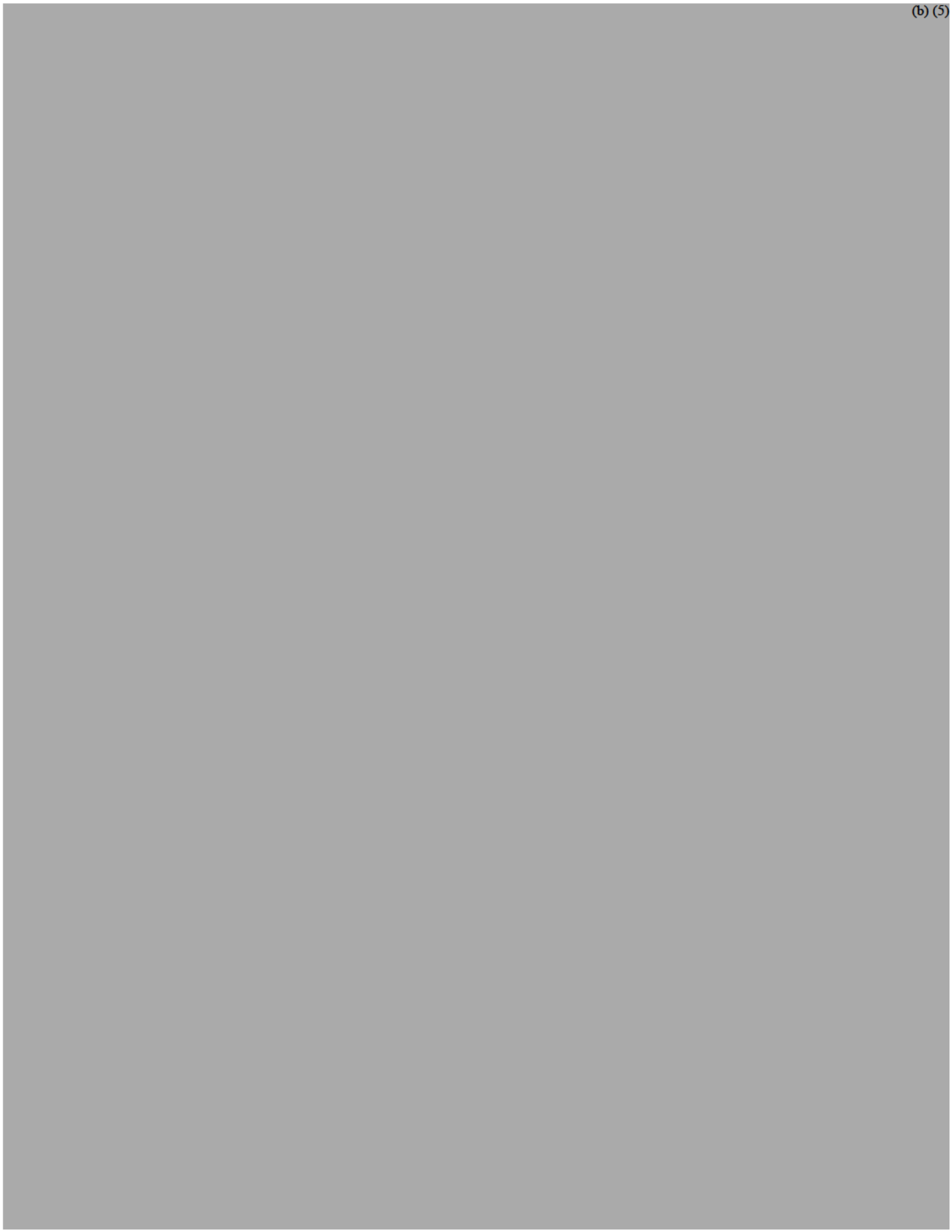
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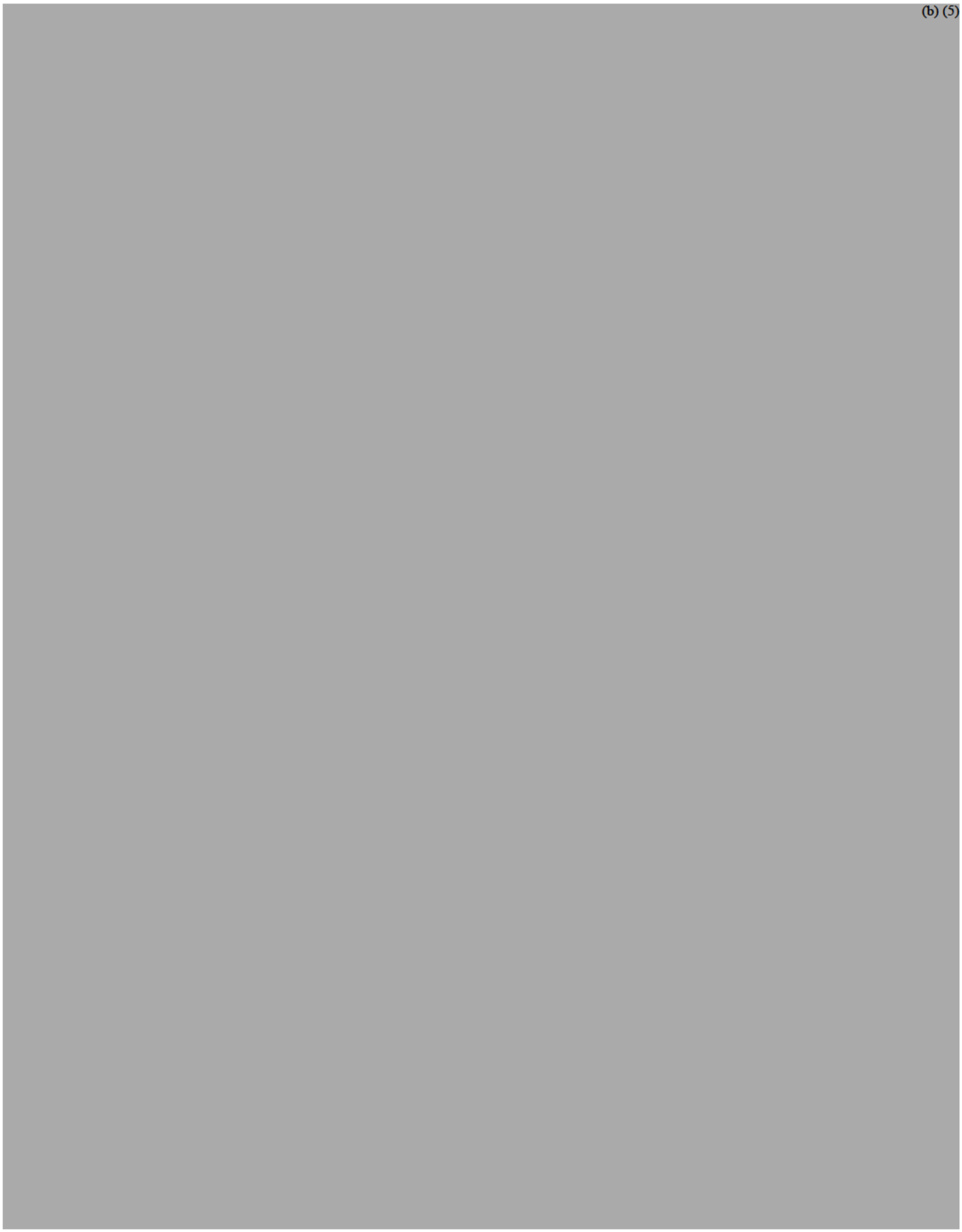
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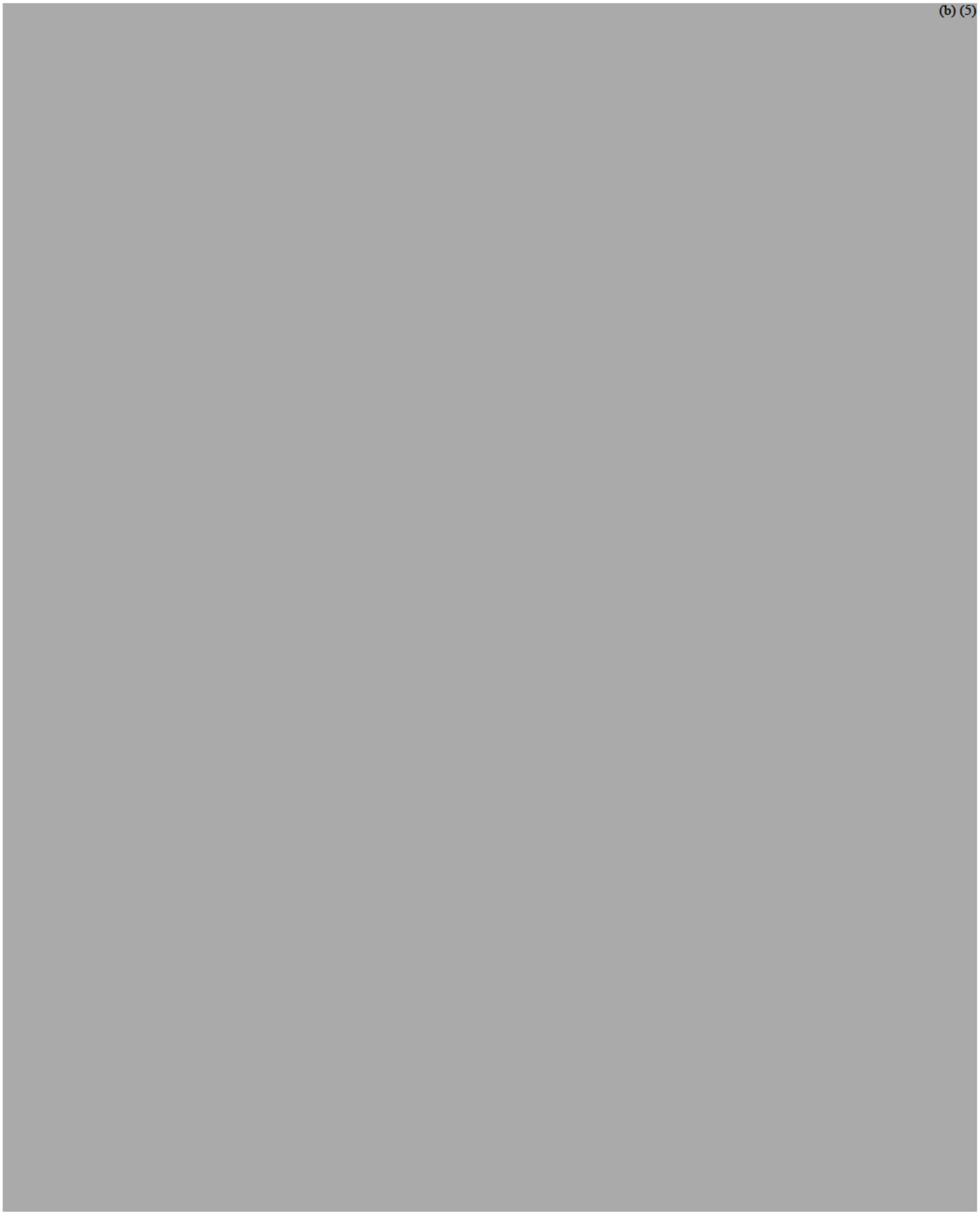
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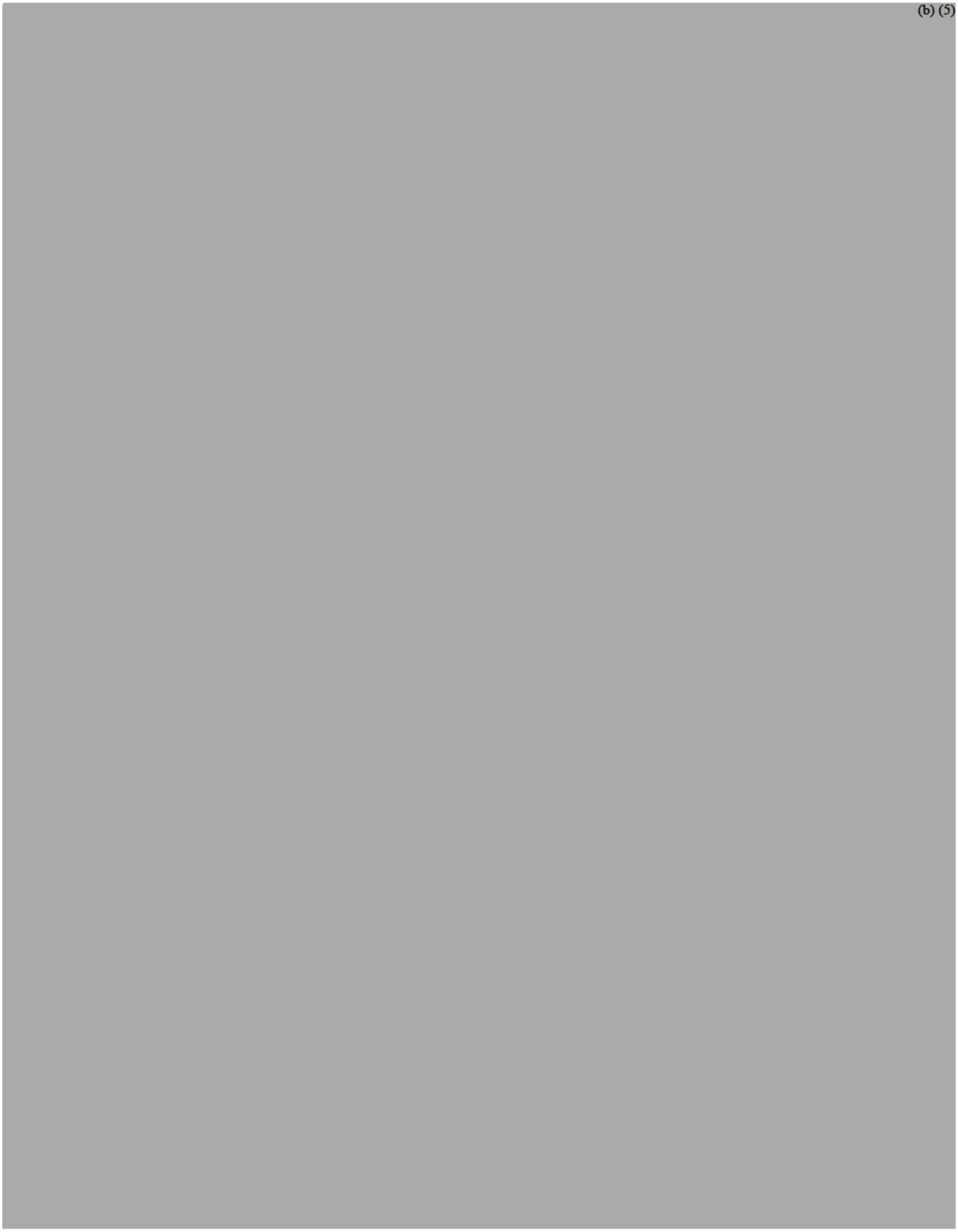
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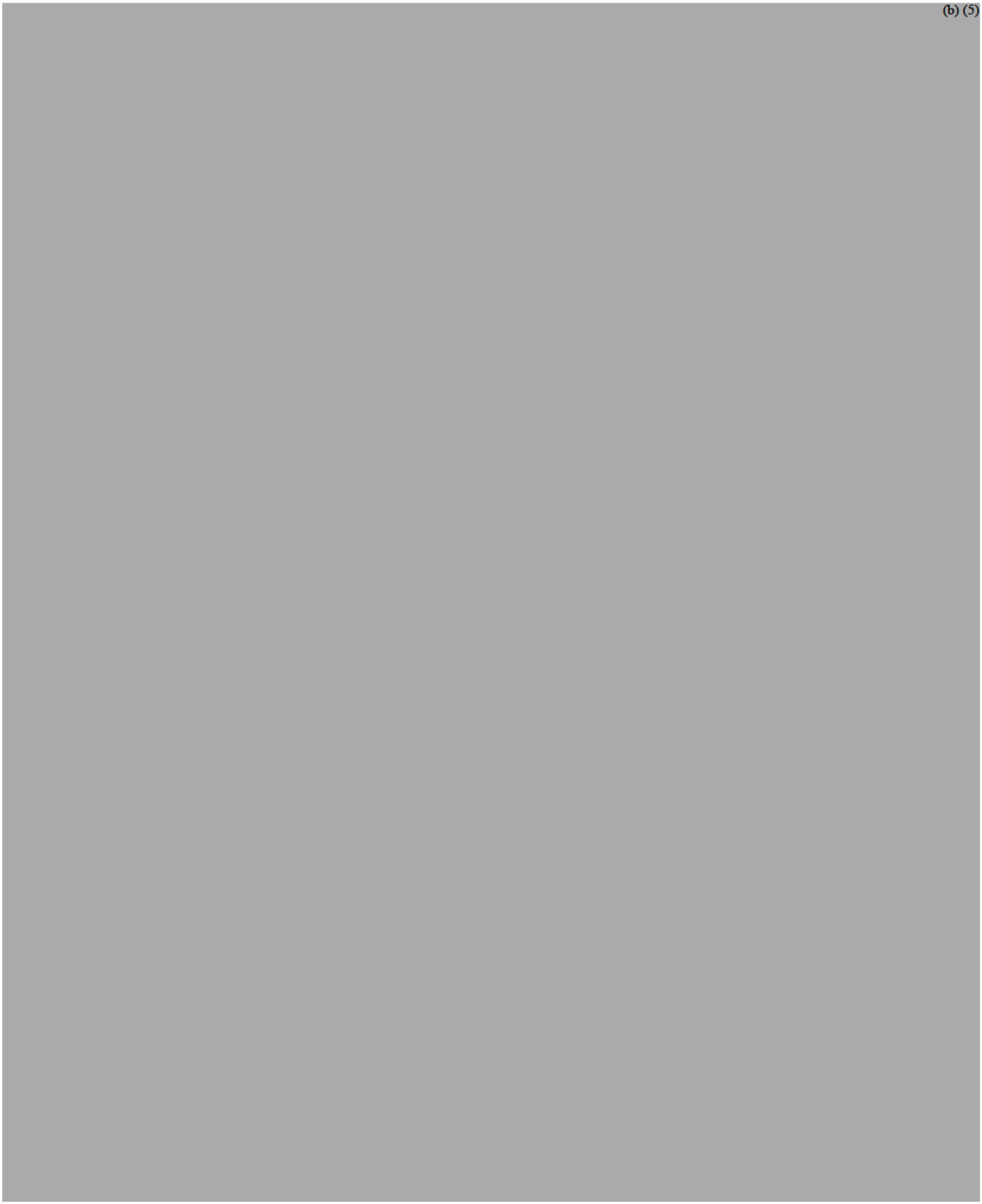
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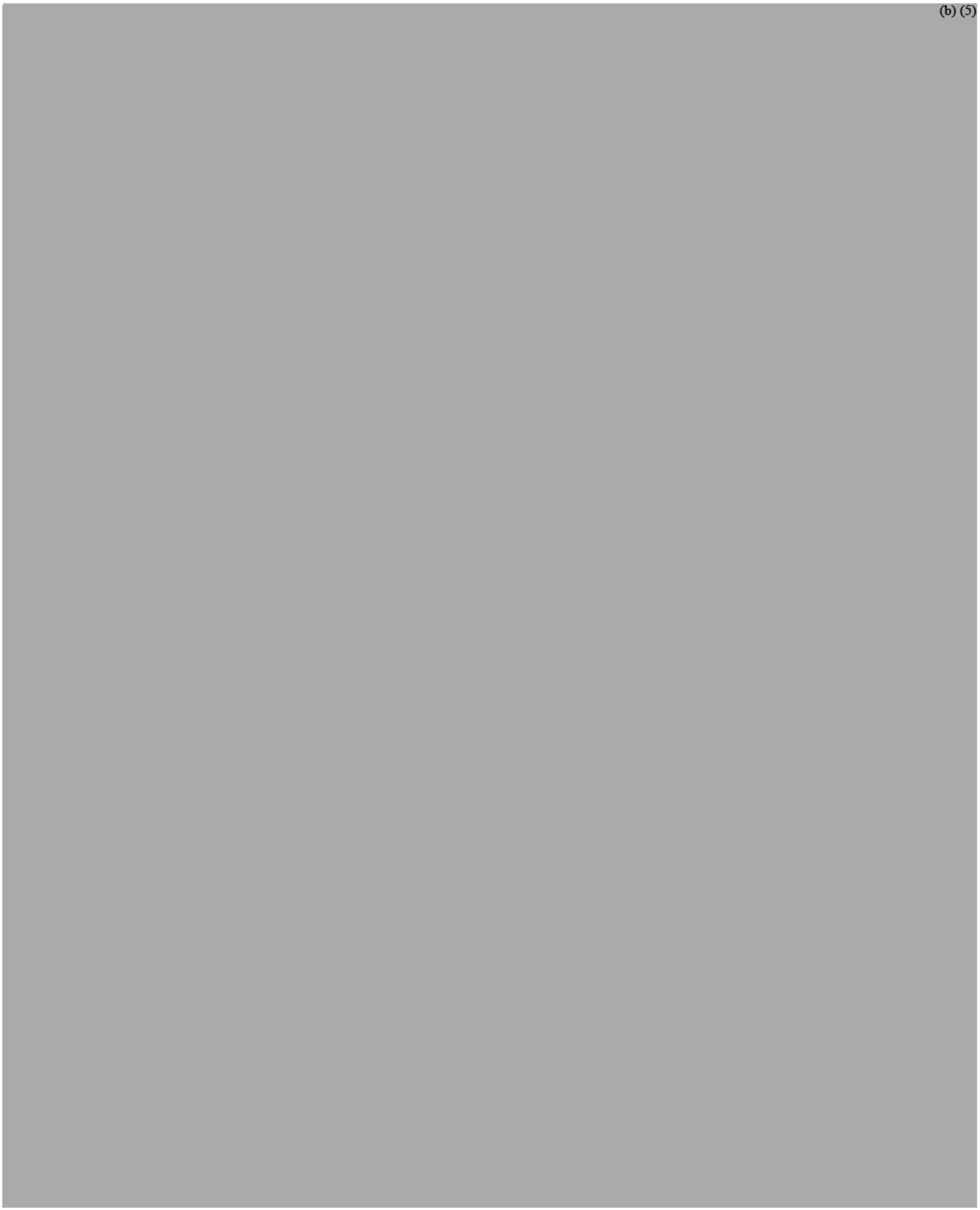
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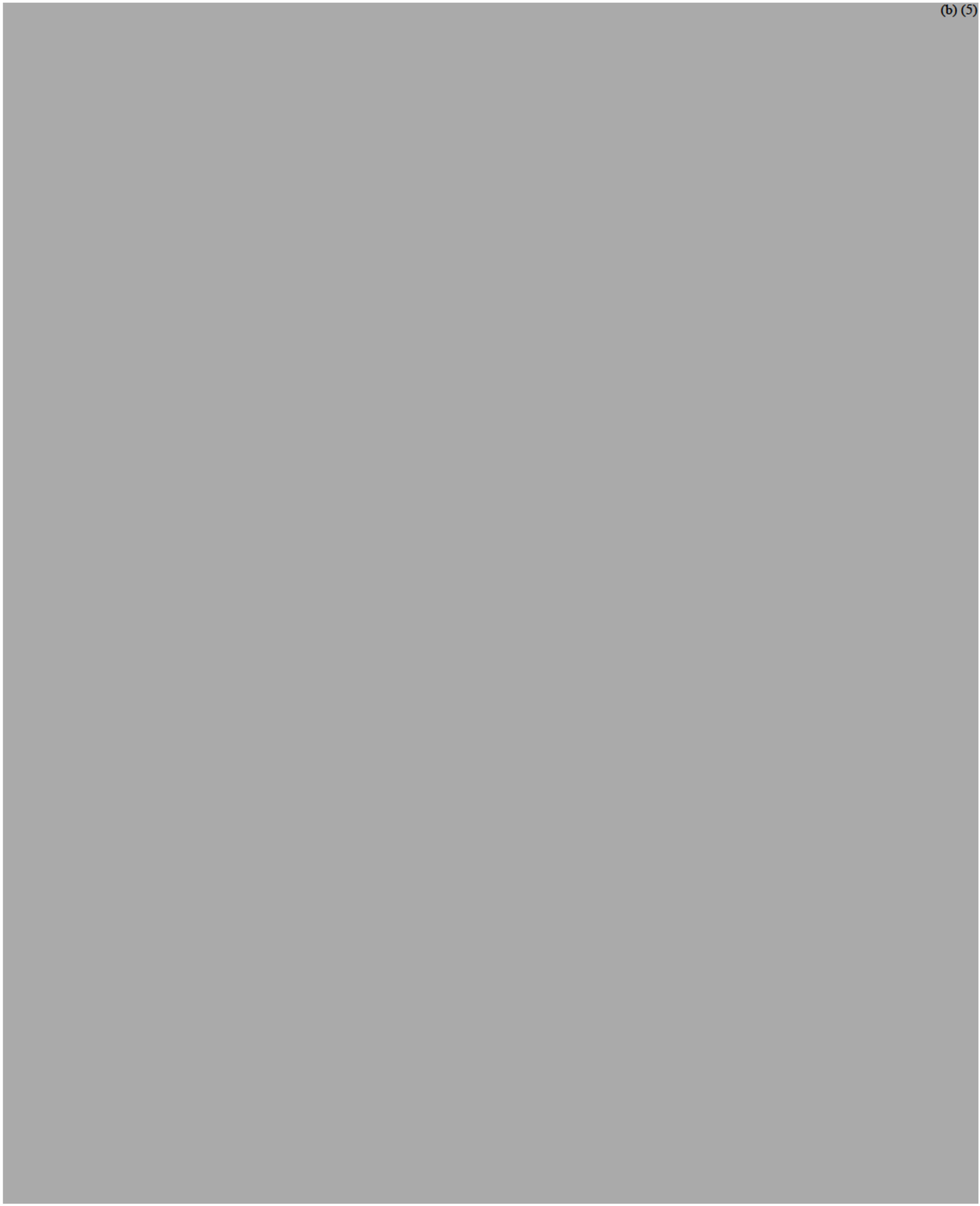
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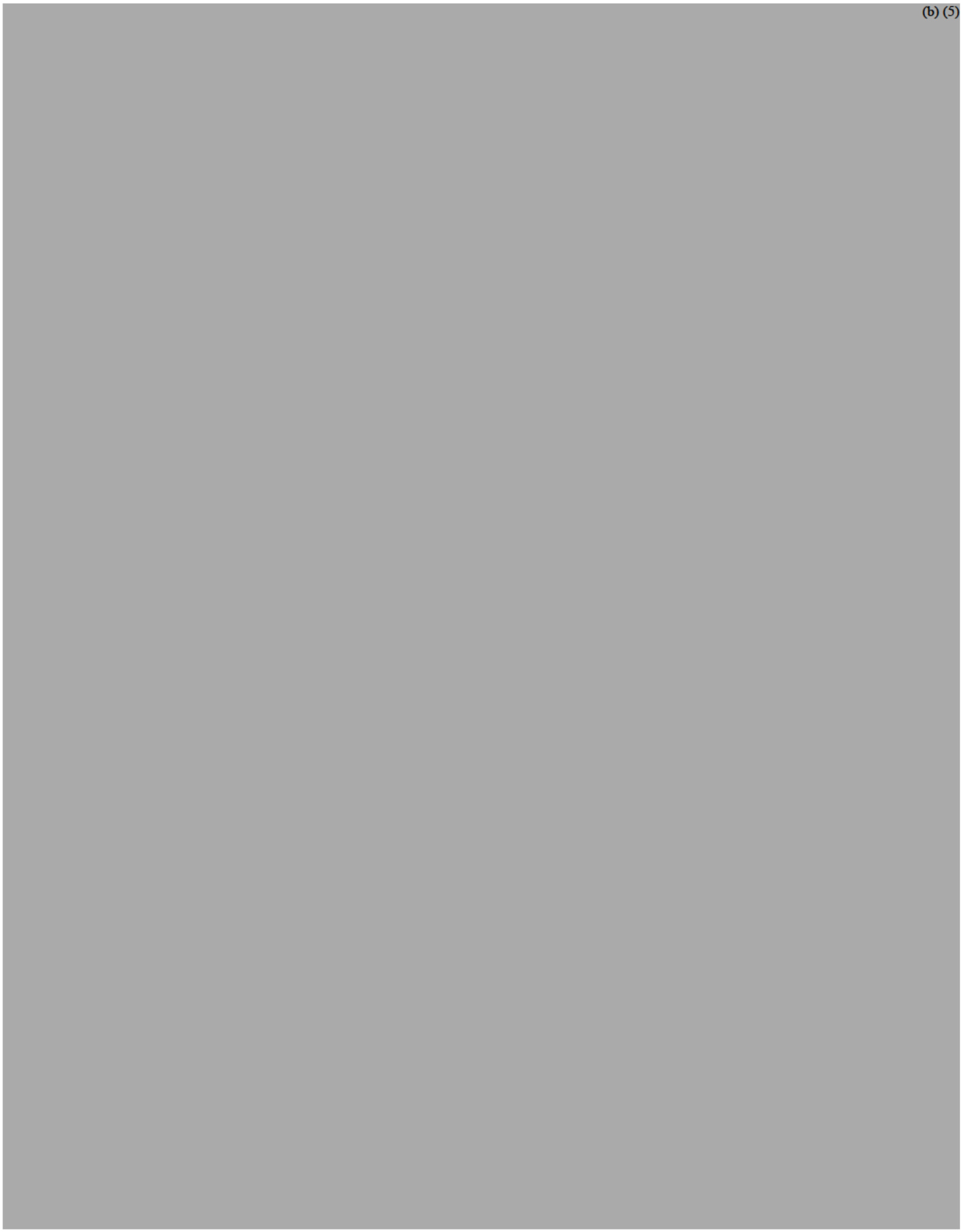
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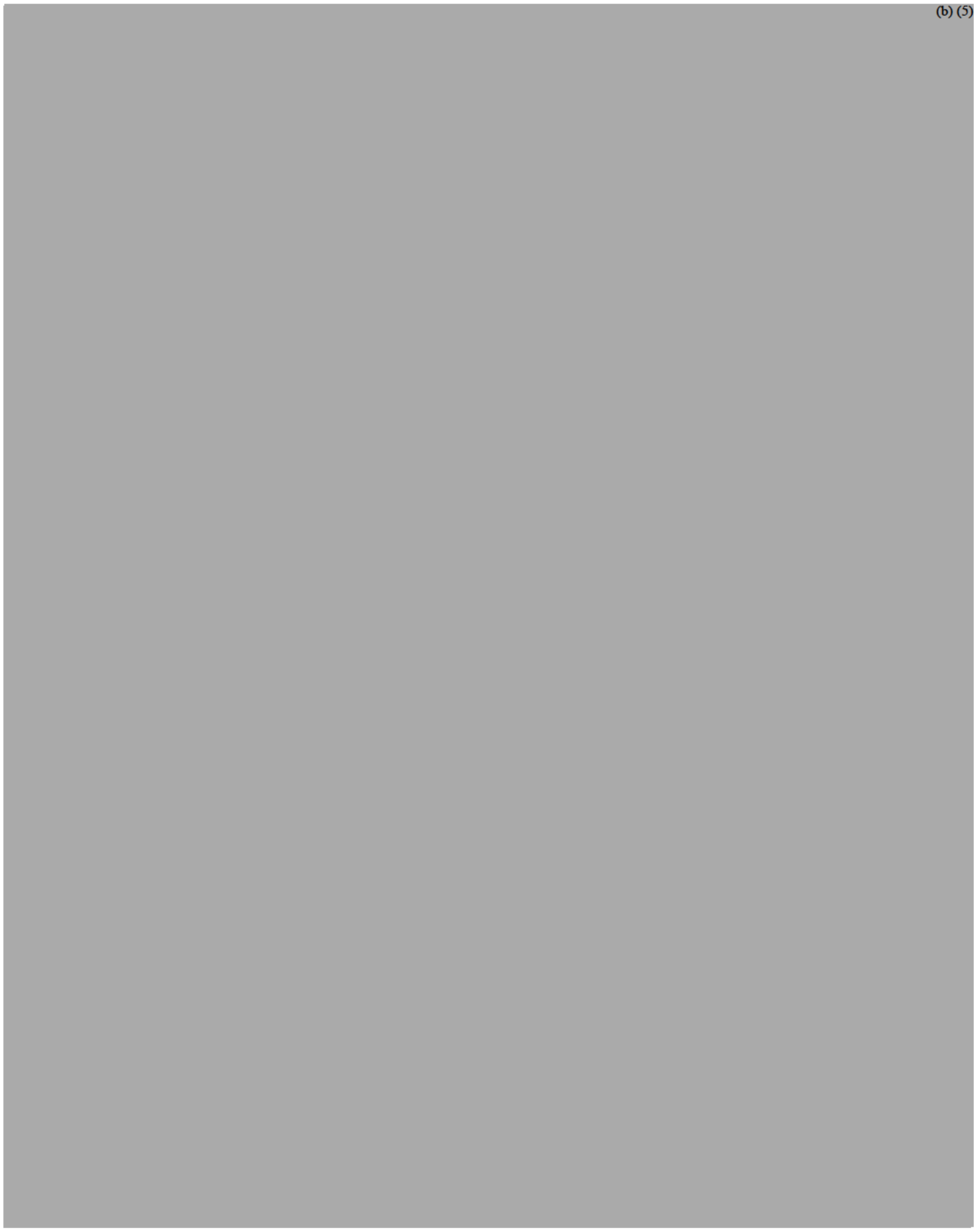

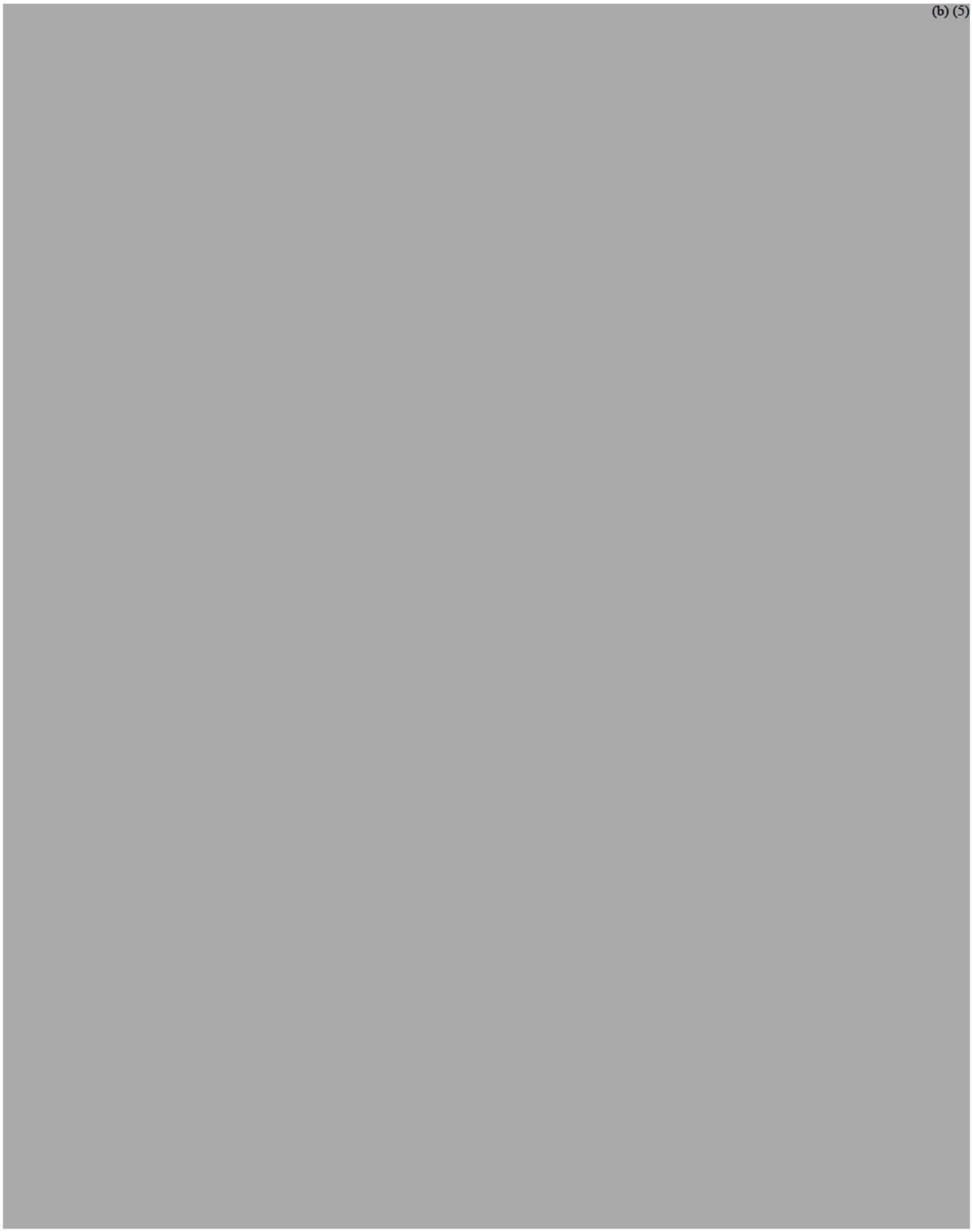
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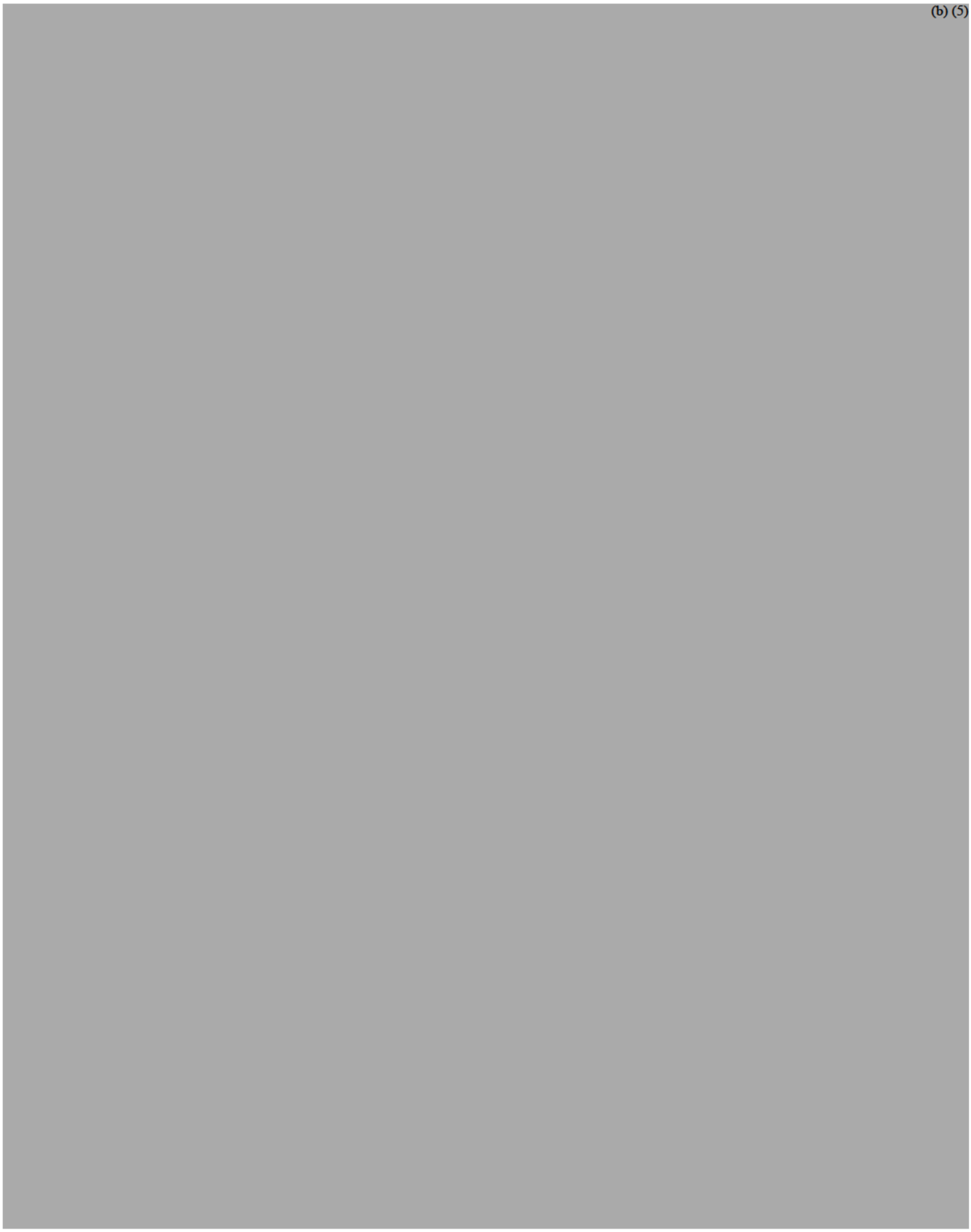
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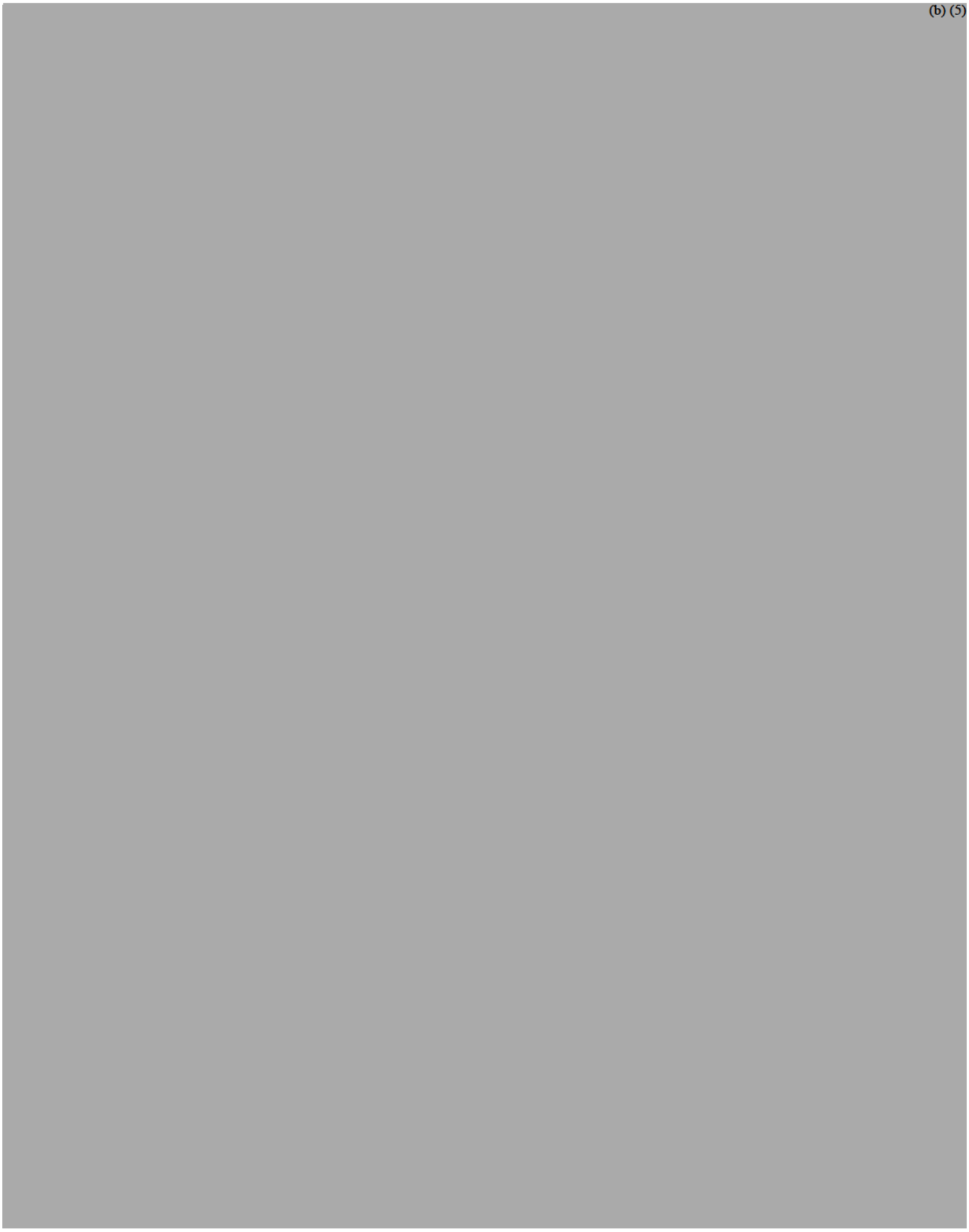
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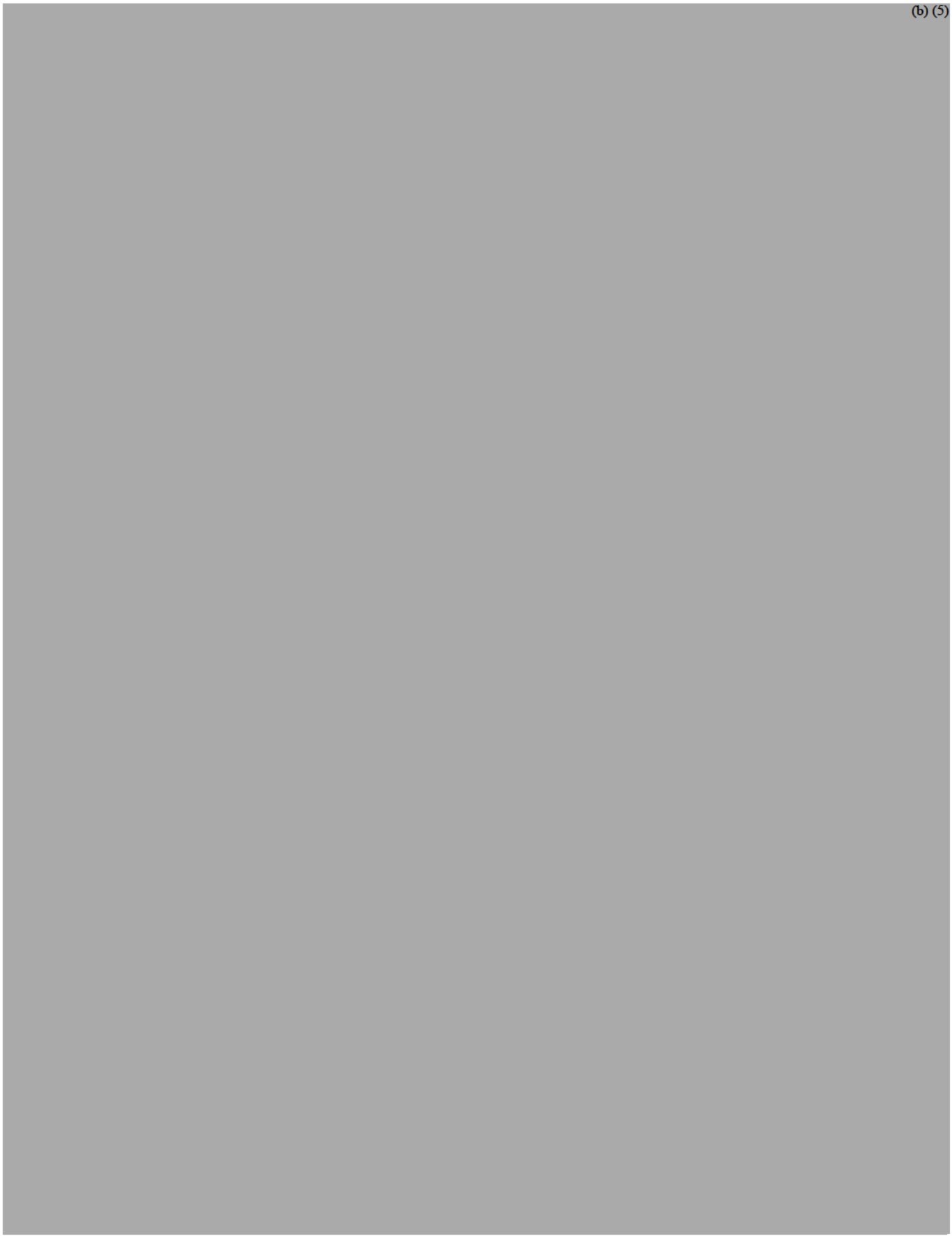
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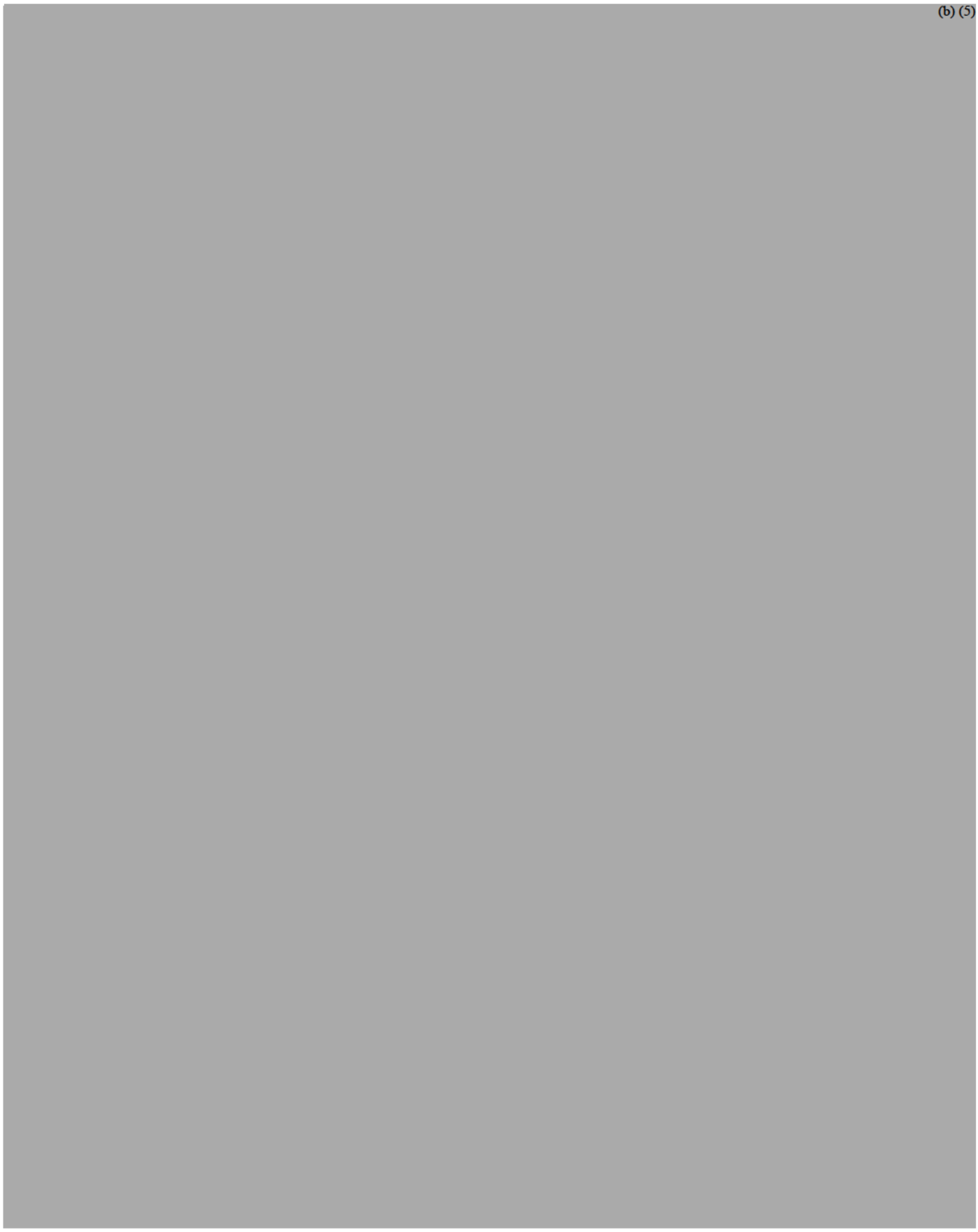
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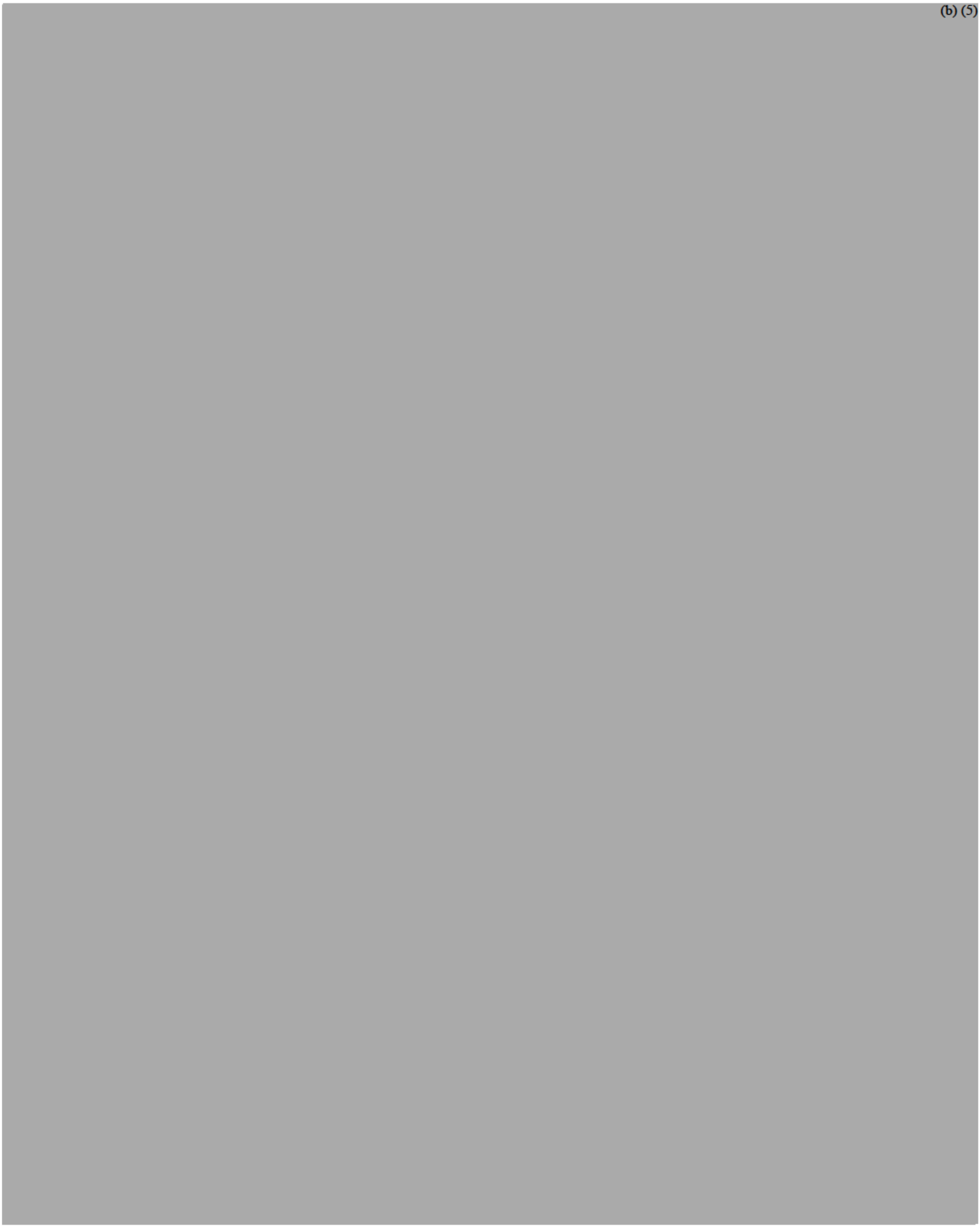
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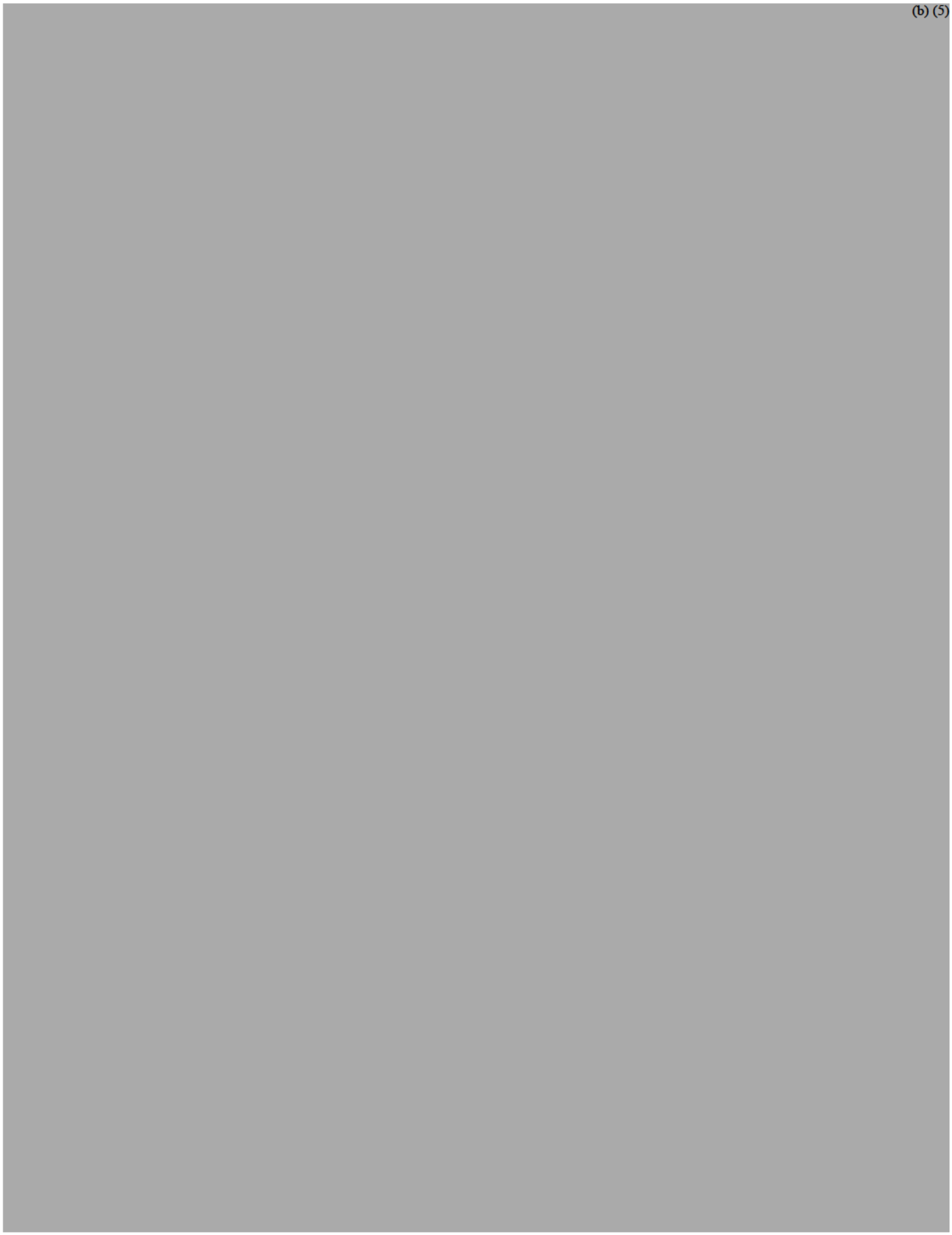
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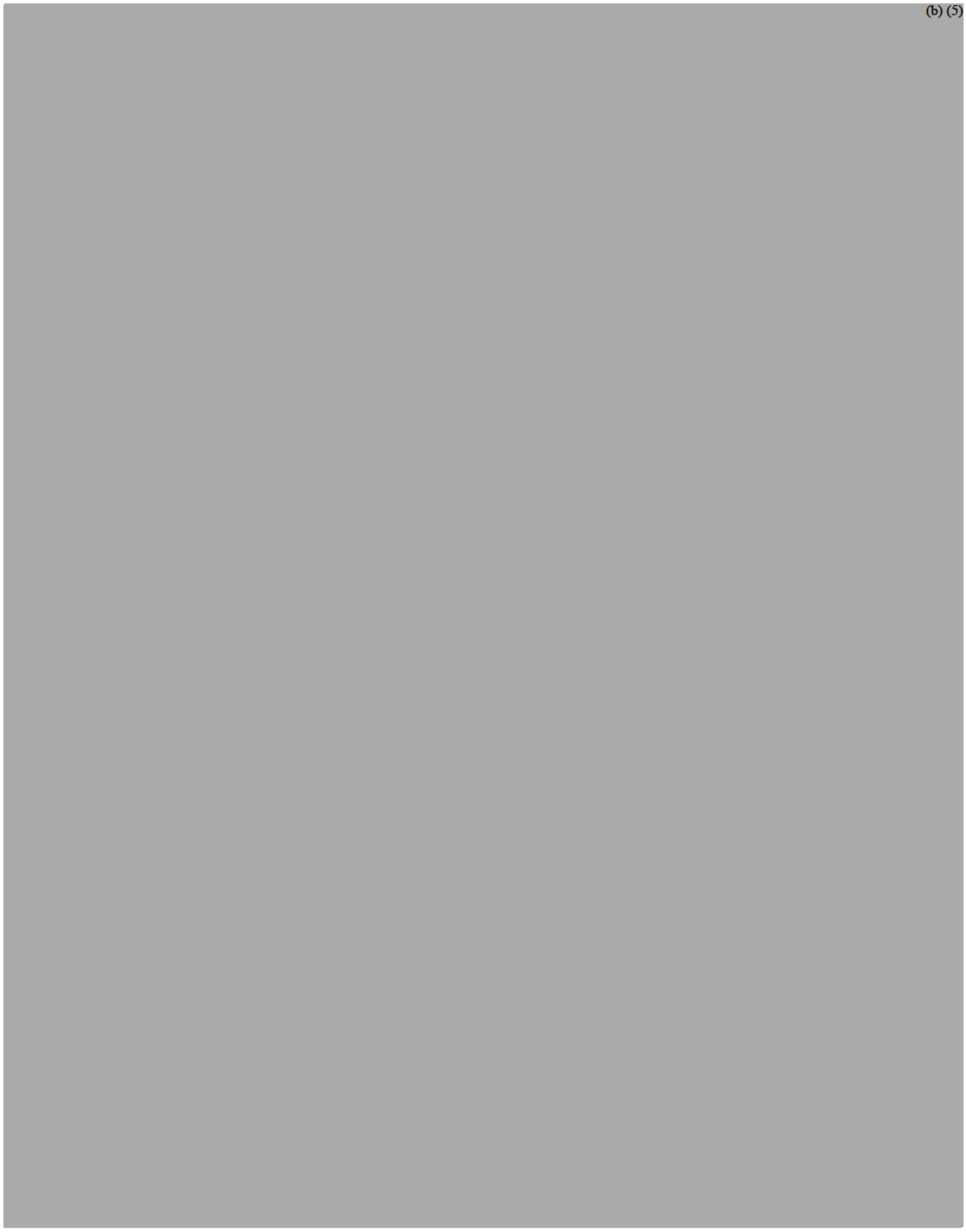

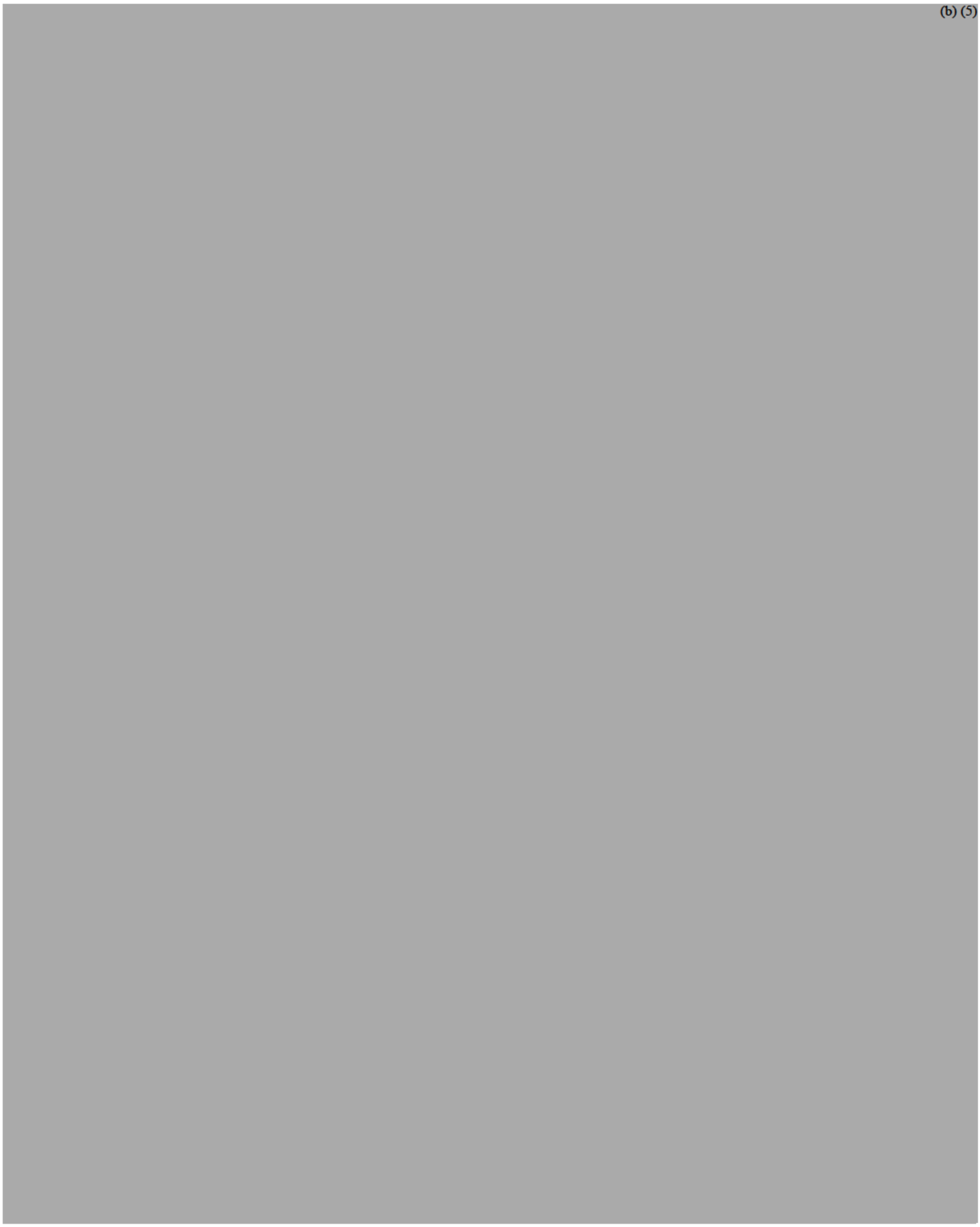
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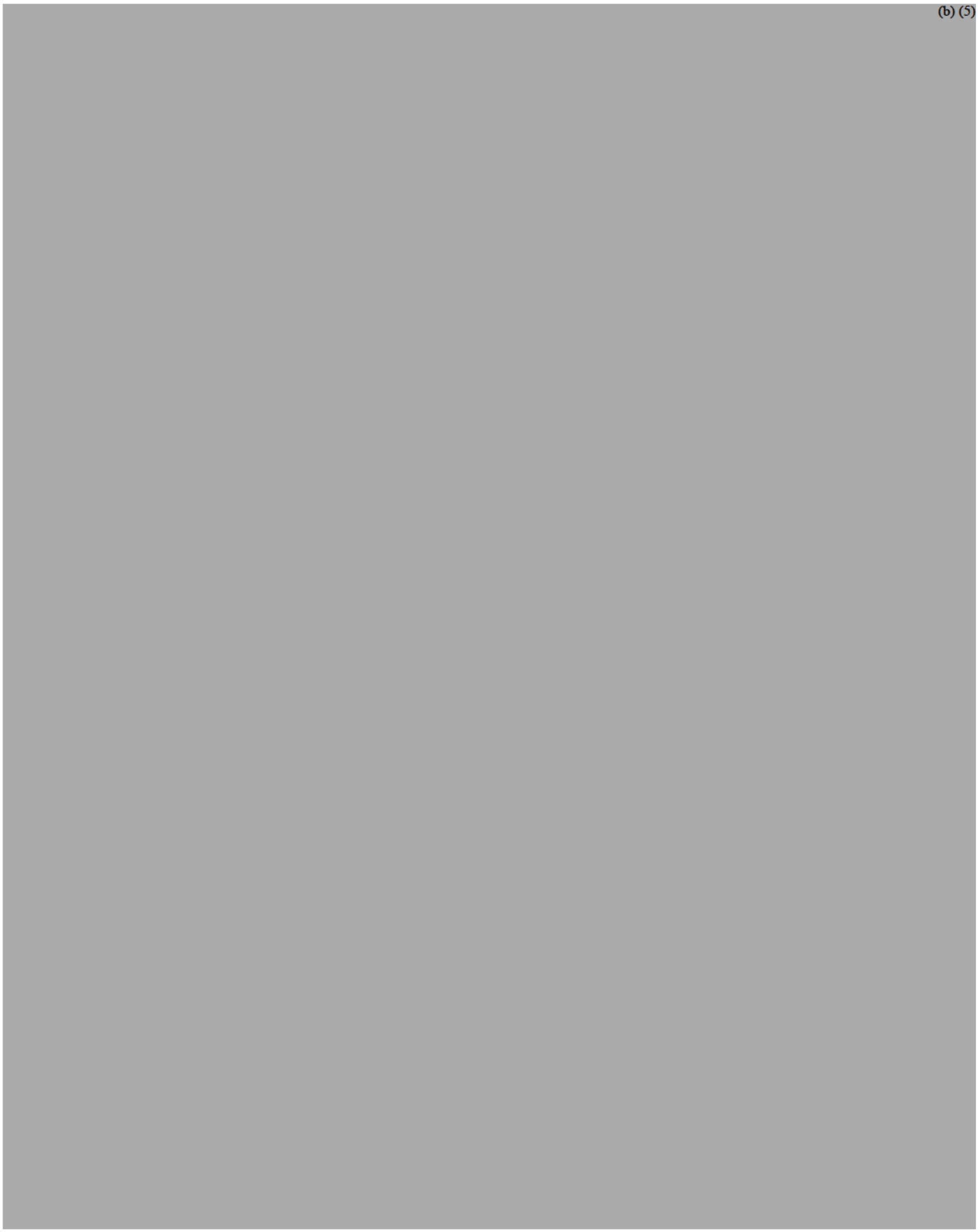
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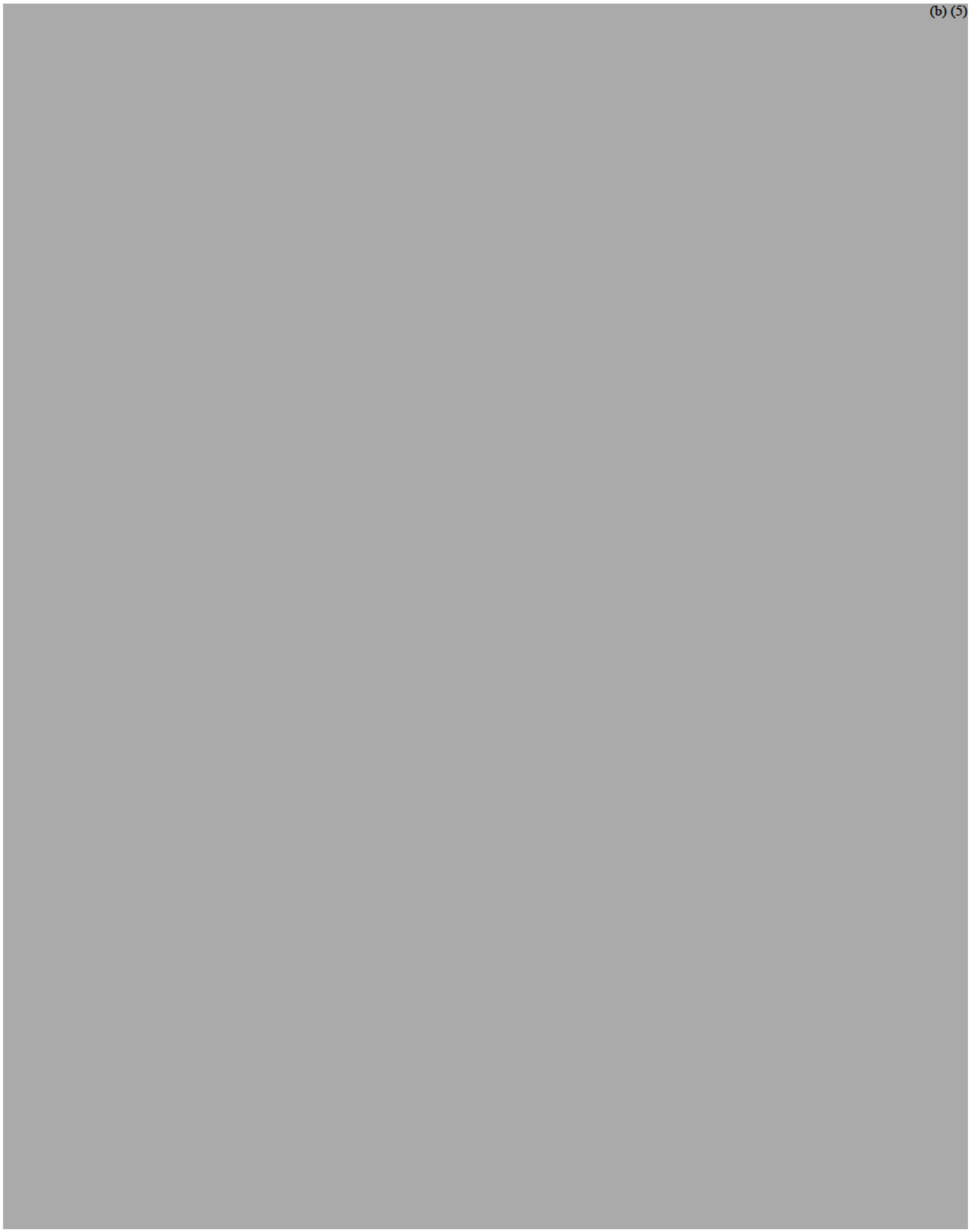
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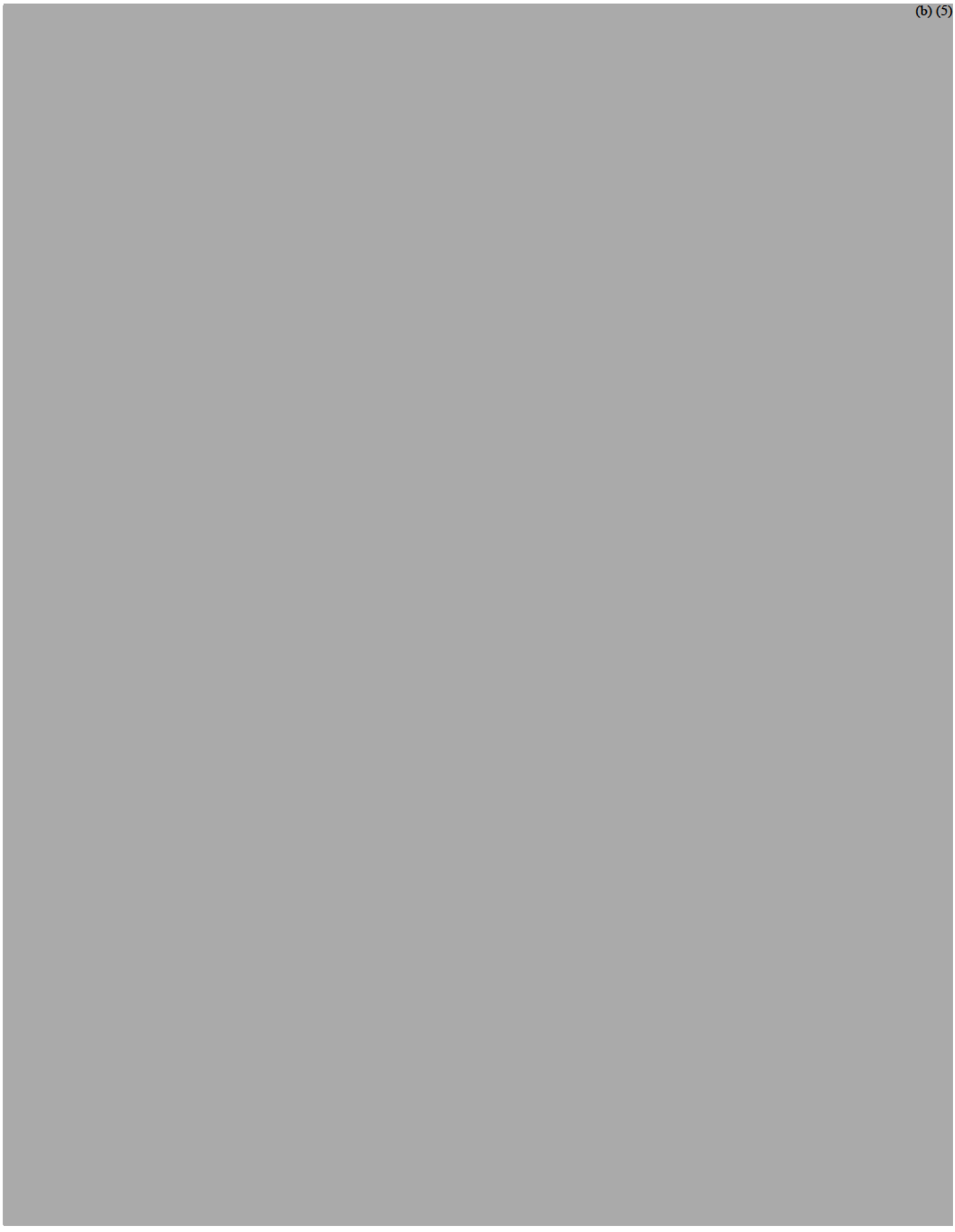
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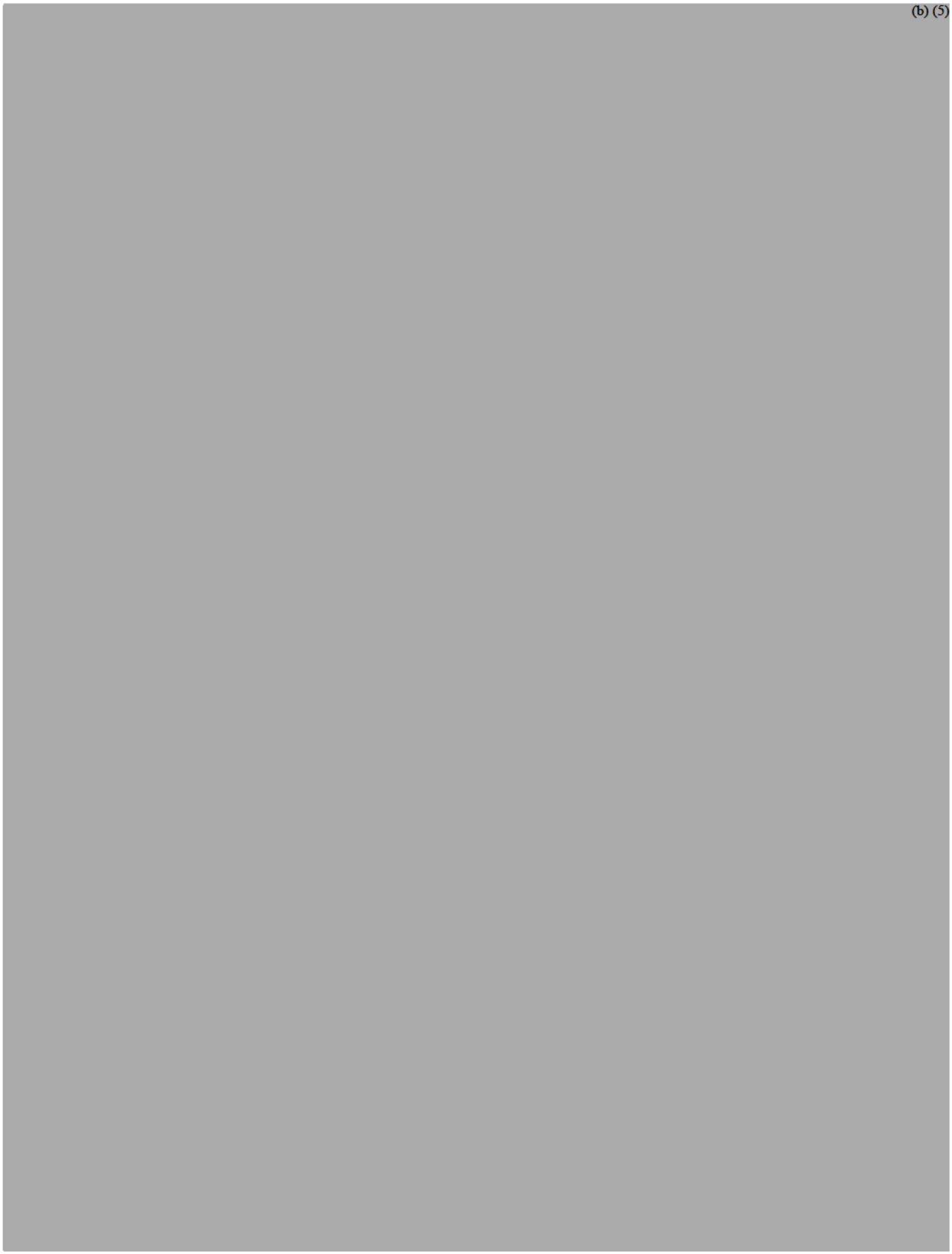
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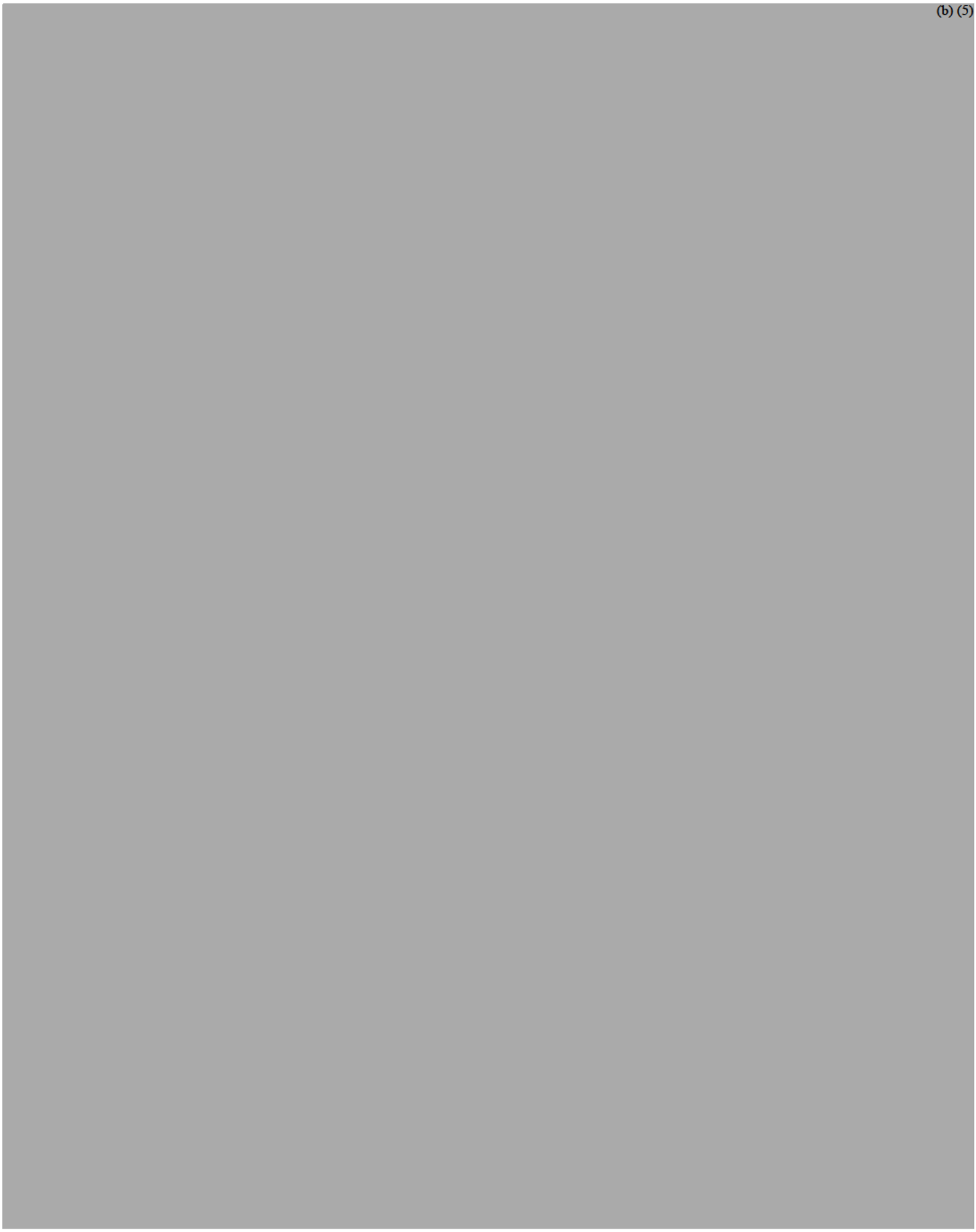
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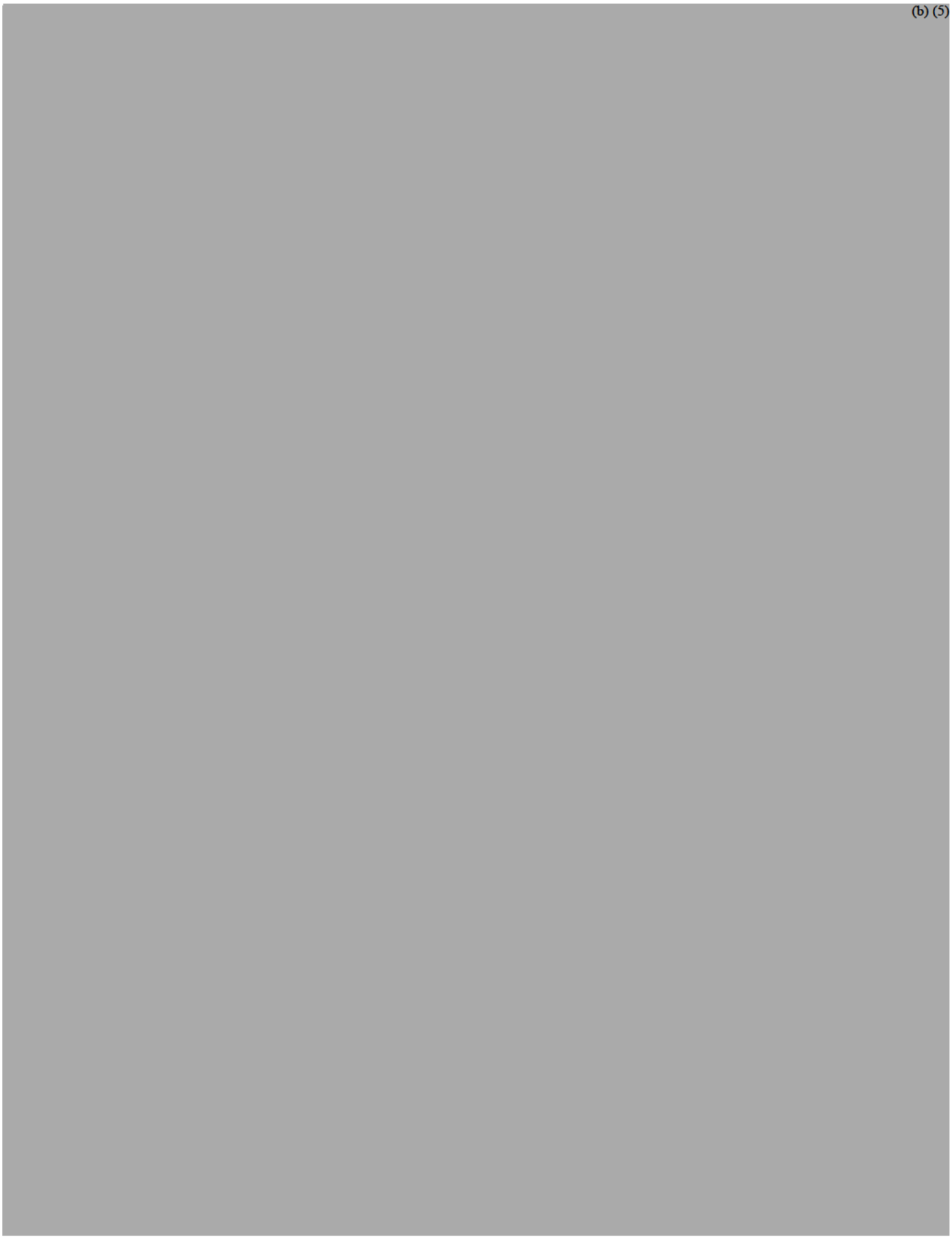

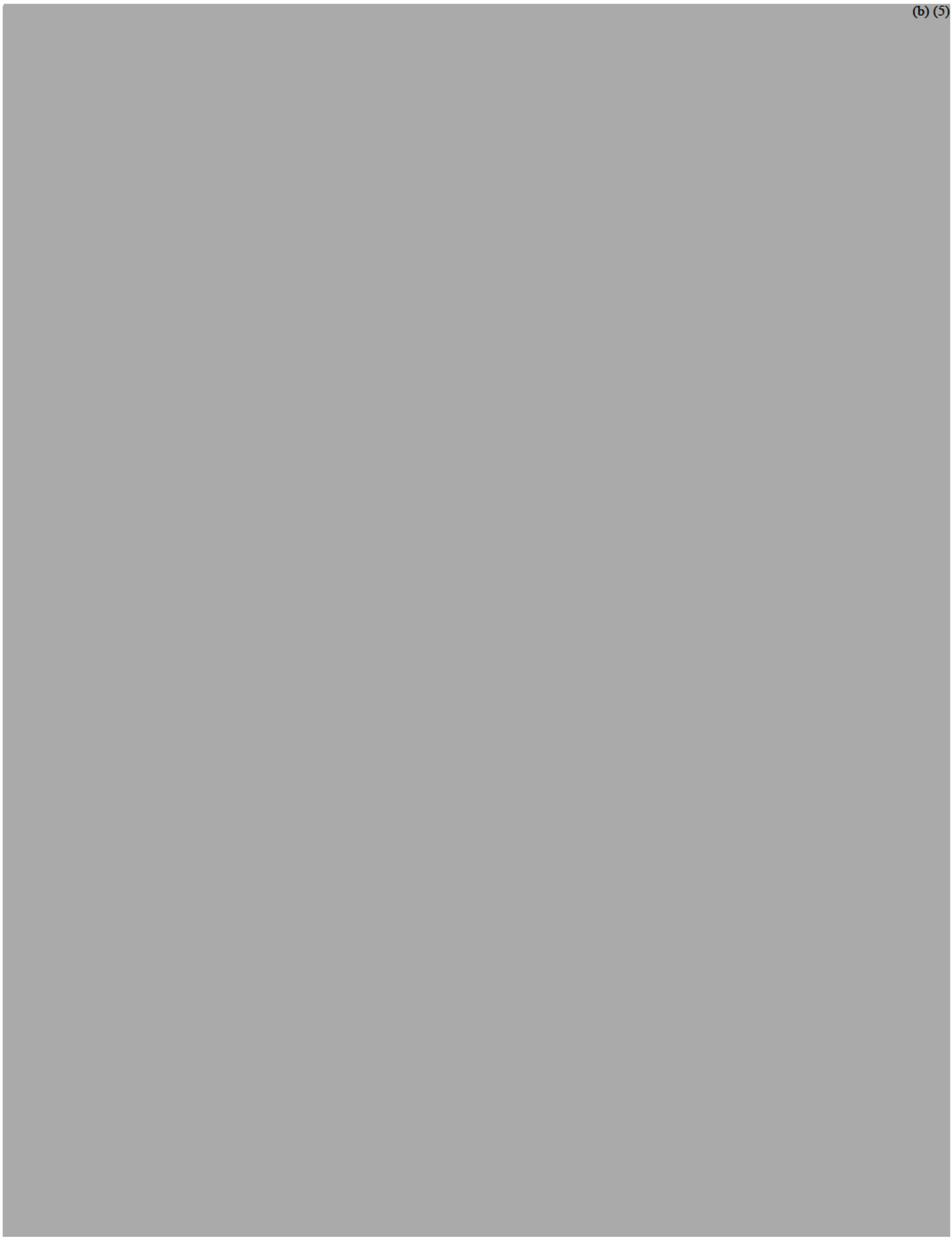

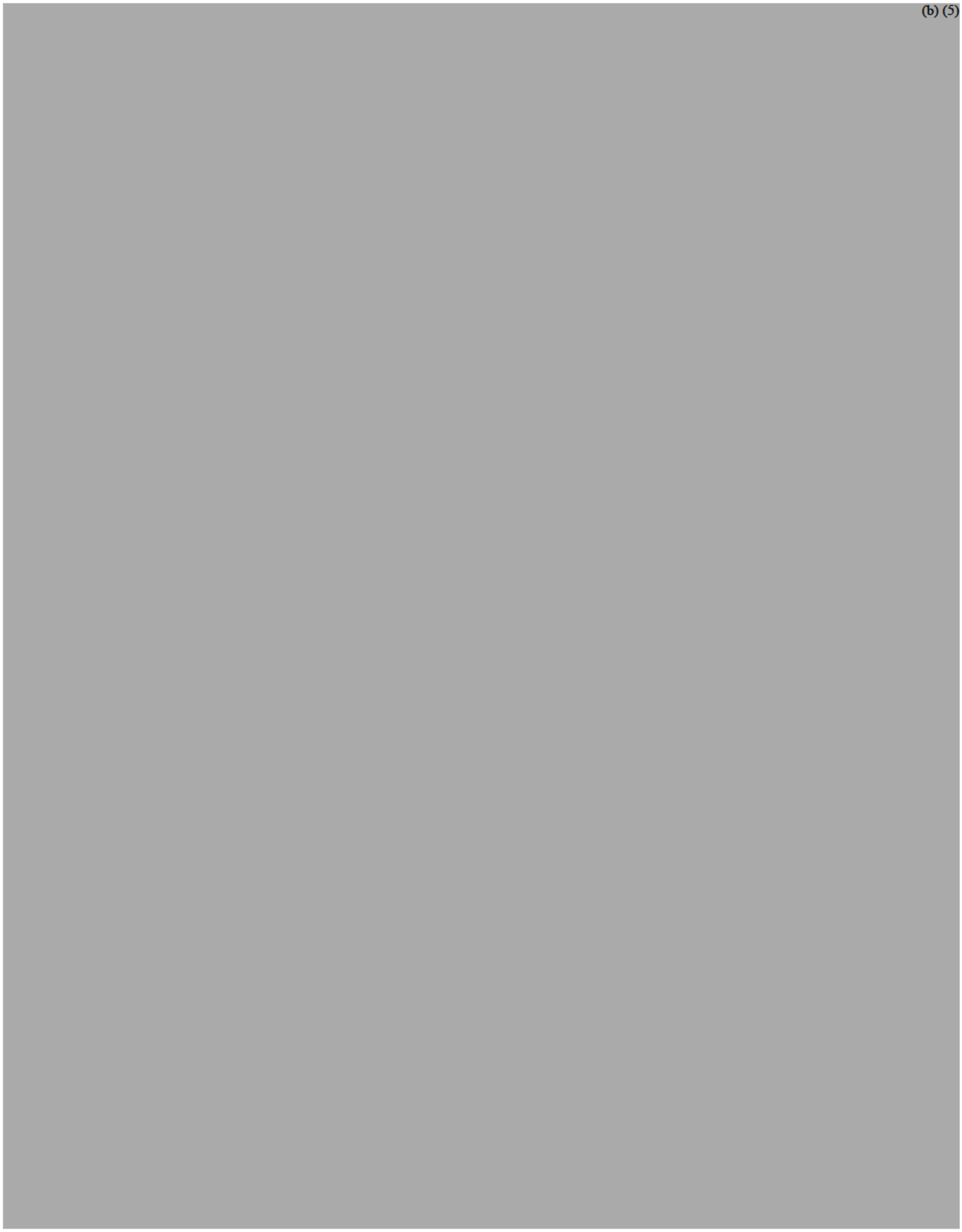
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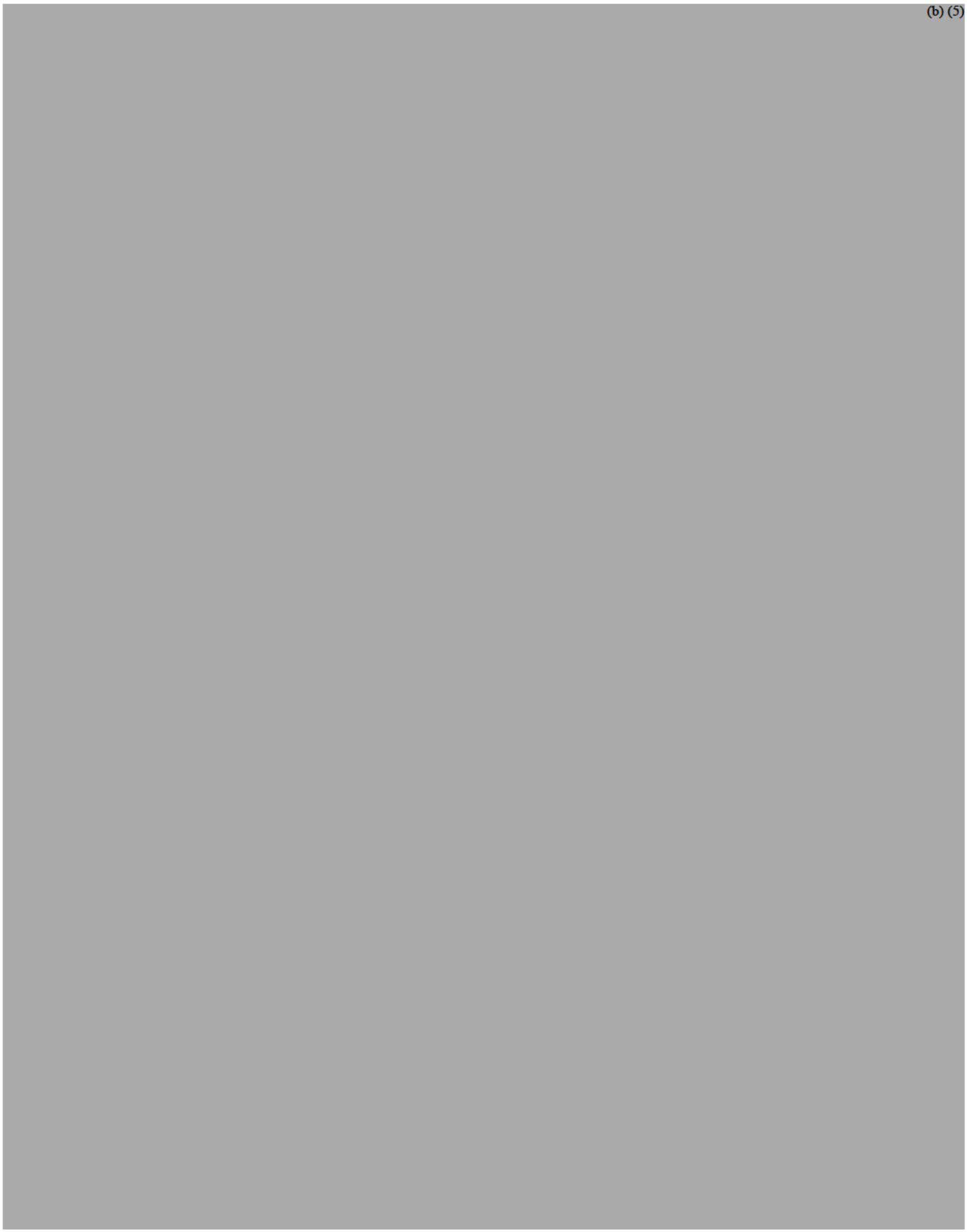
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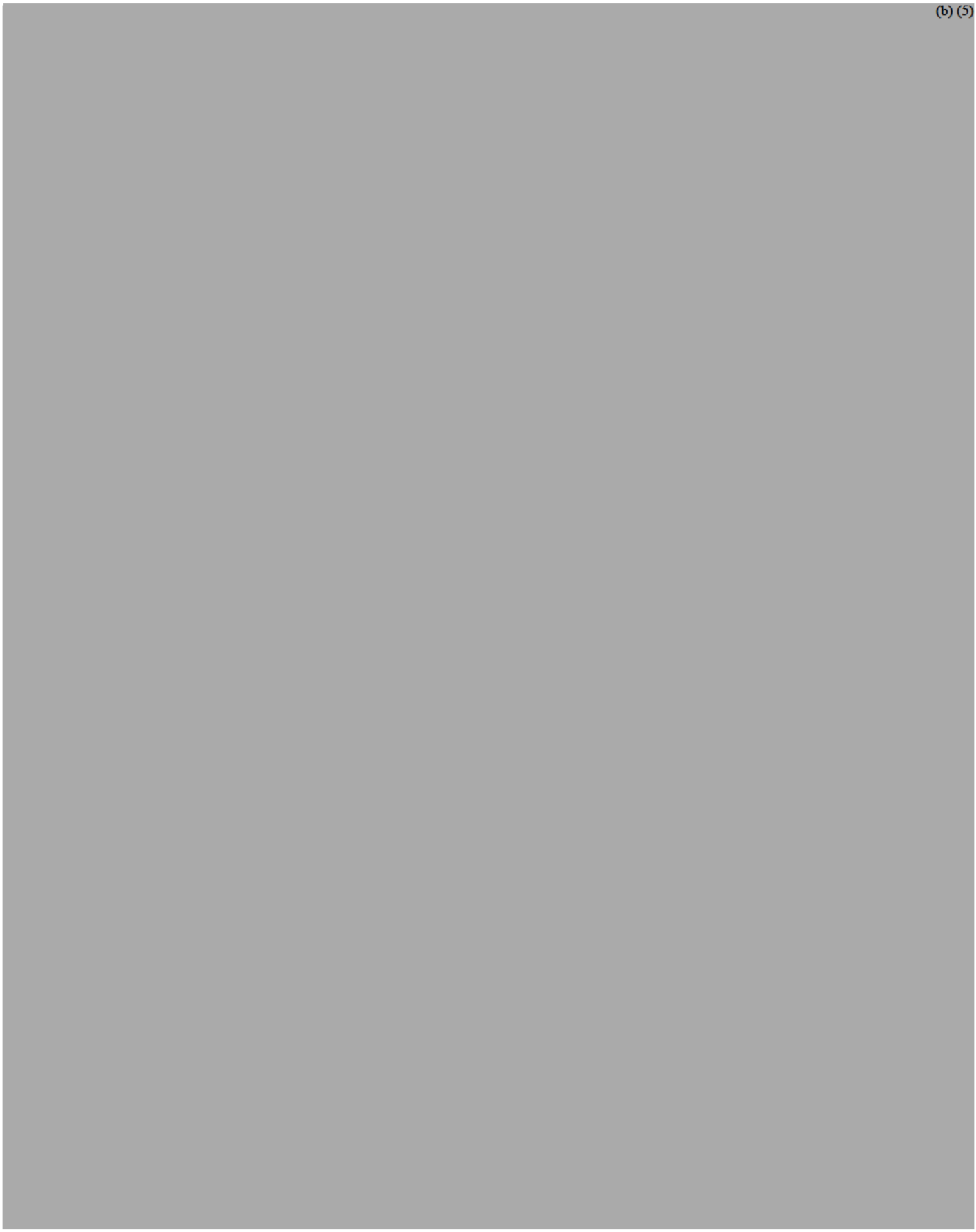
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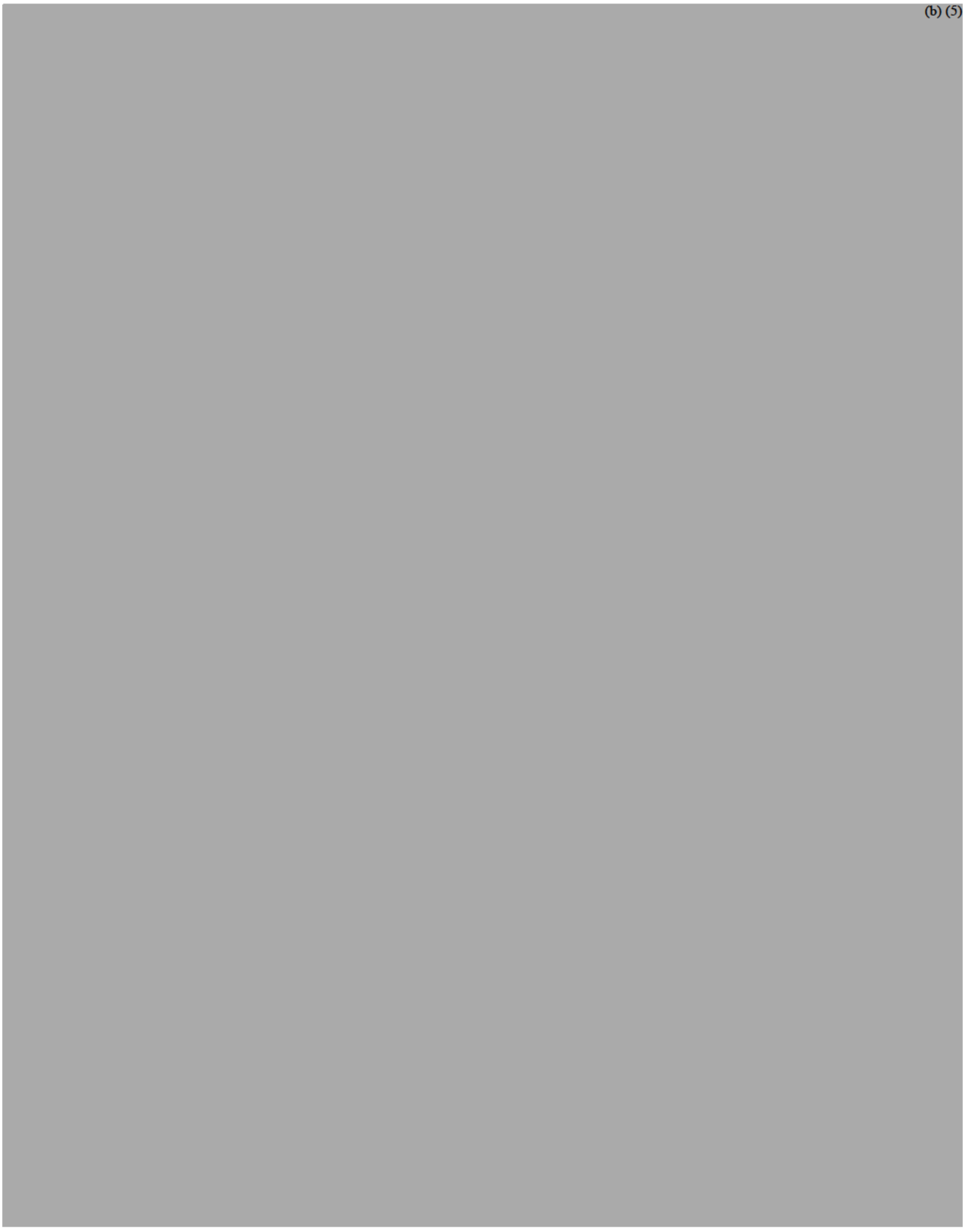
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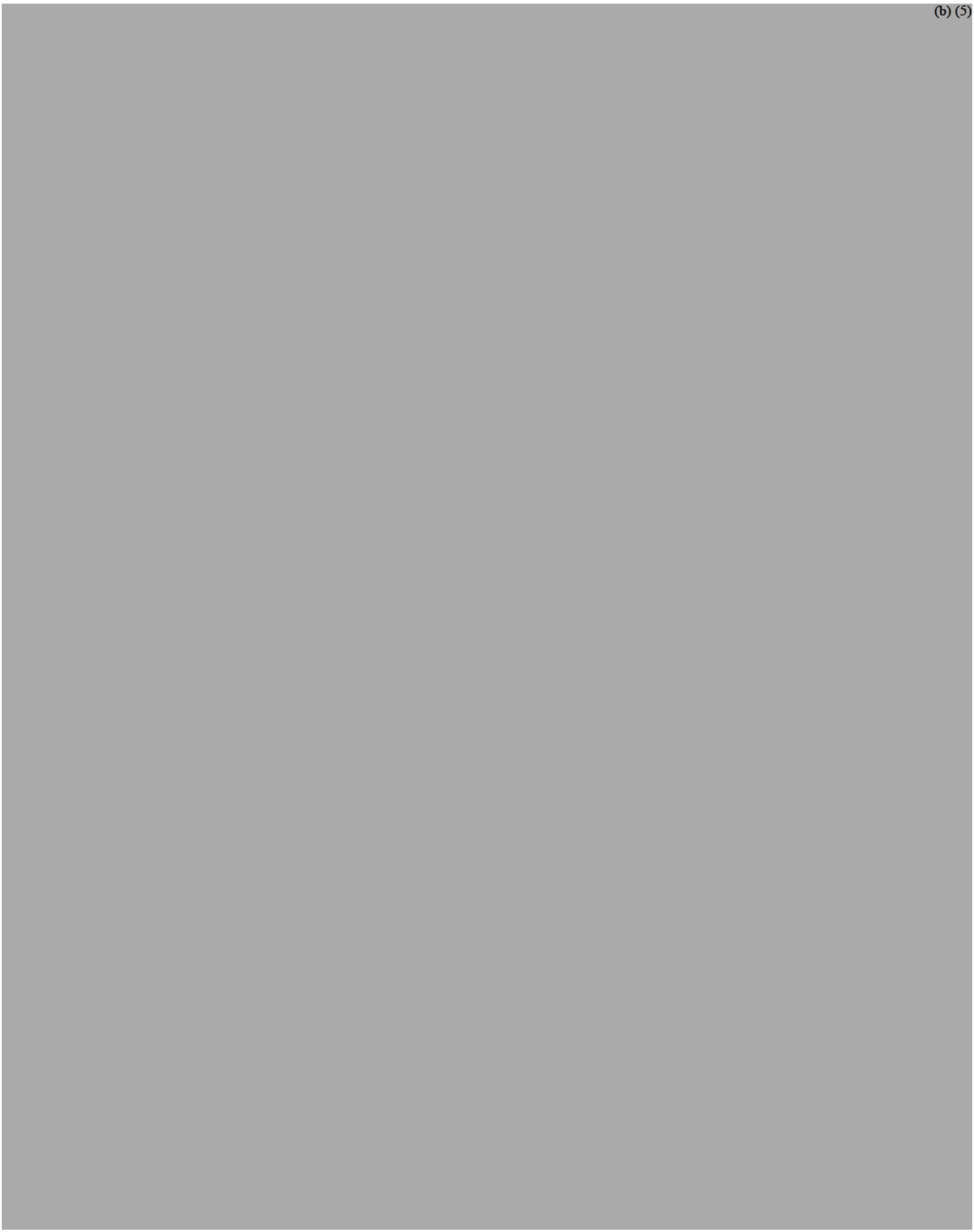
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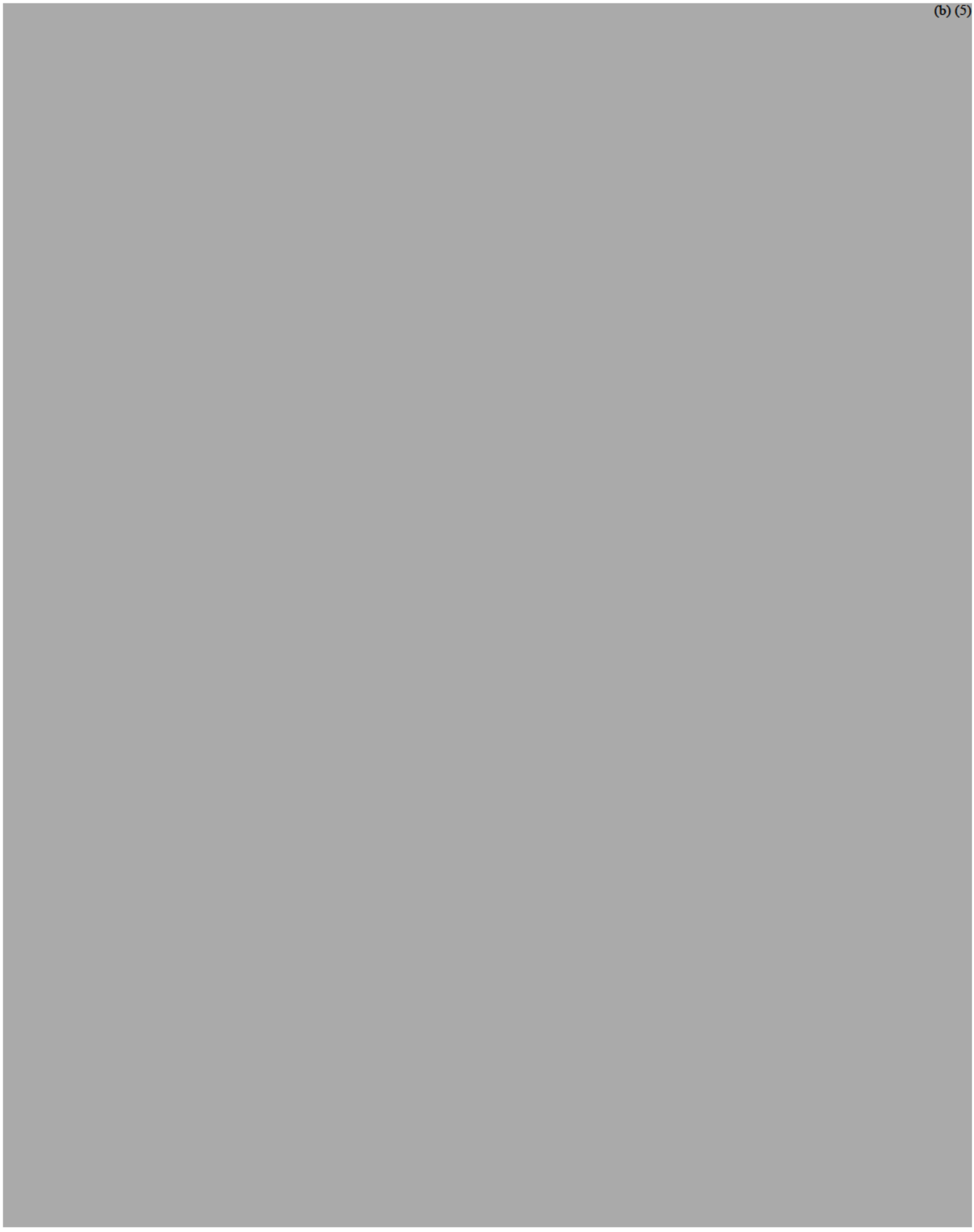
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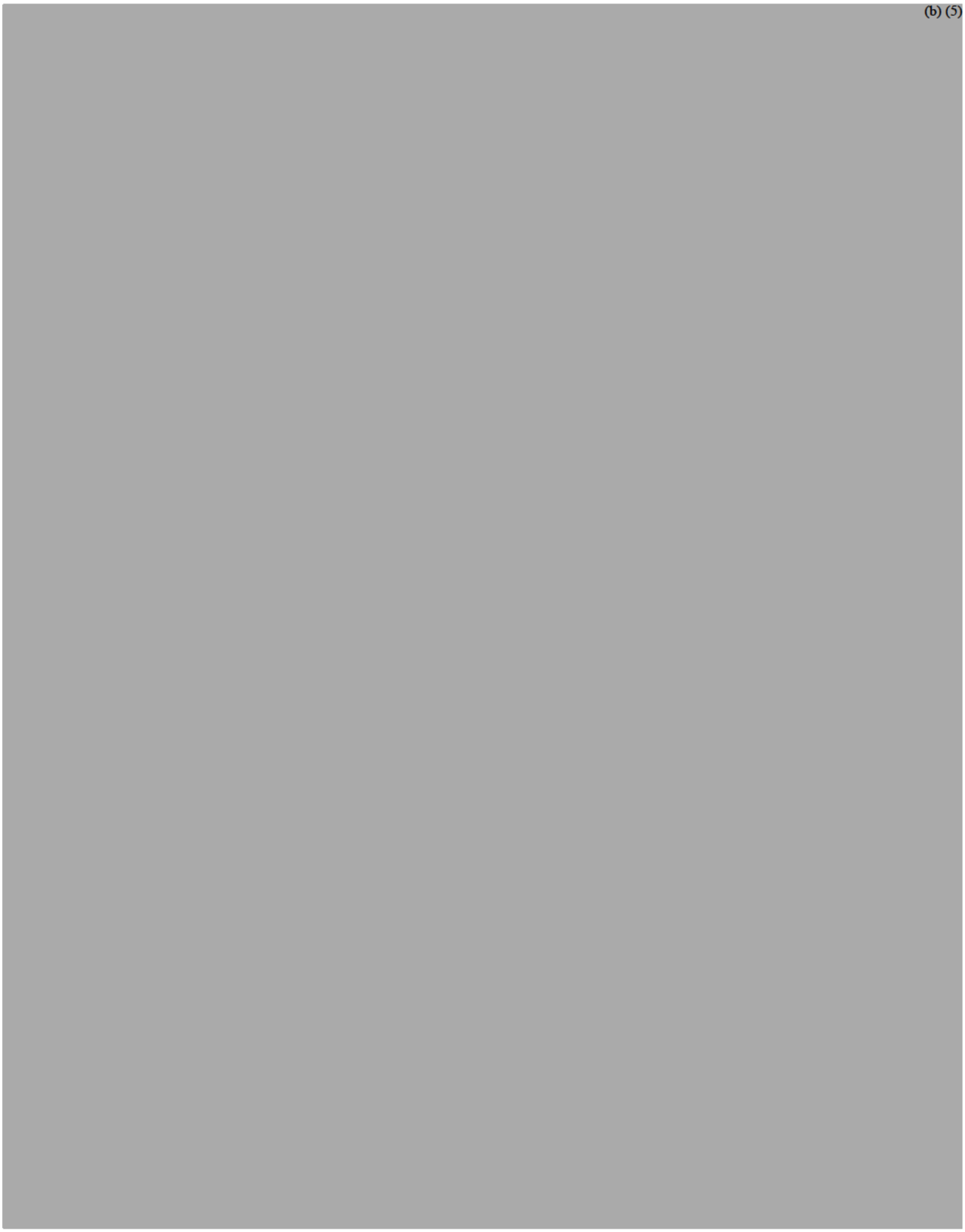
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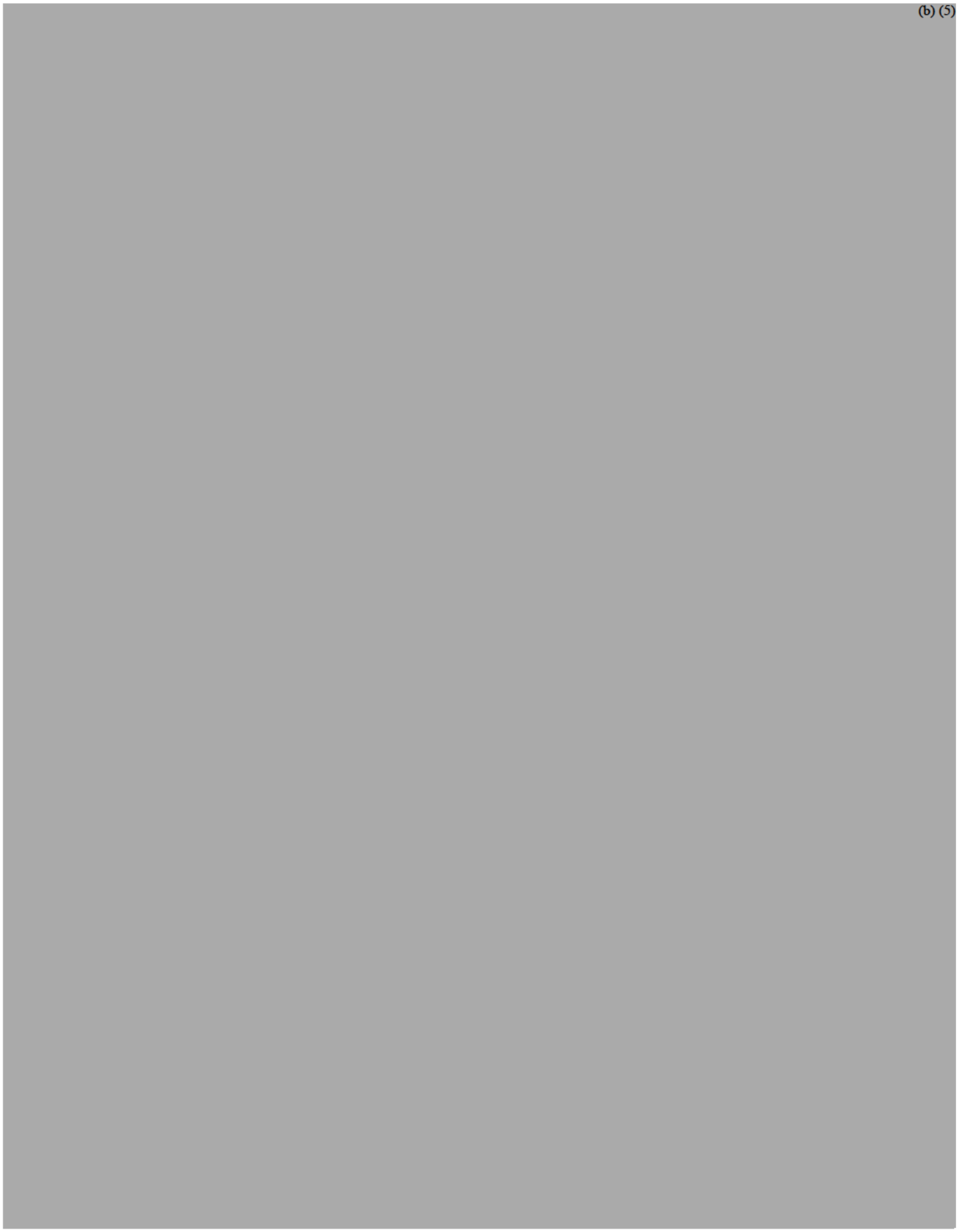
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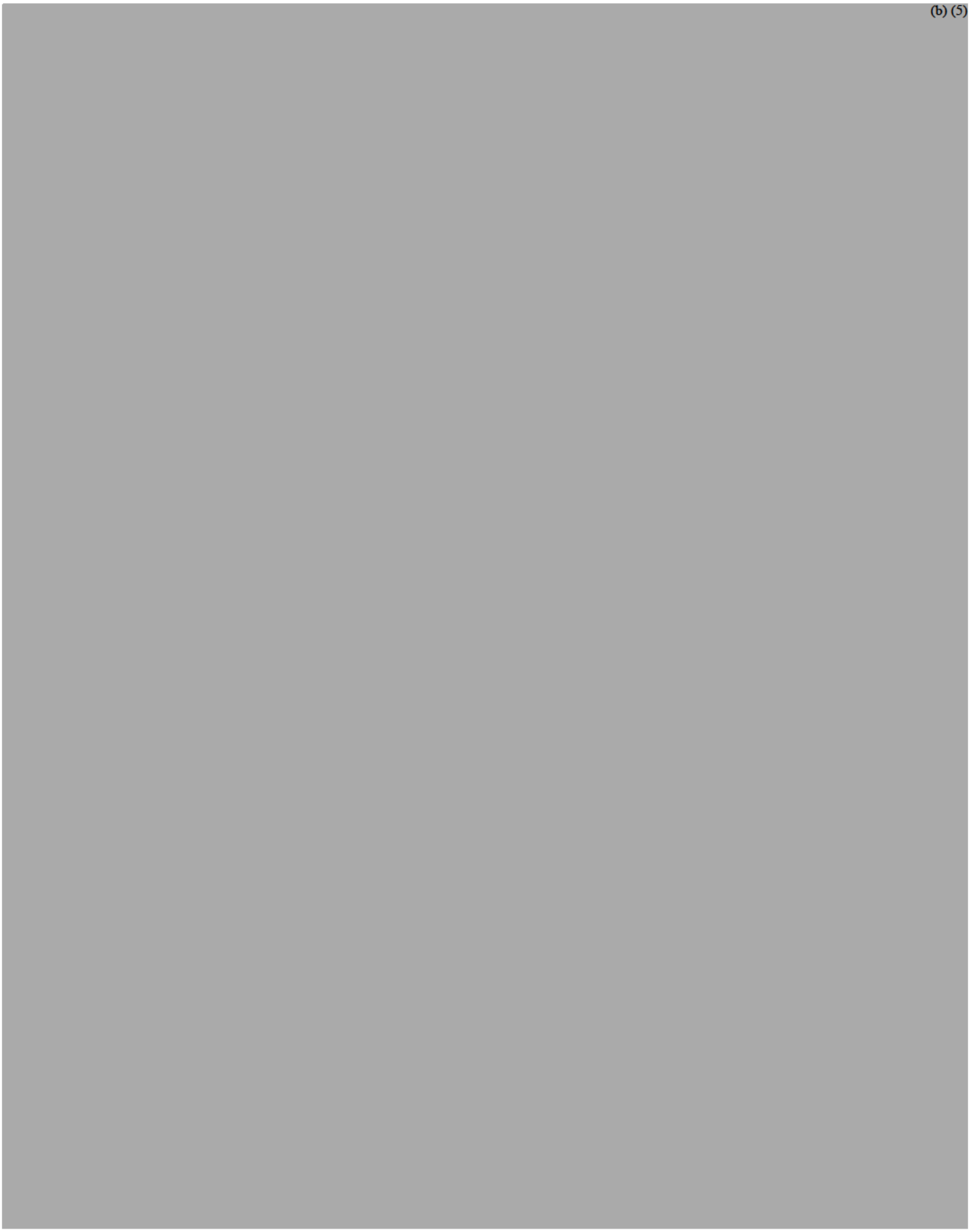
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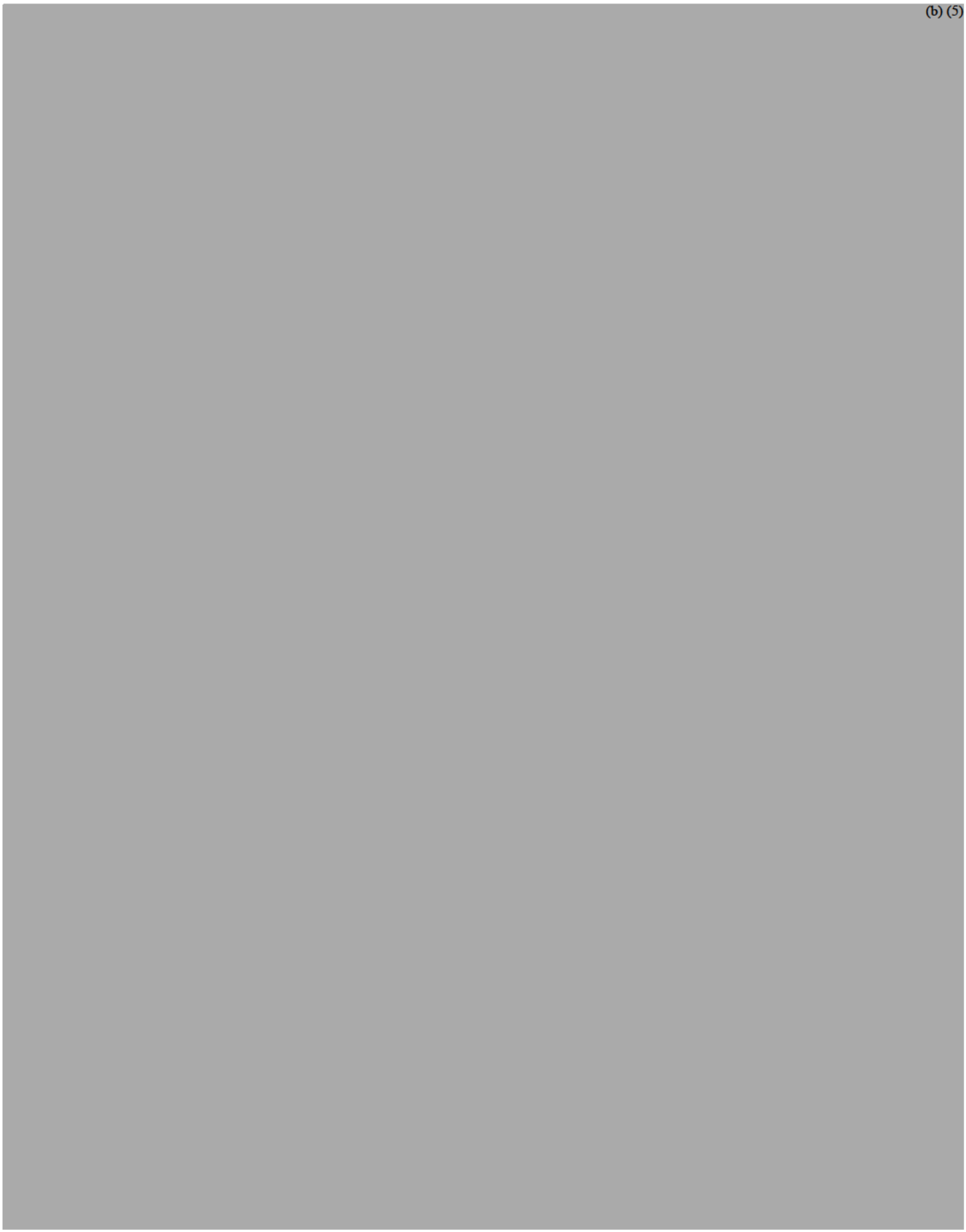
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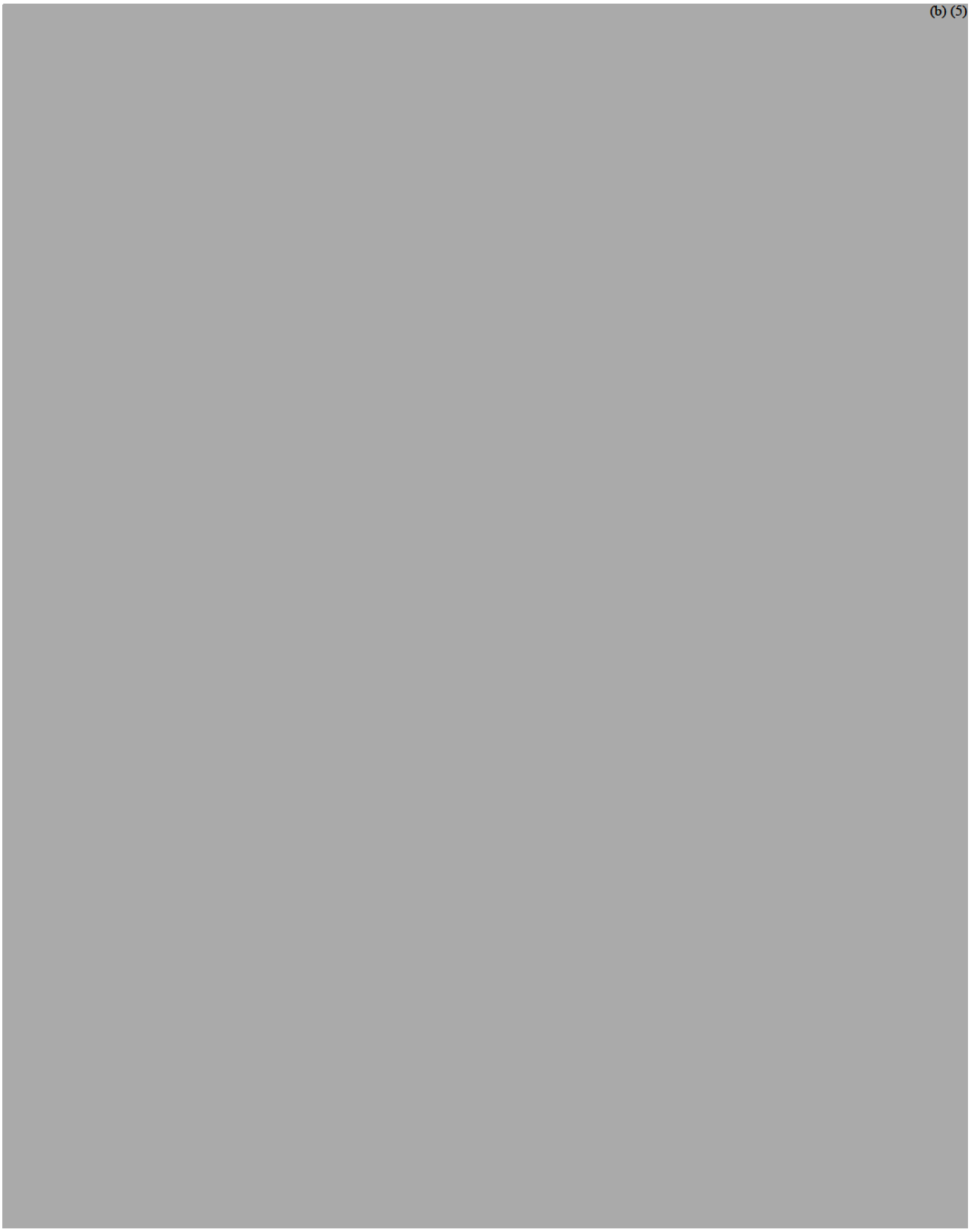
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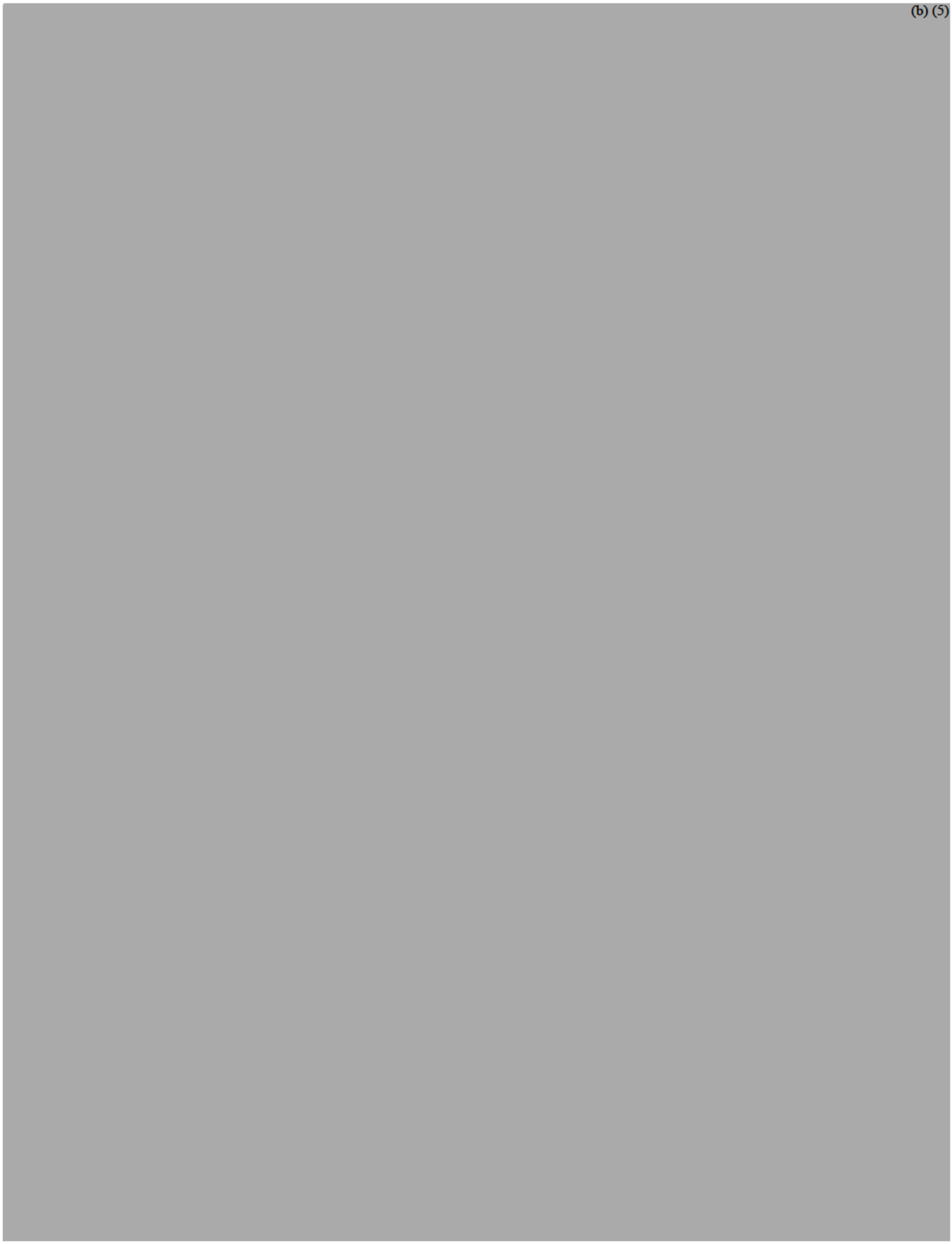
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Chapter 4 Centers of Excellence

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Alzheimer's Disease Research Centers

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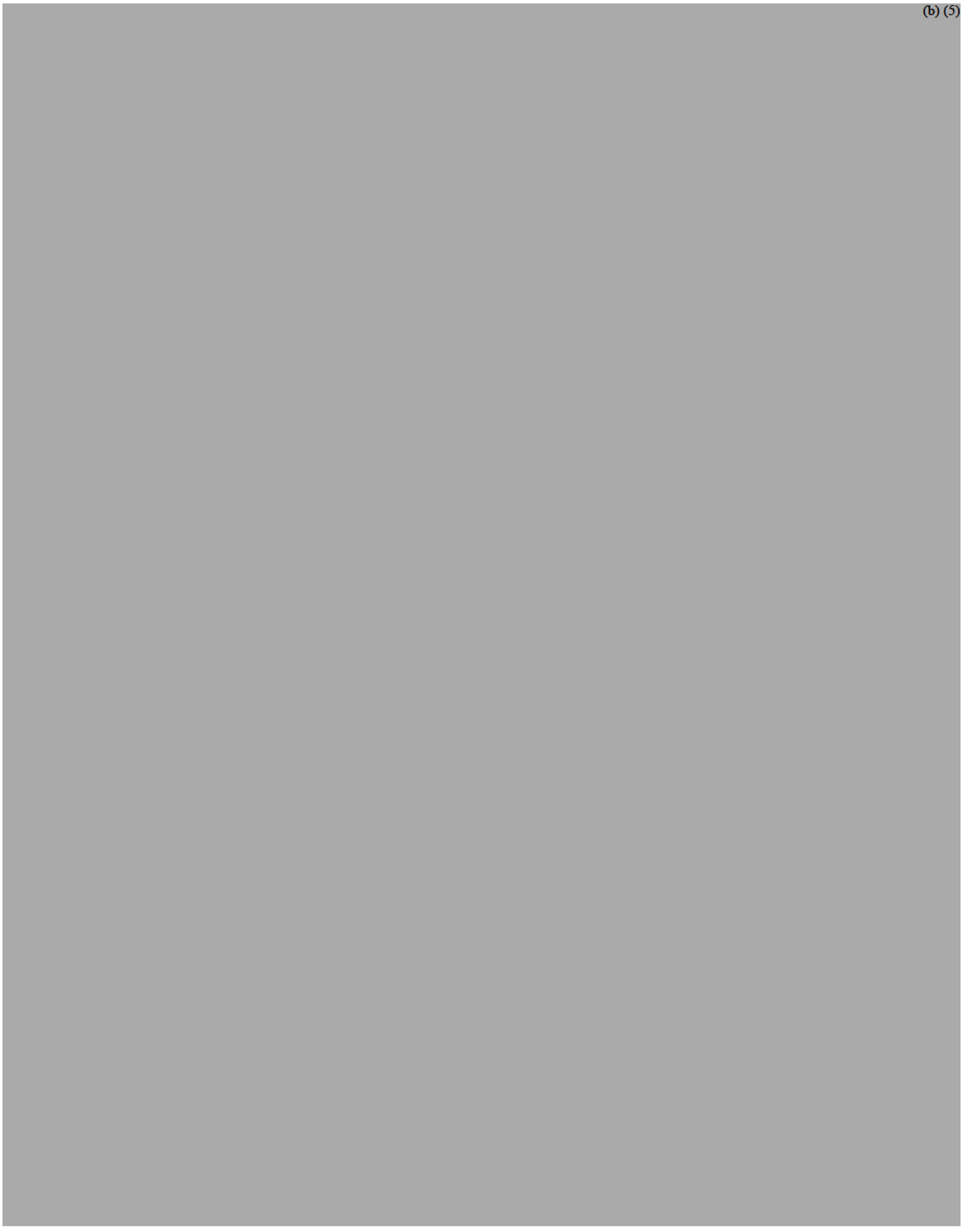
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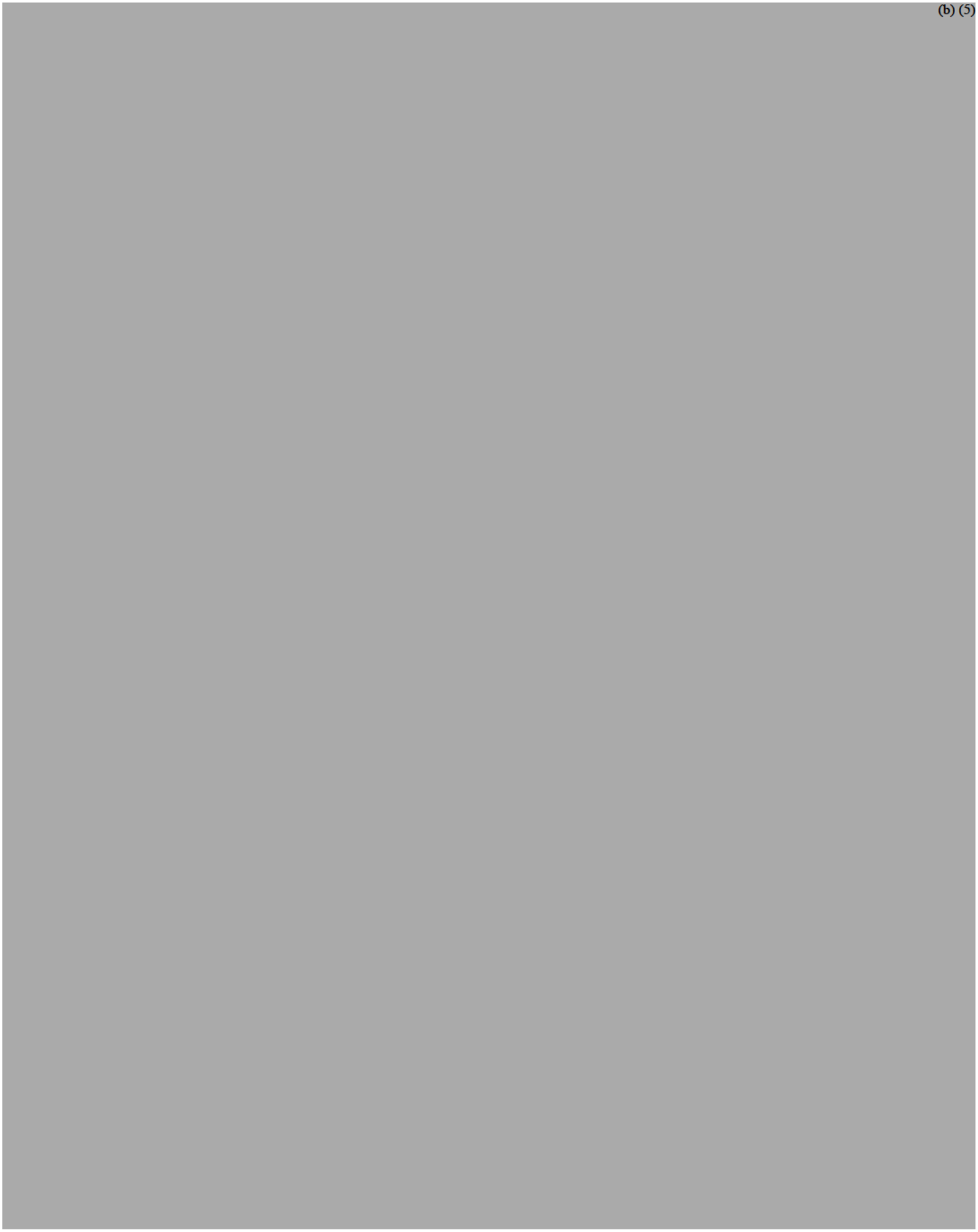
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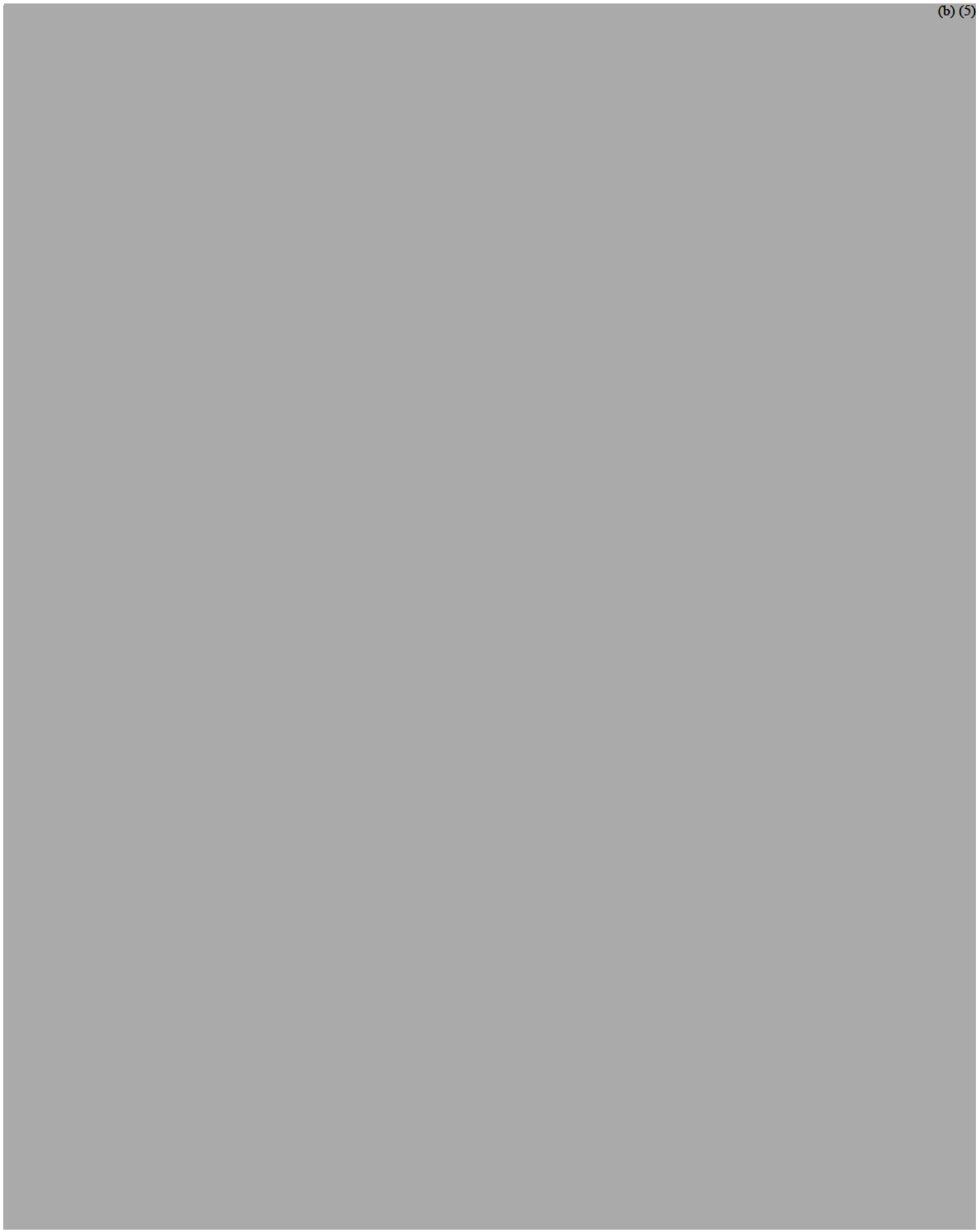
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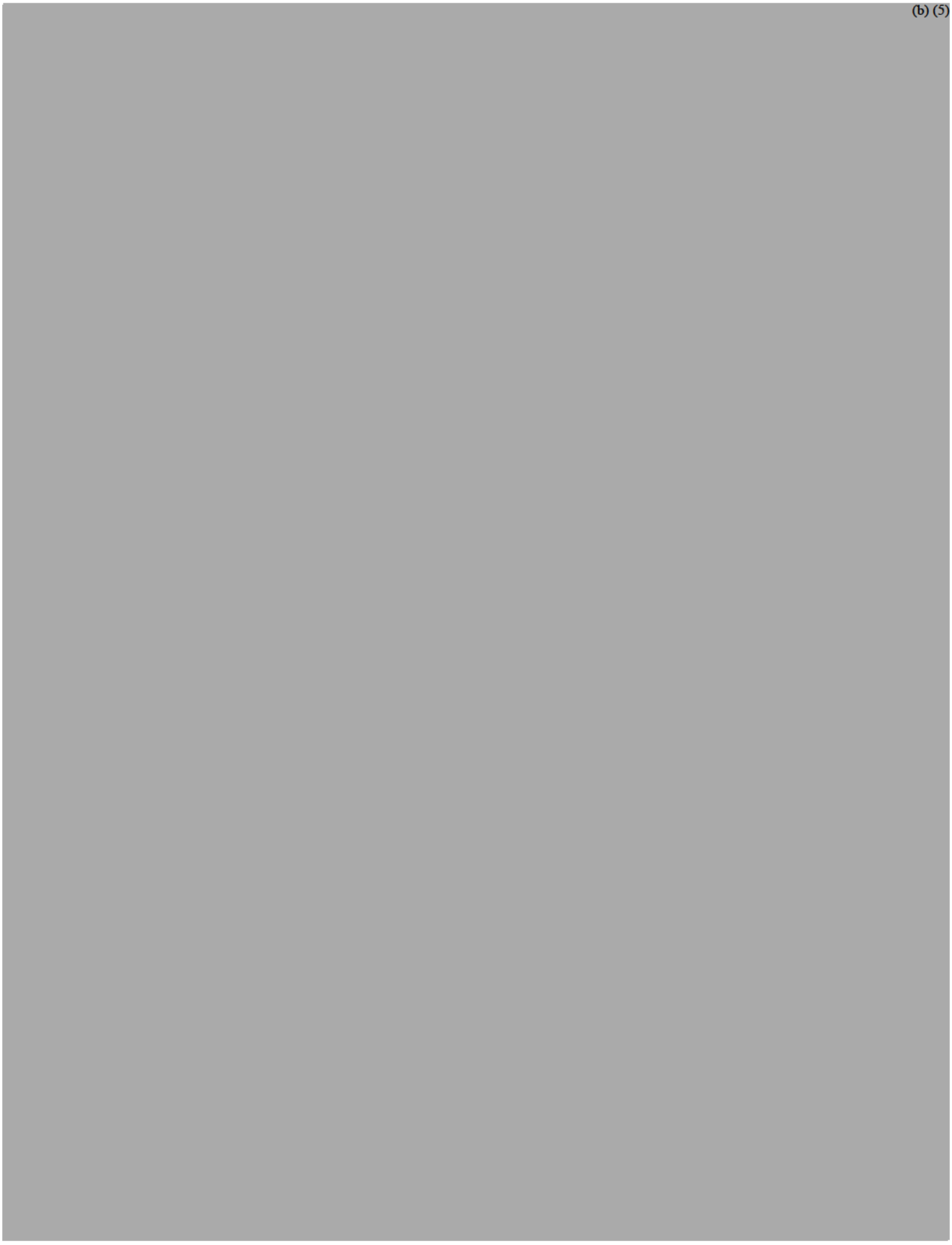
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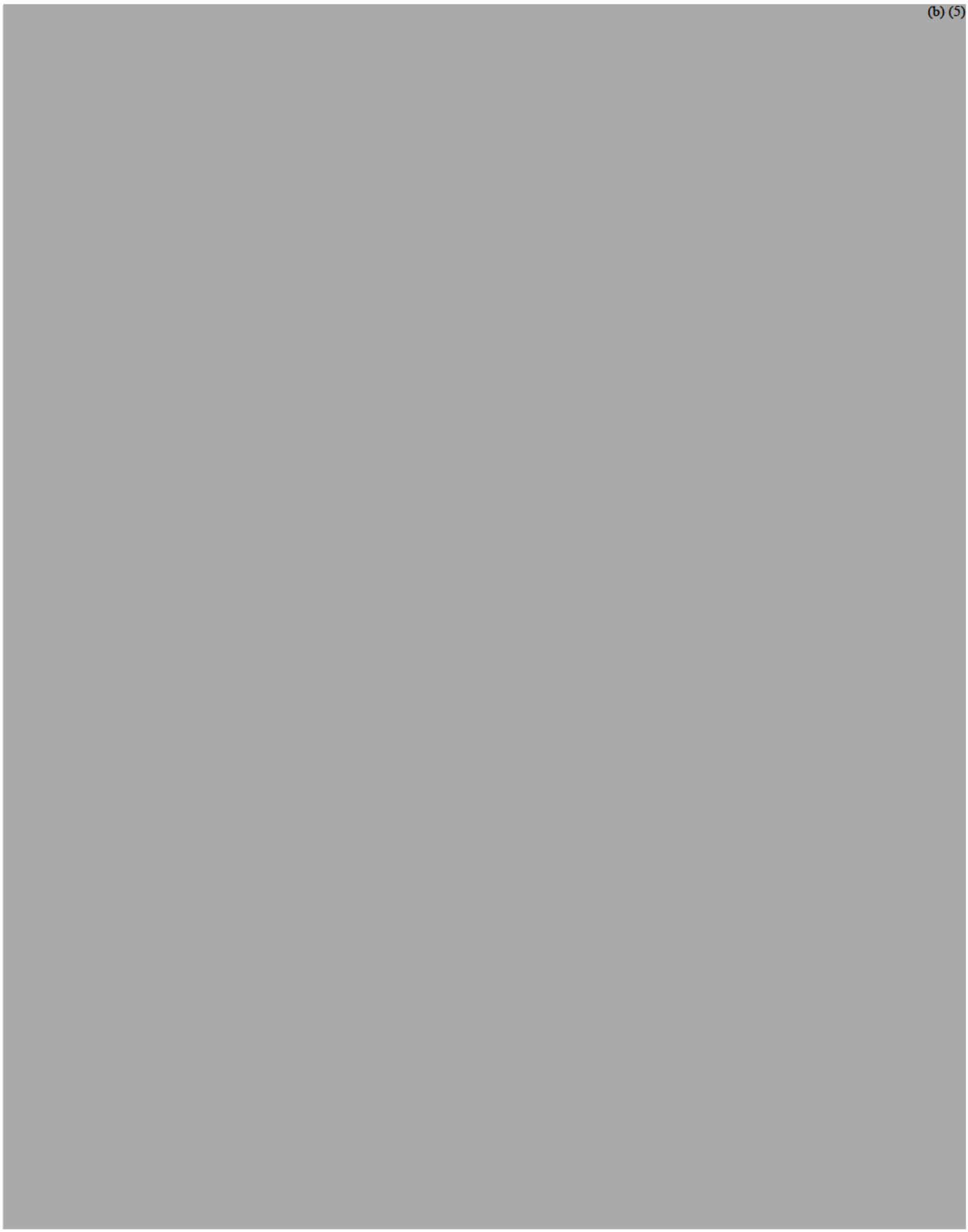
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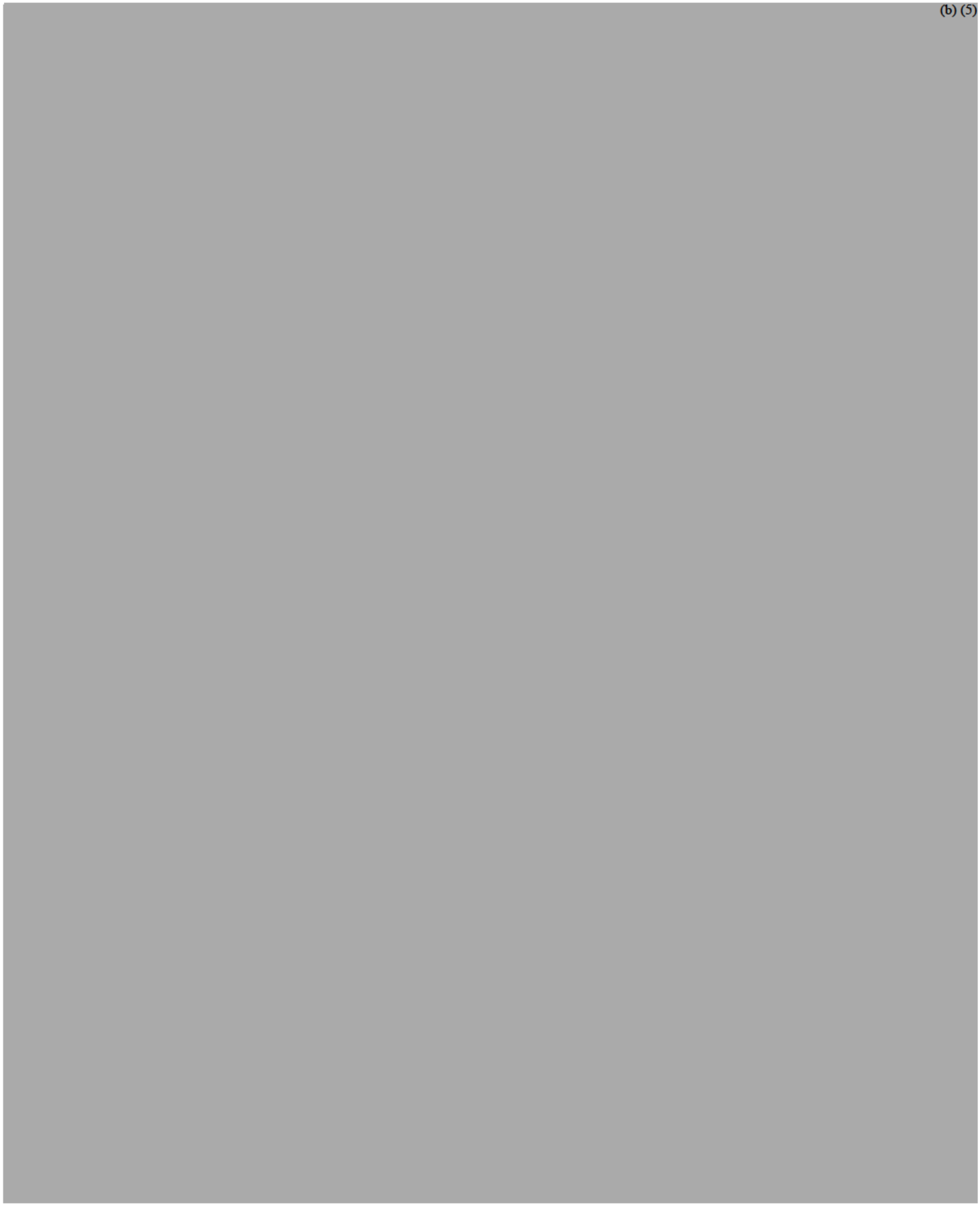
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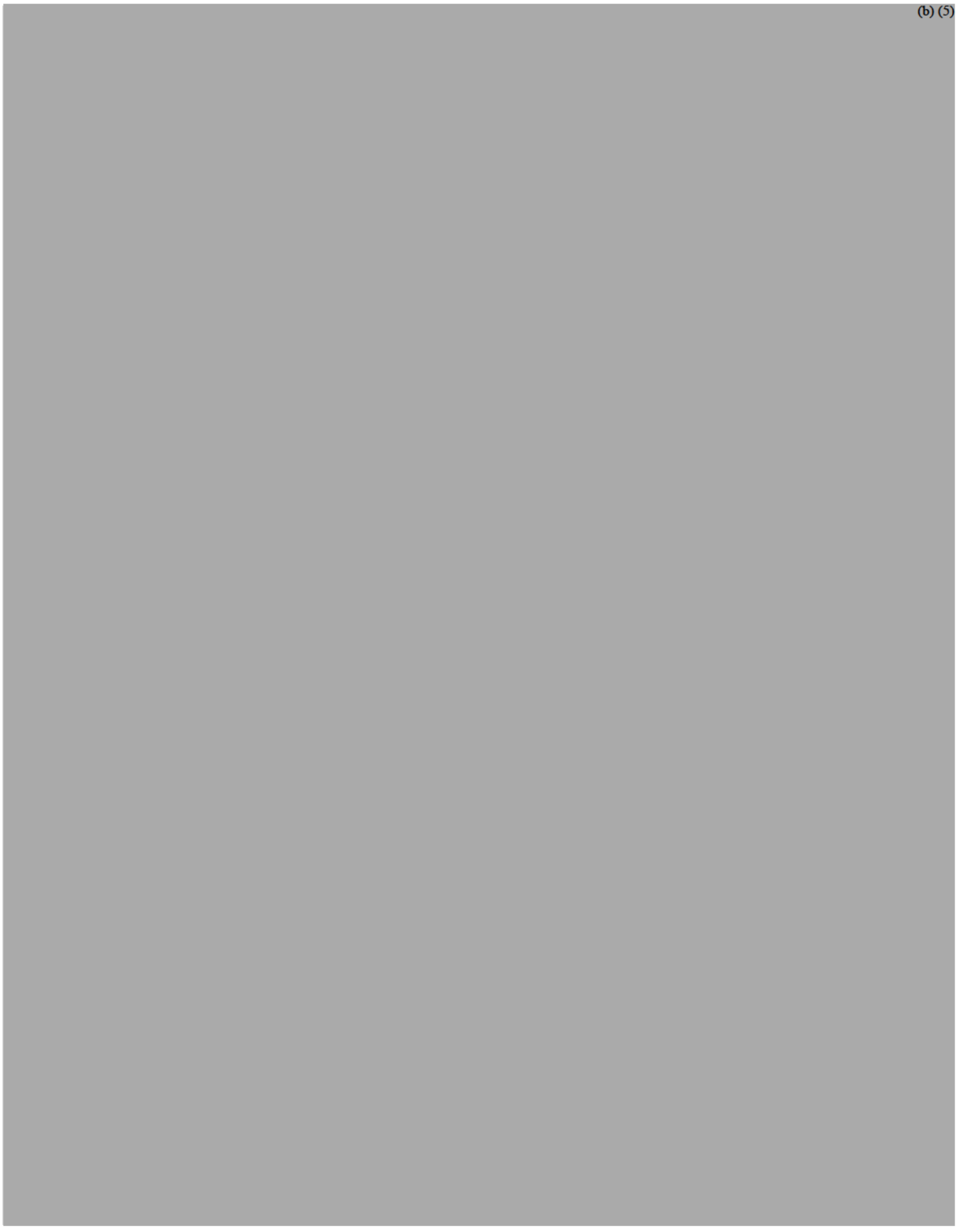
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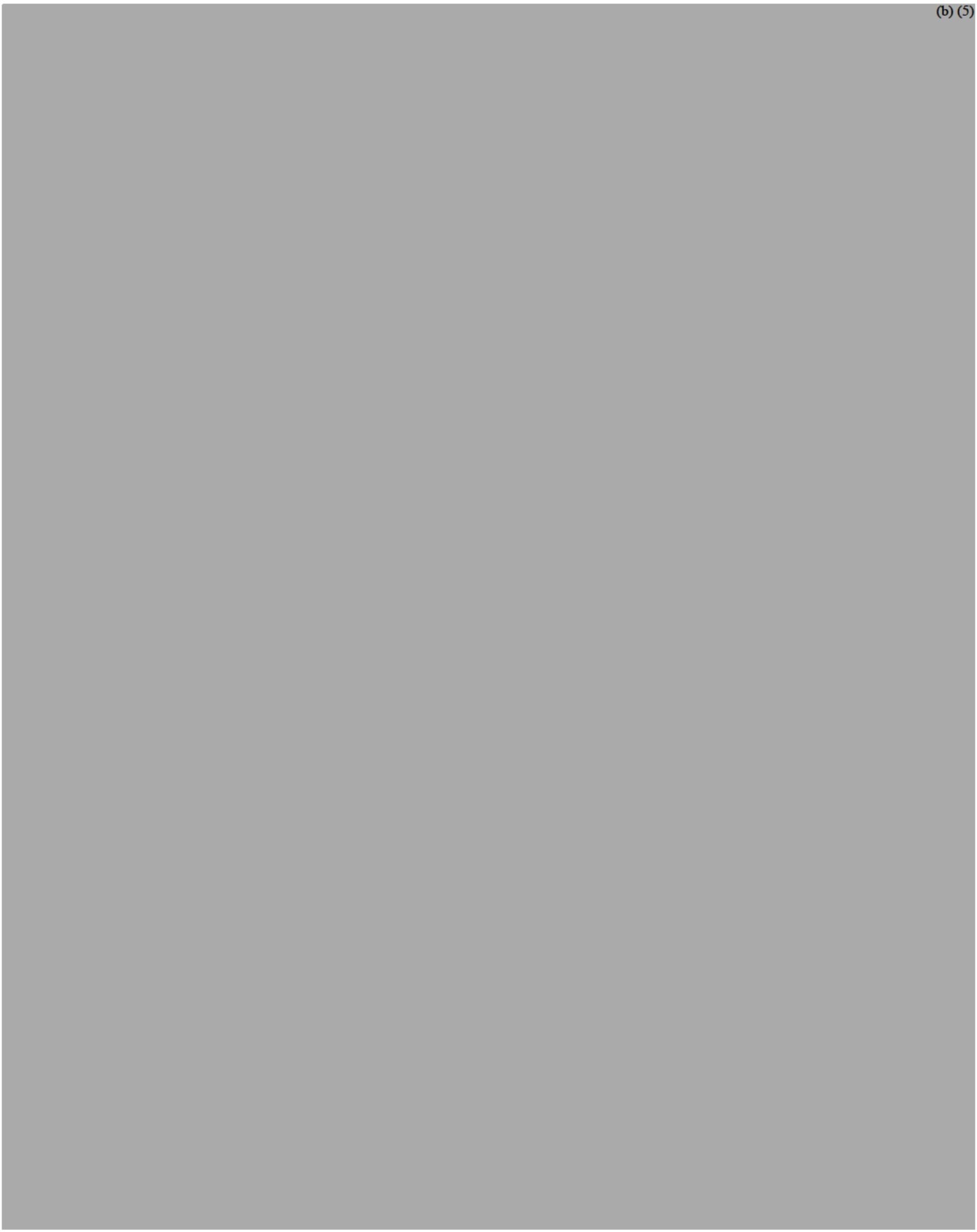
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Claude D. Pepper Older Americans Independence Centers

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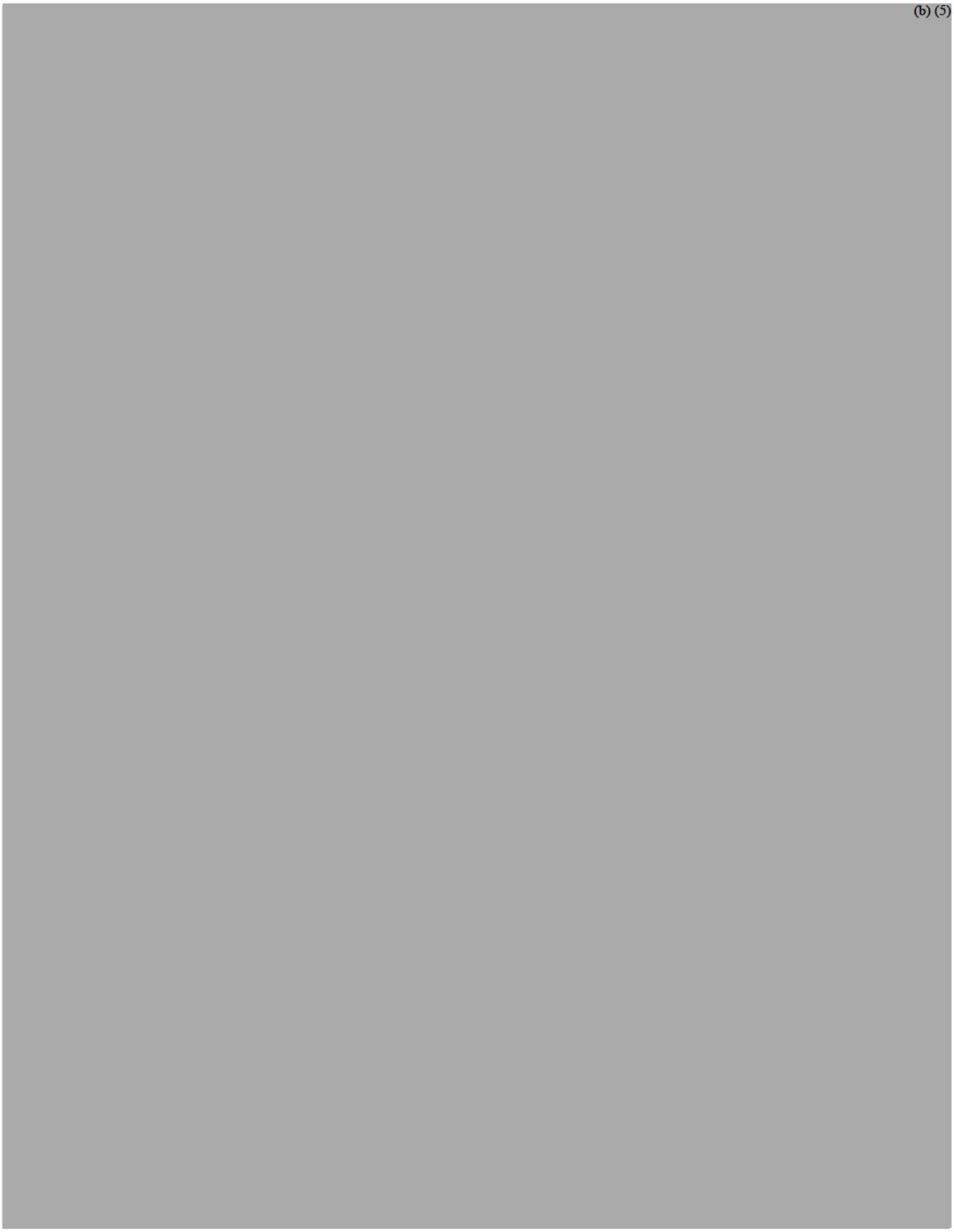

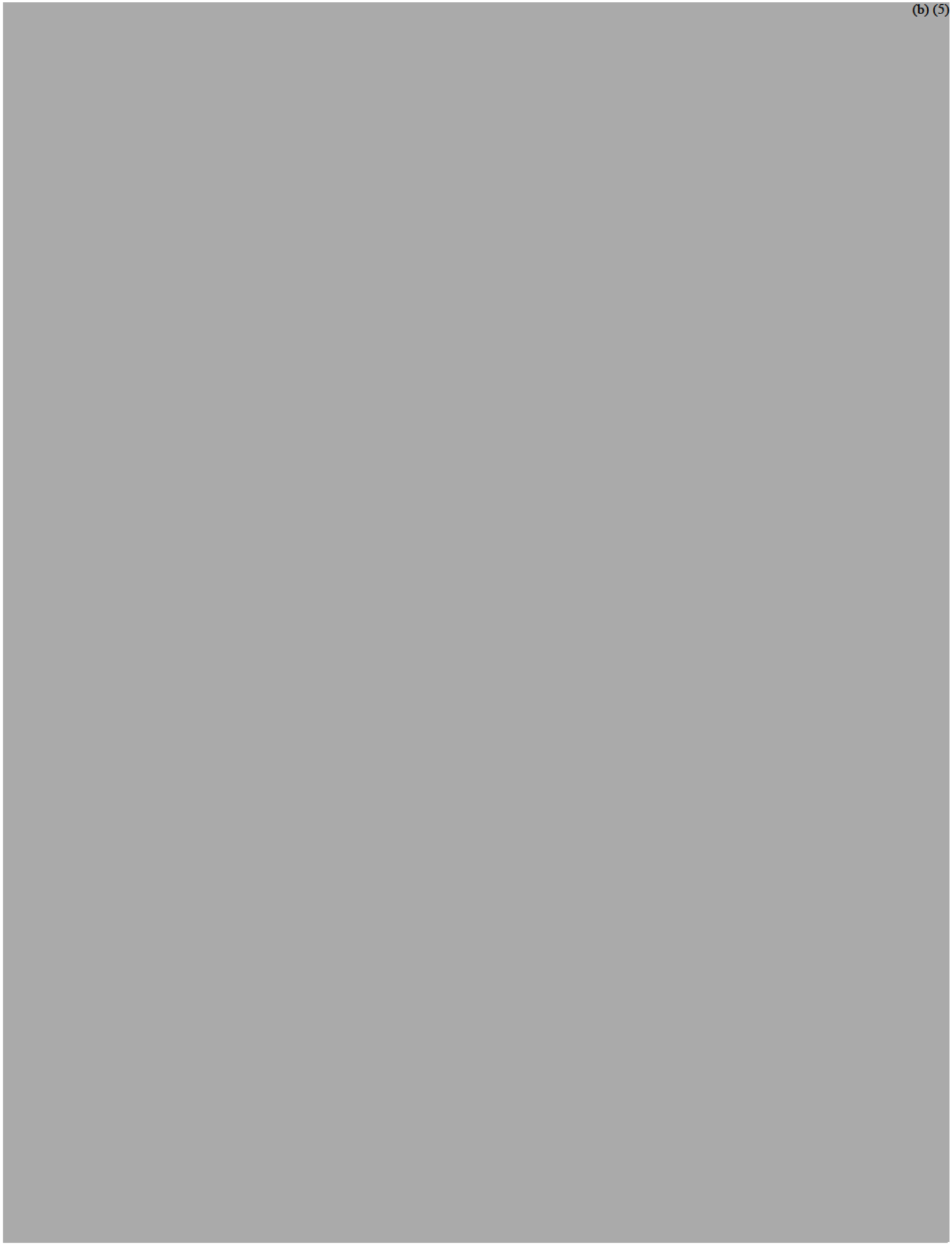
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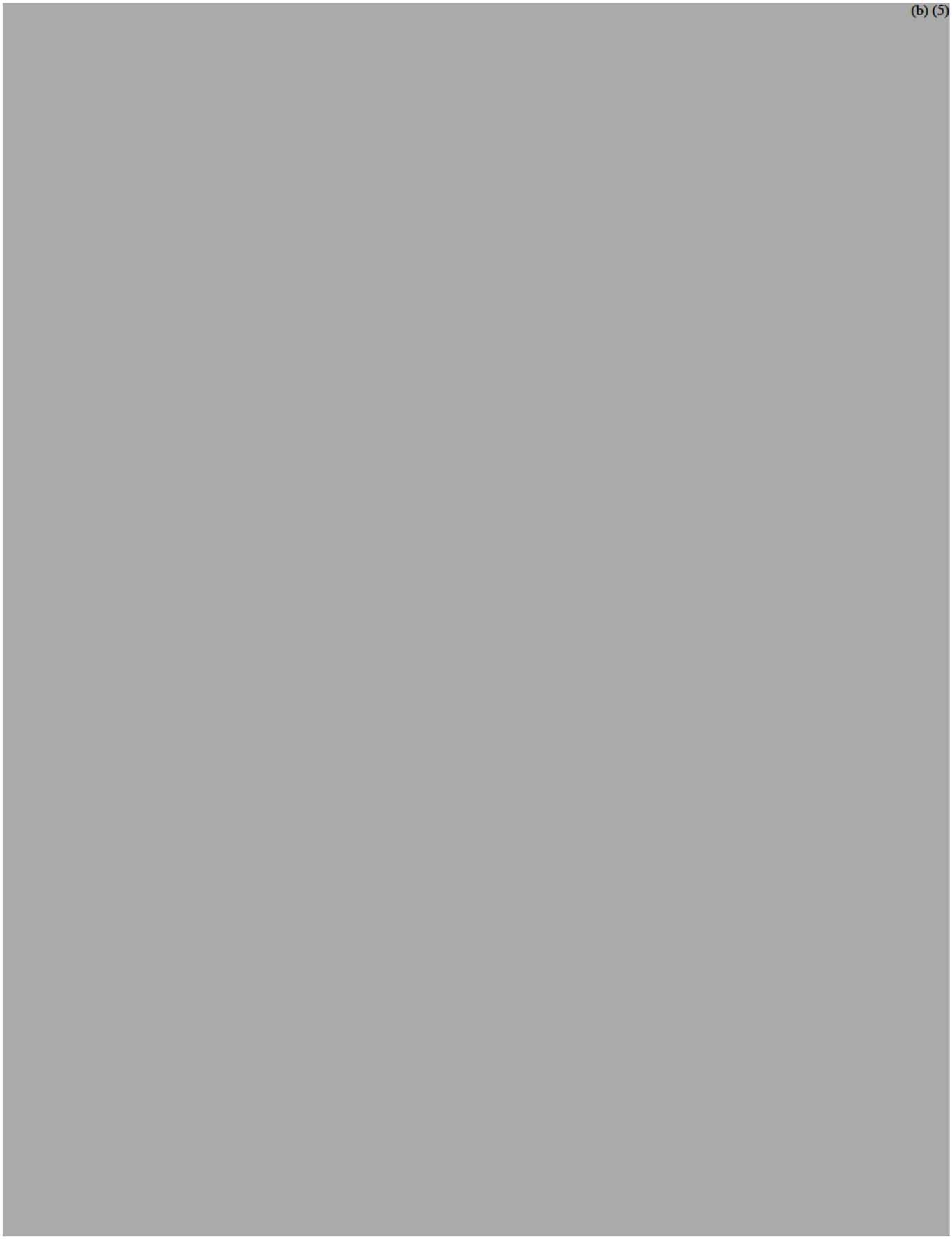
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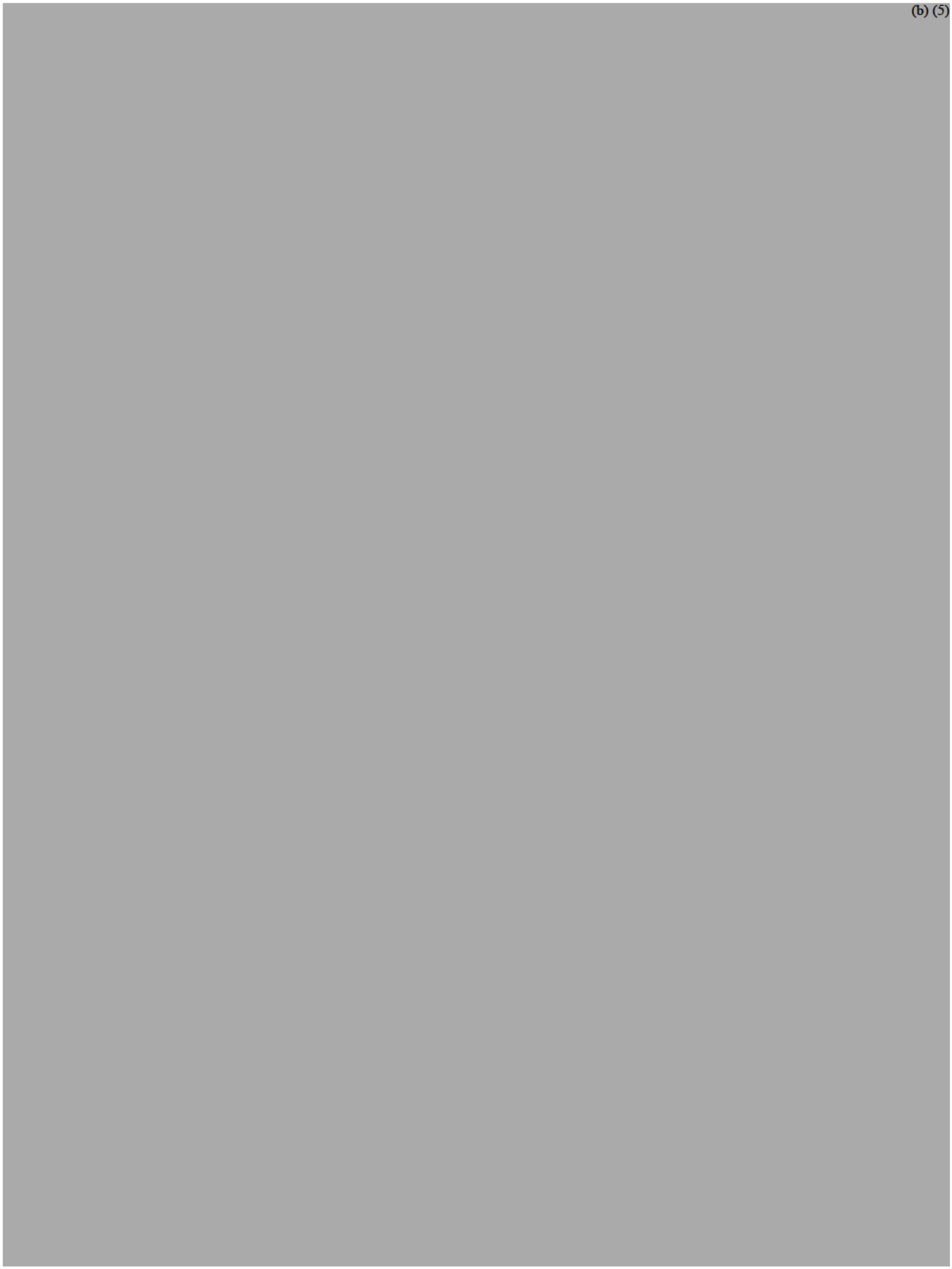
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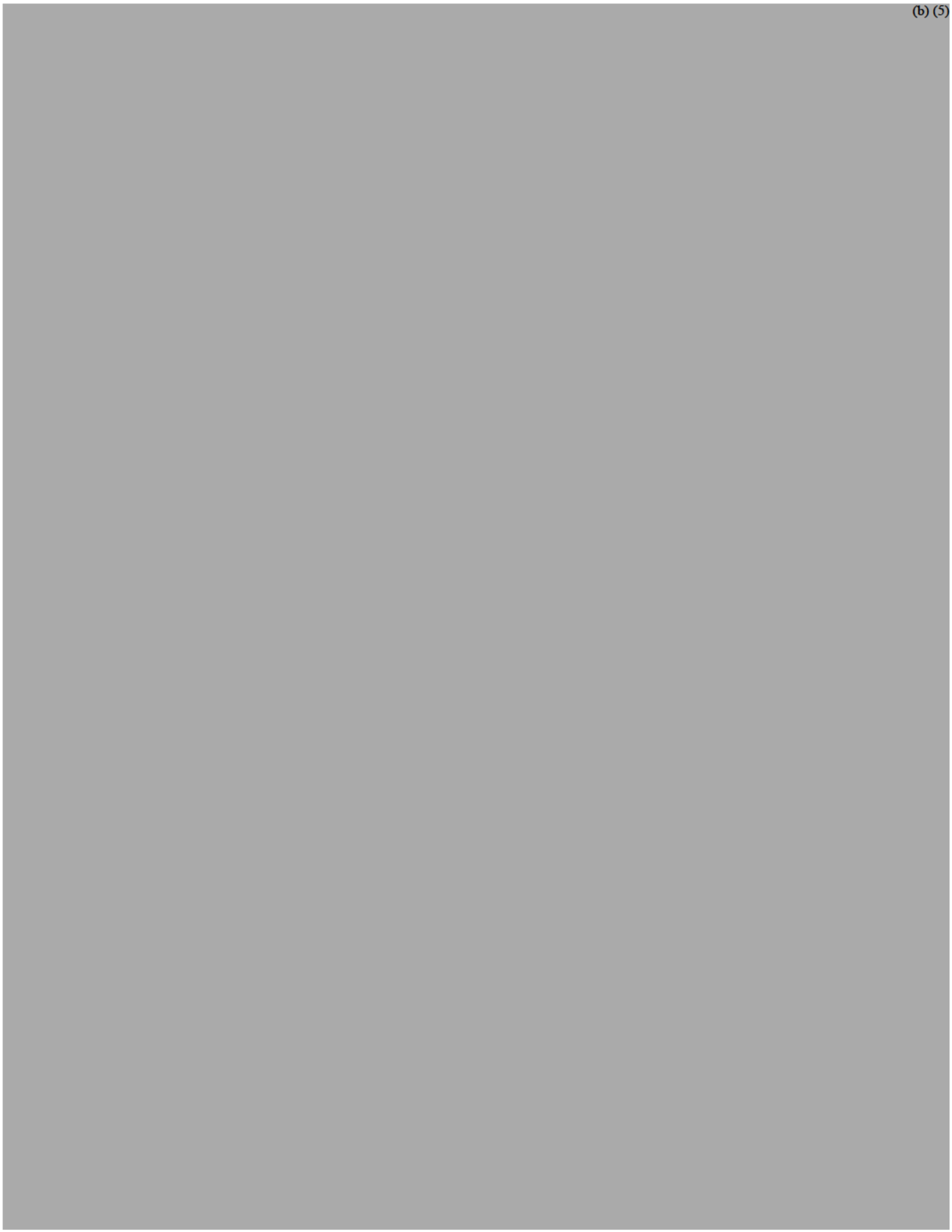
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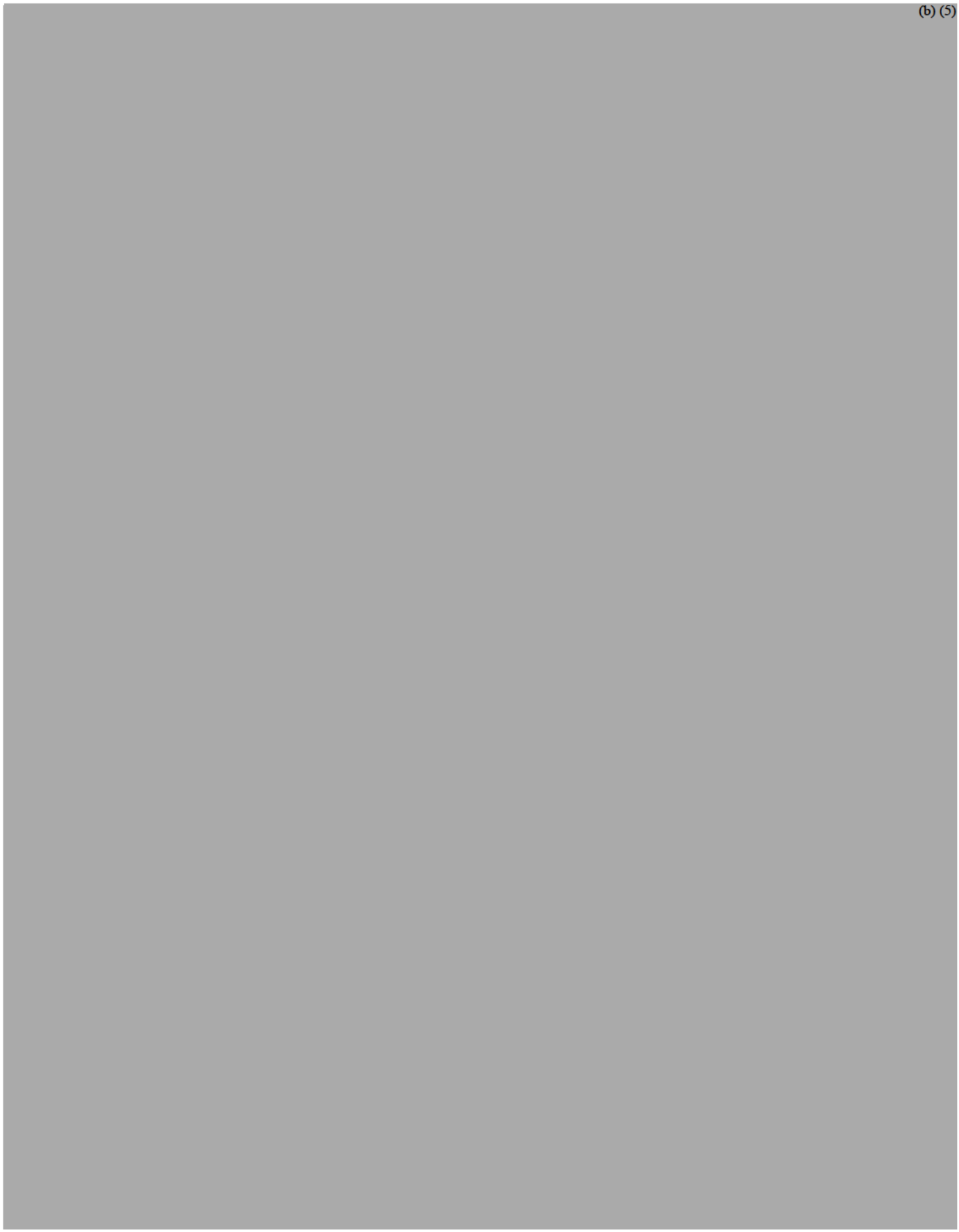
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Paul D. Wellstone Muscular Dystrophy Cooperative Research Centers

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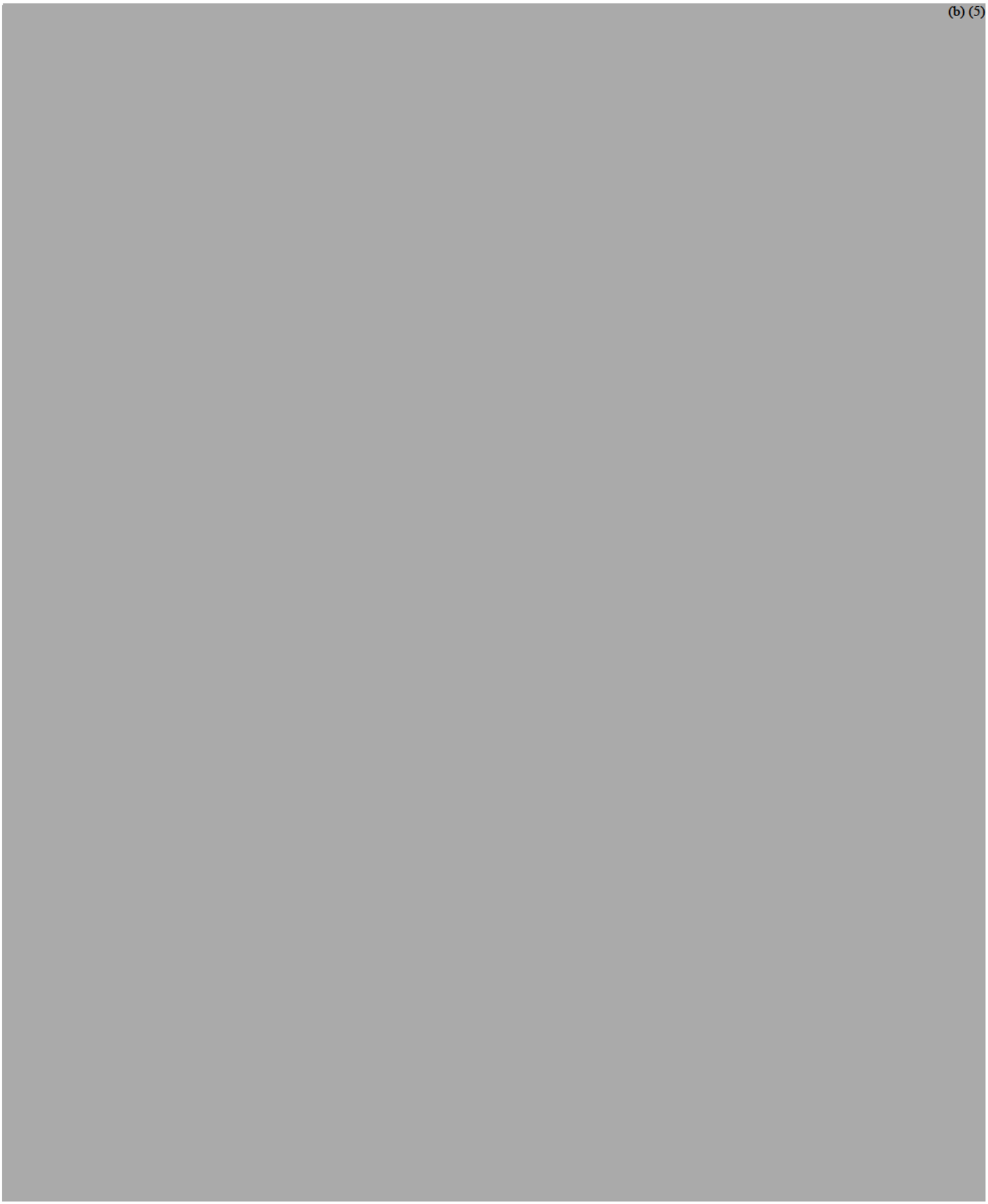
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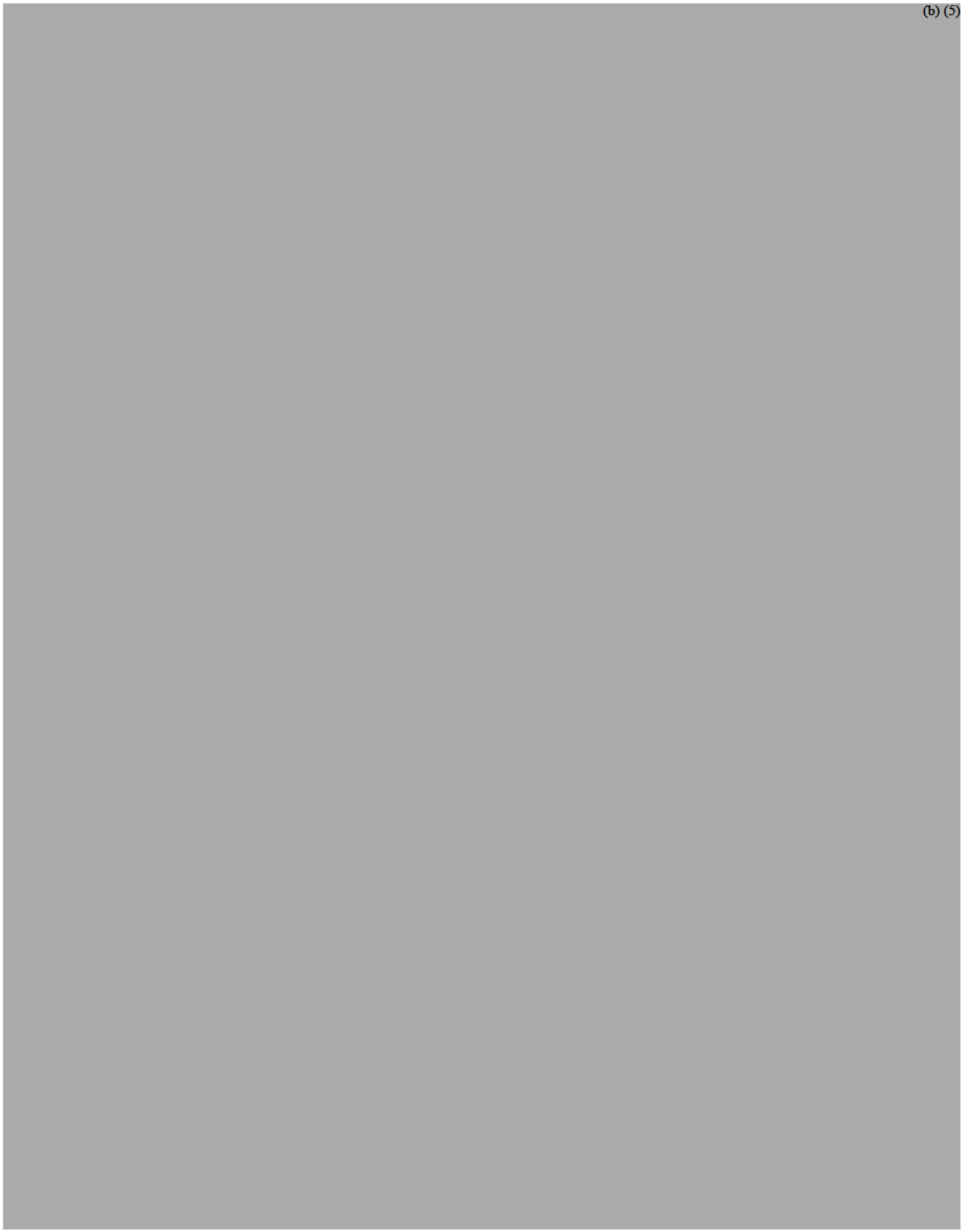
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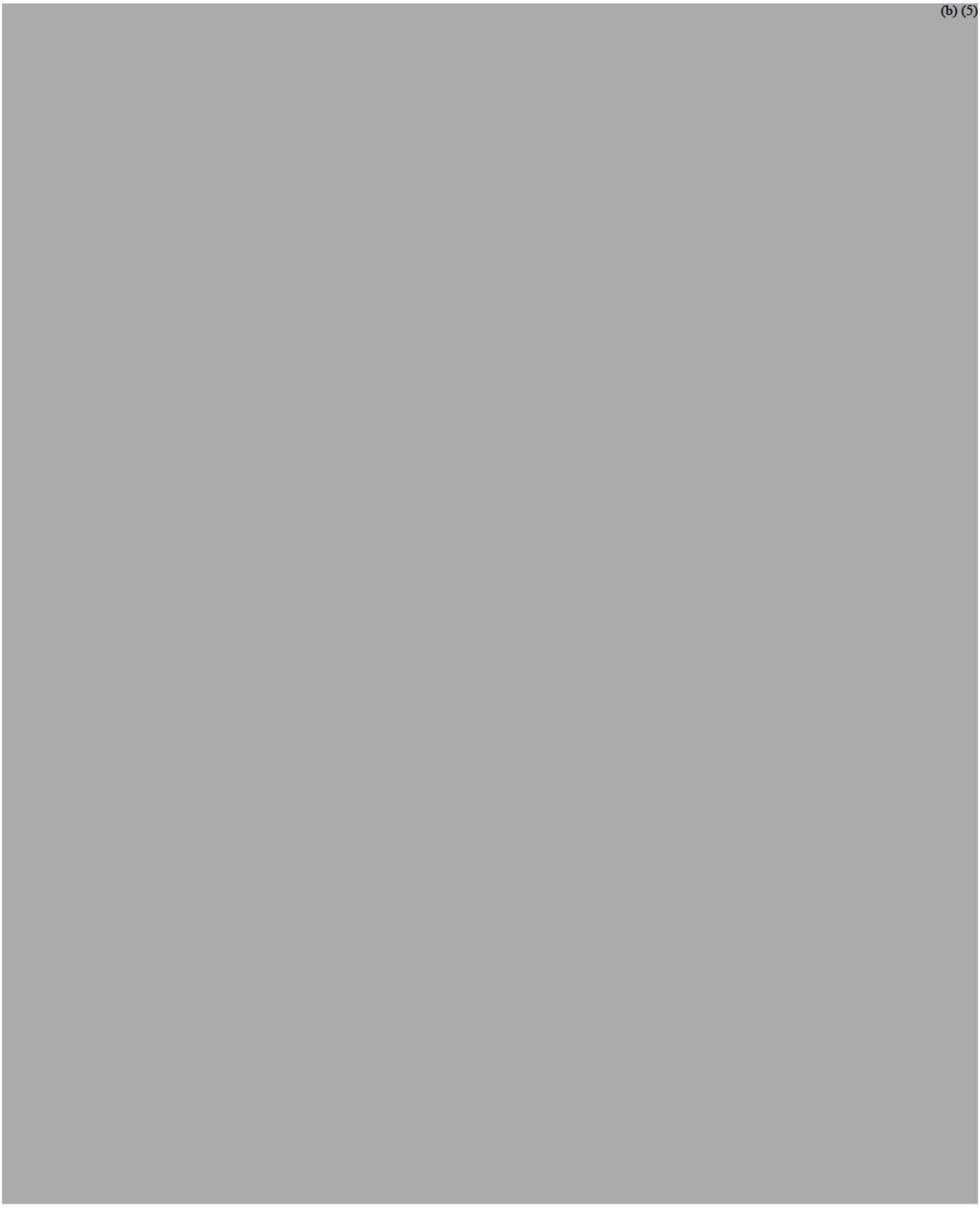
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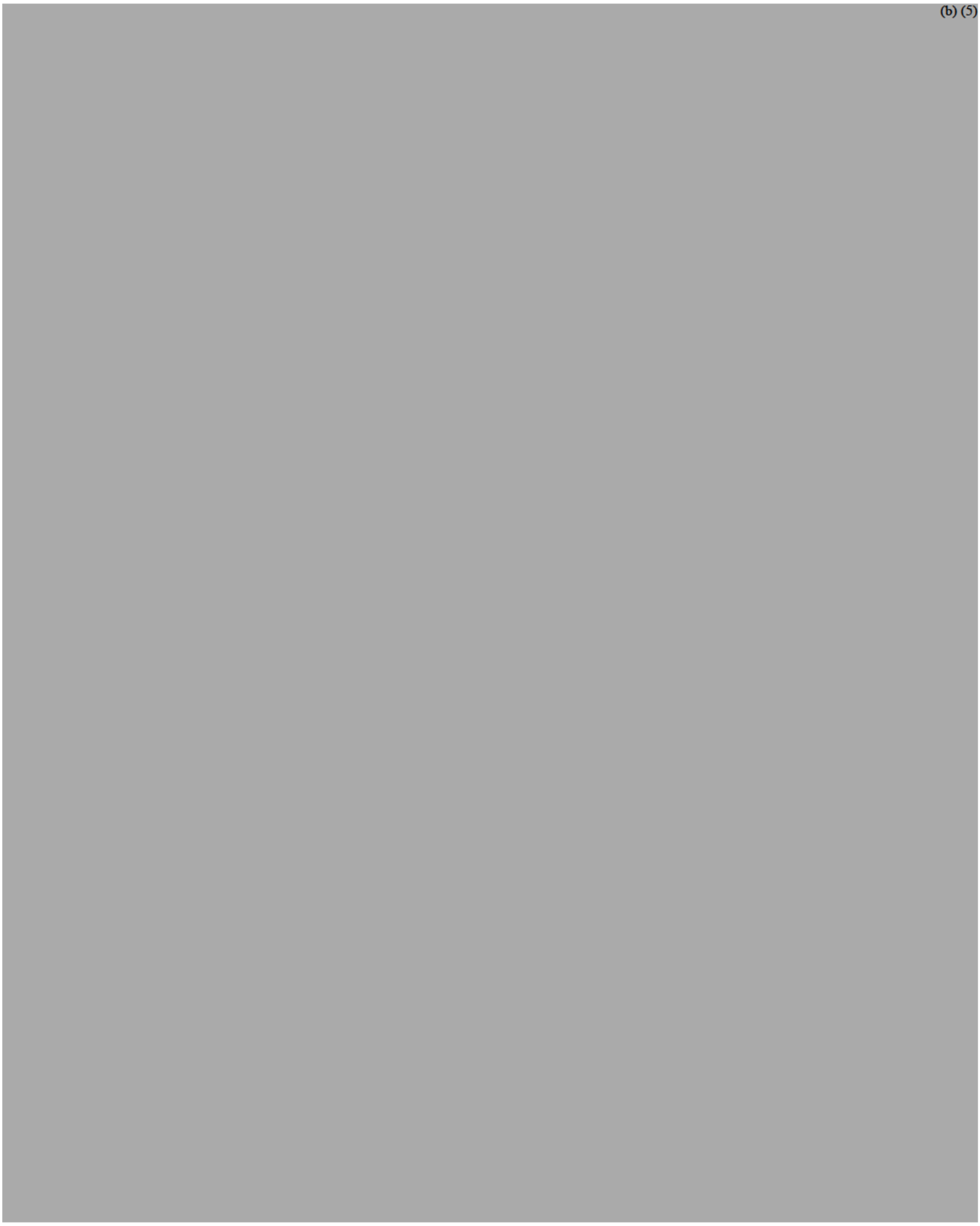
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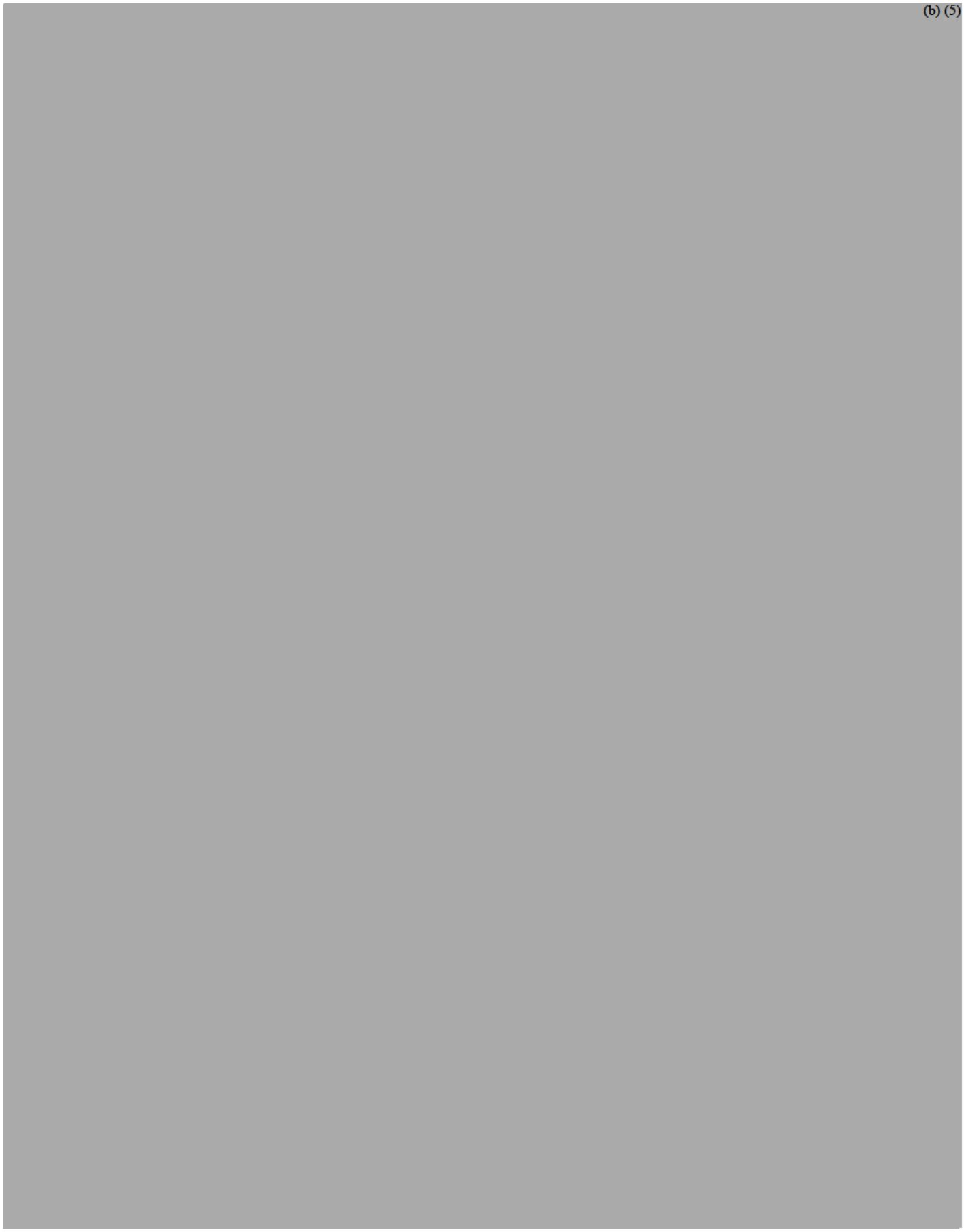
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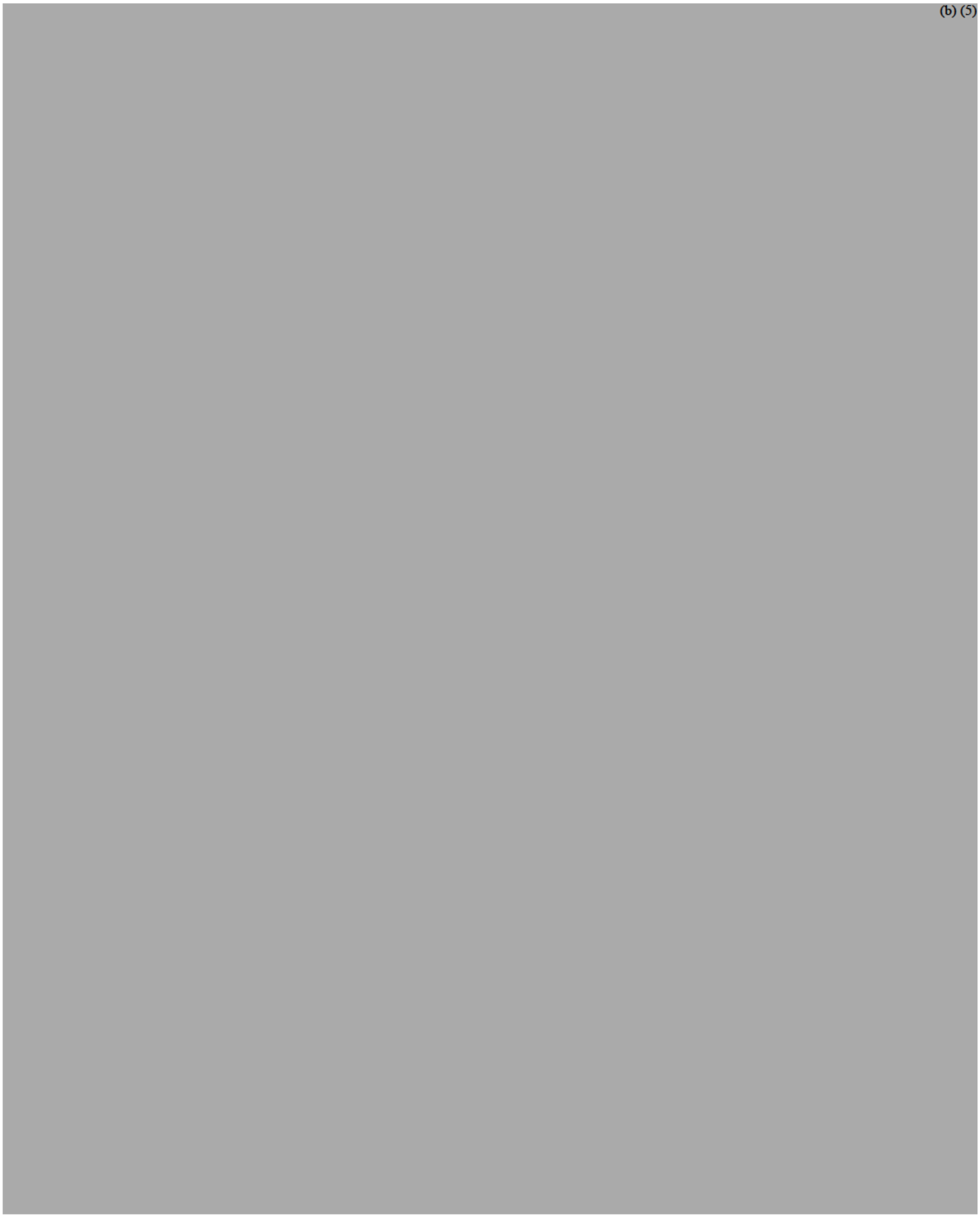
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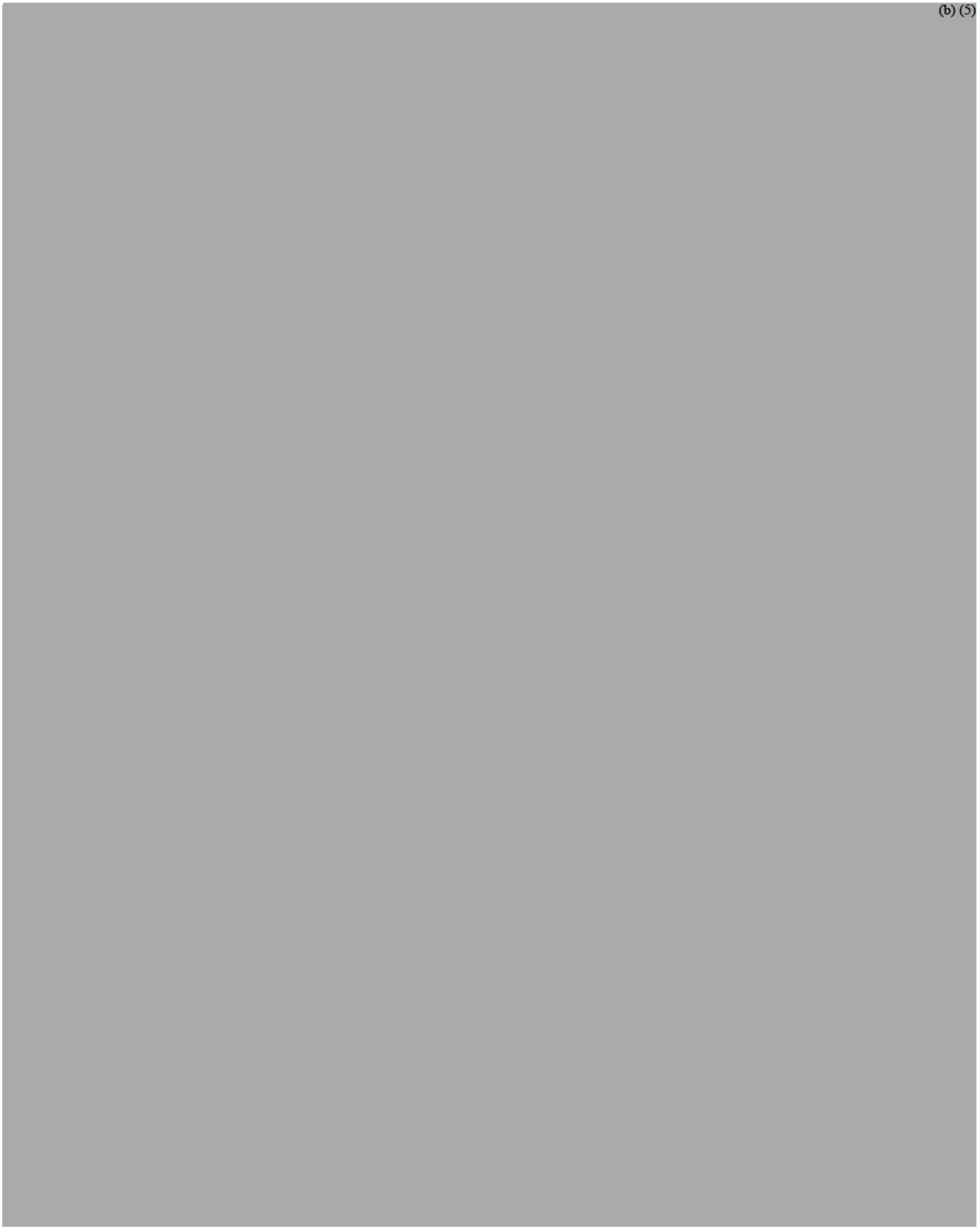
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National Institute on Minority Health and Health Disparities Centers of Excellence

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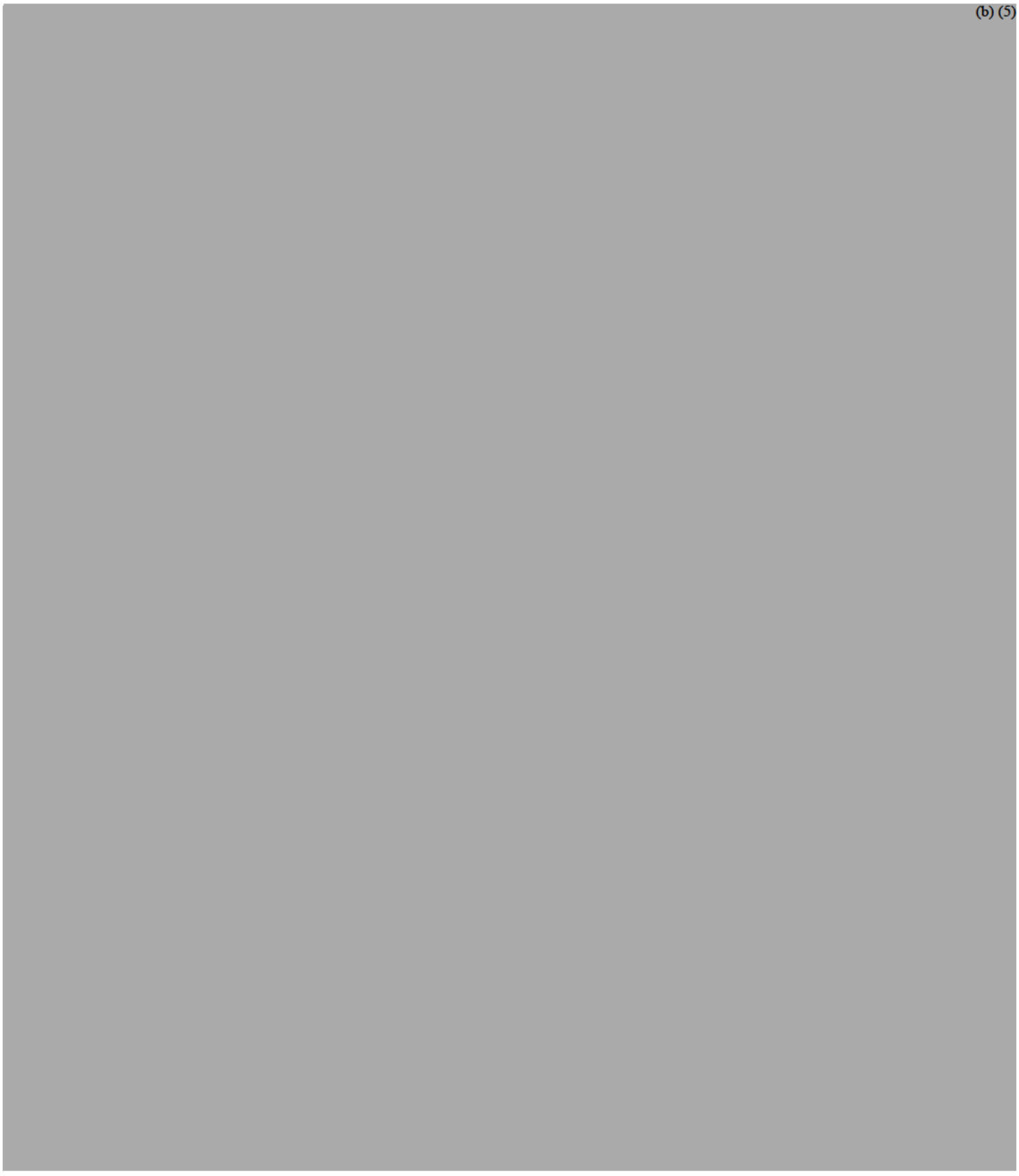

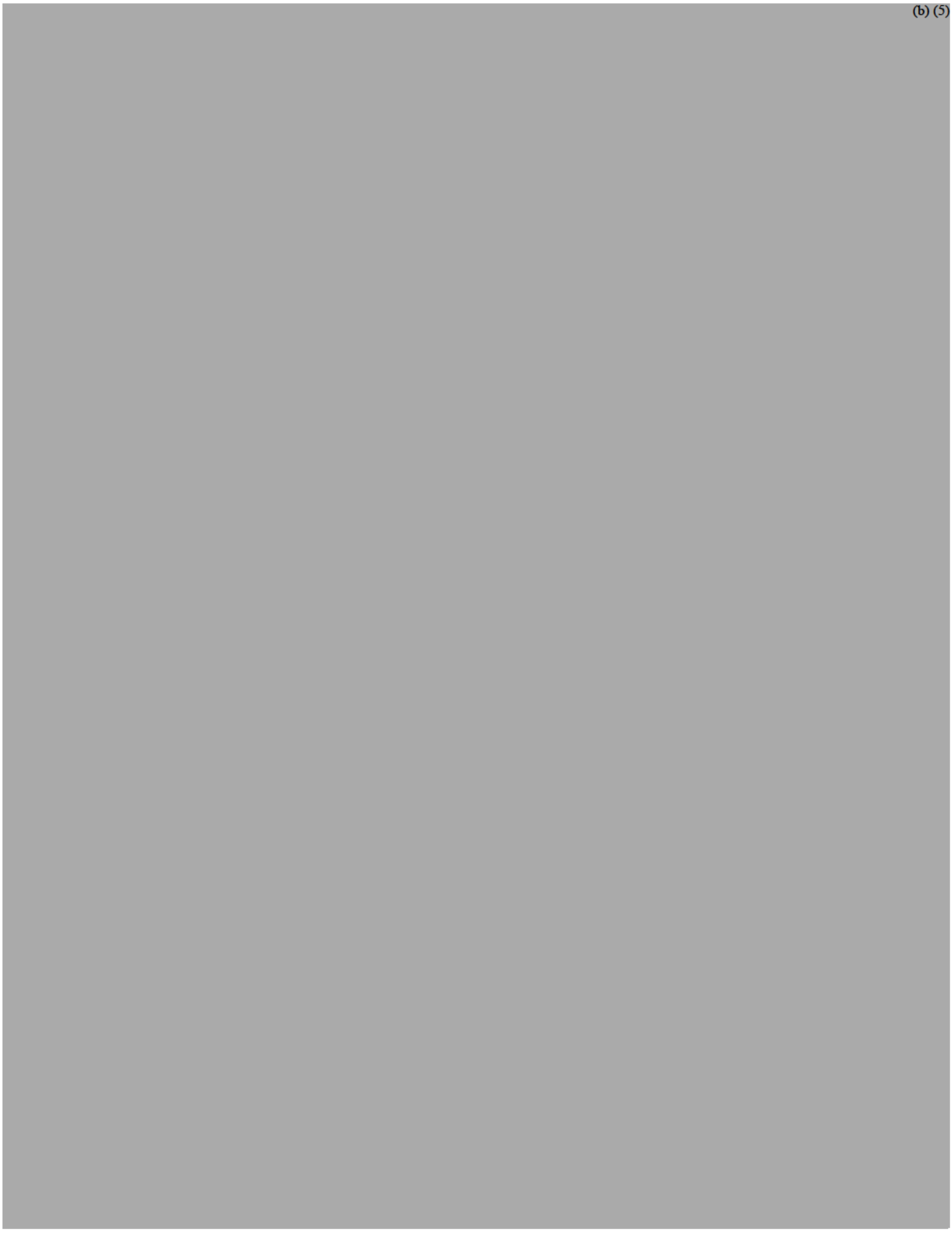
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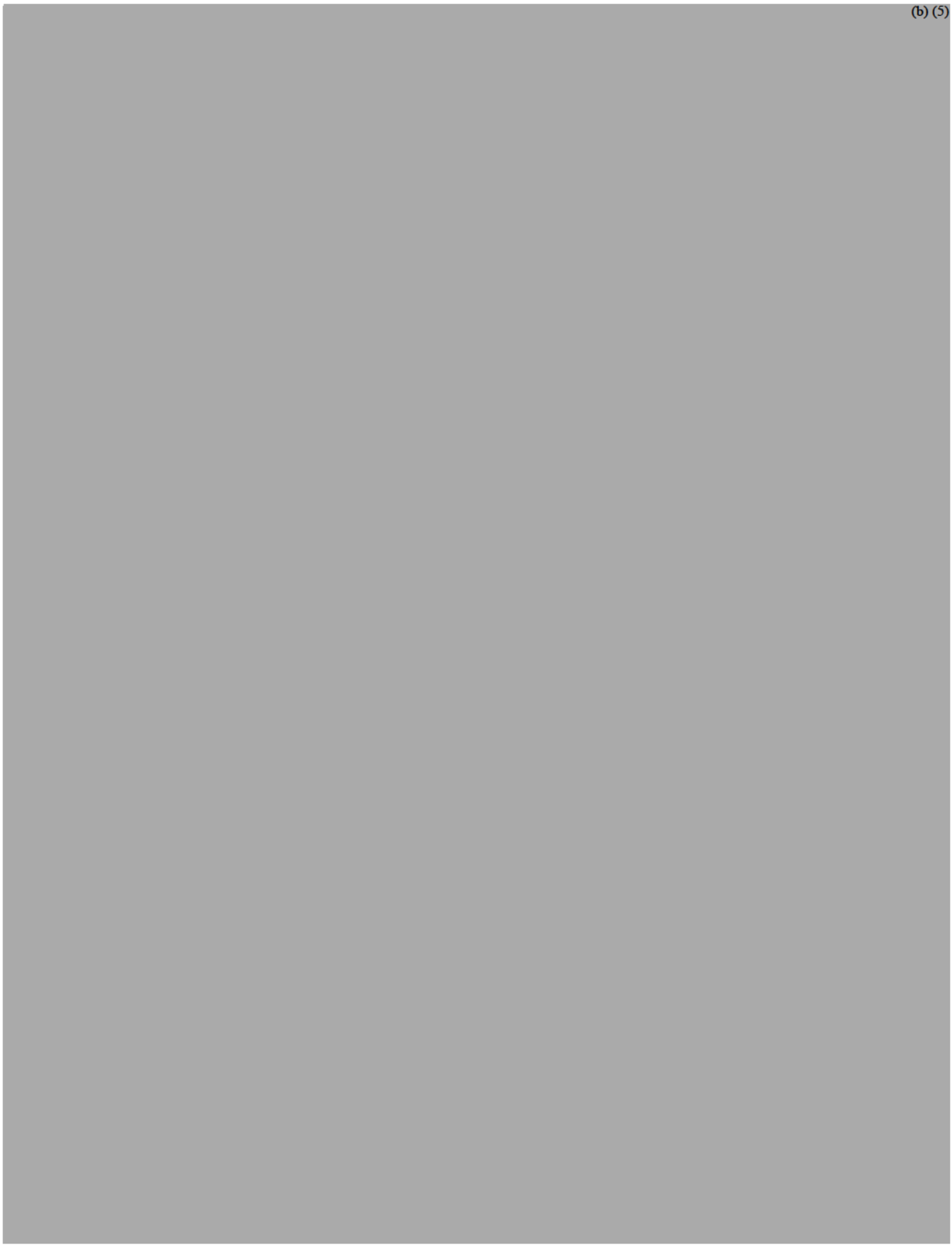
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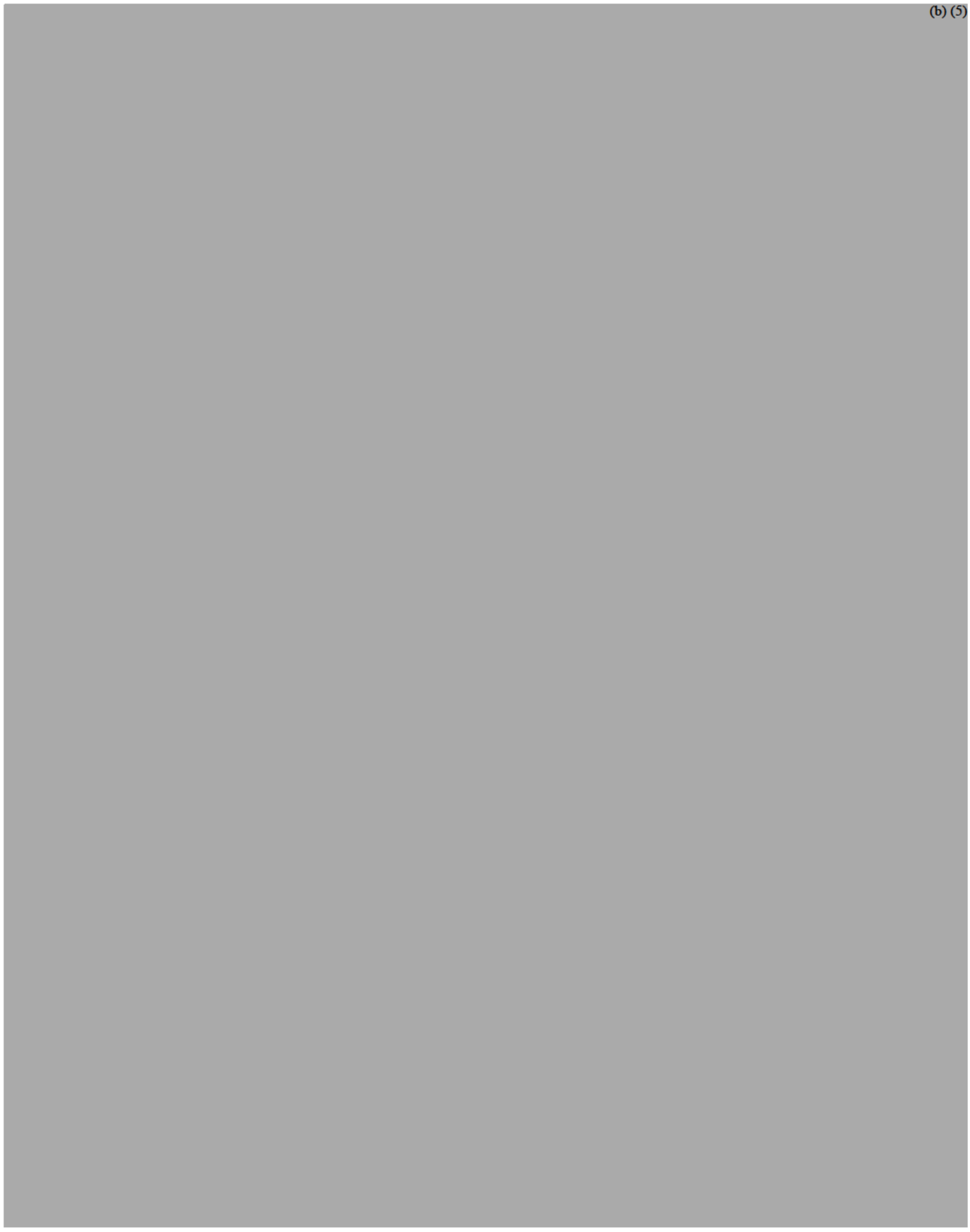
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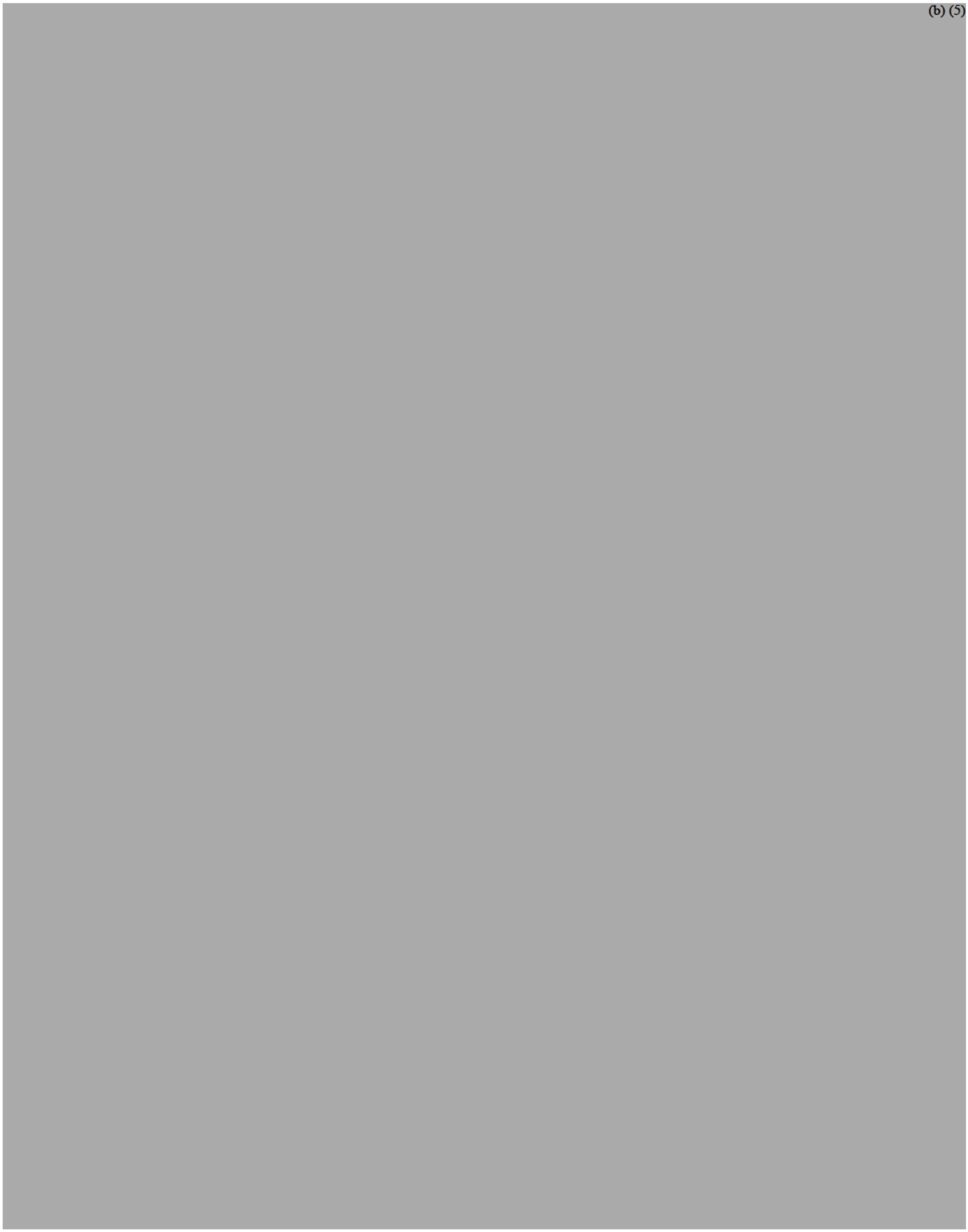
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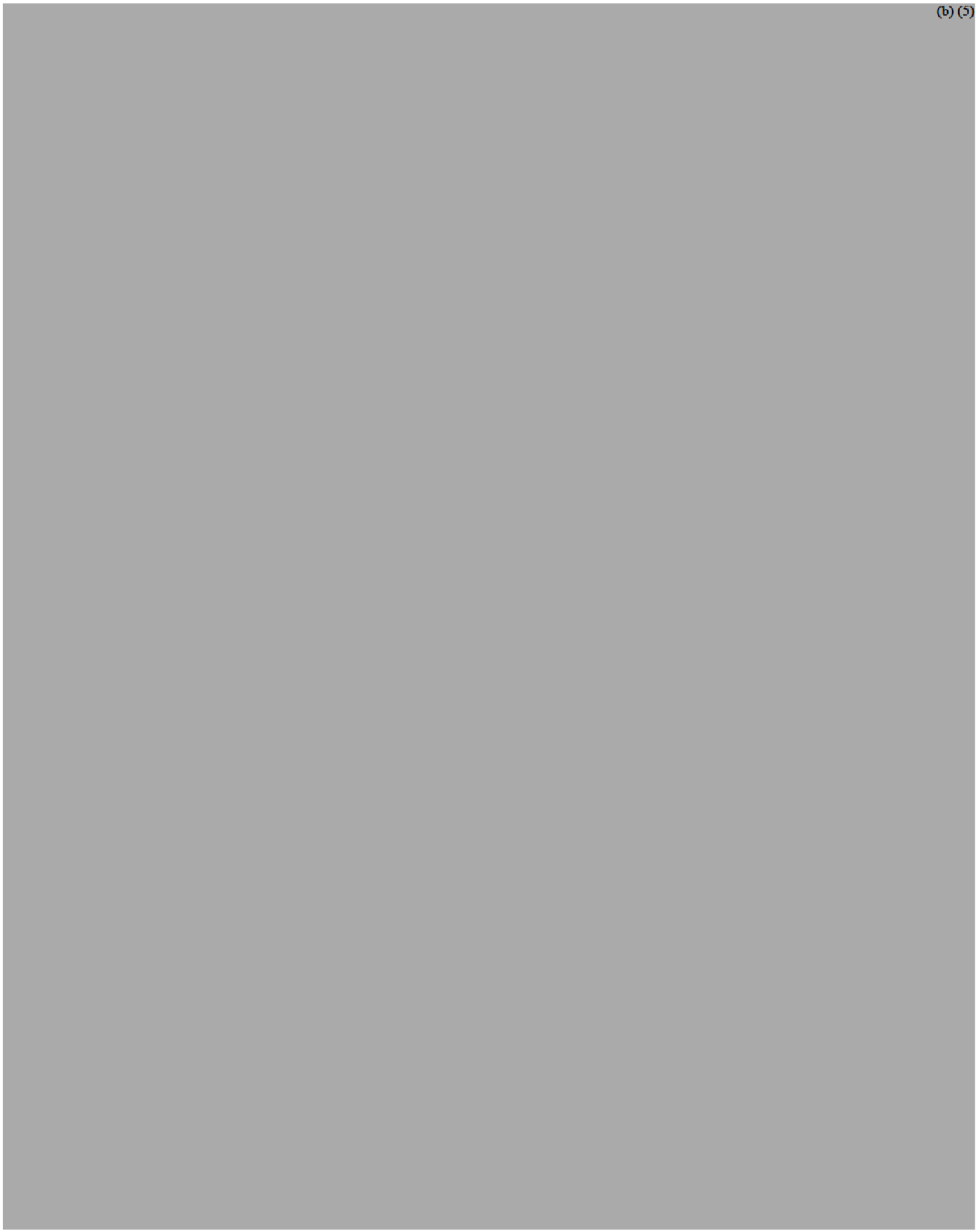
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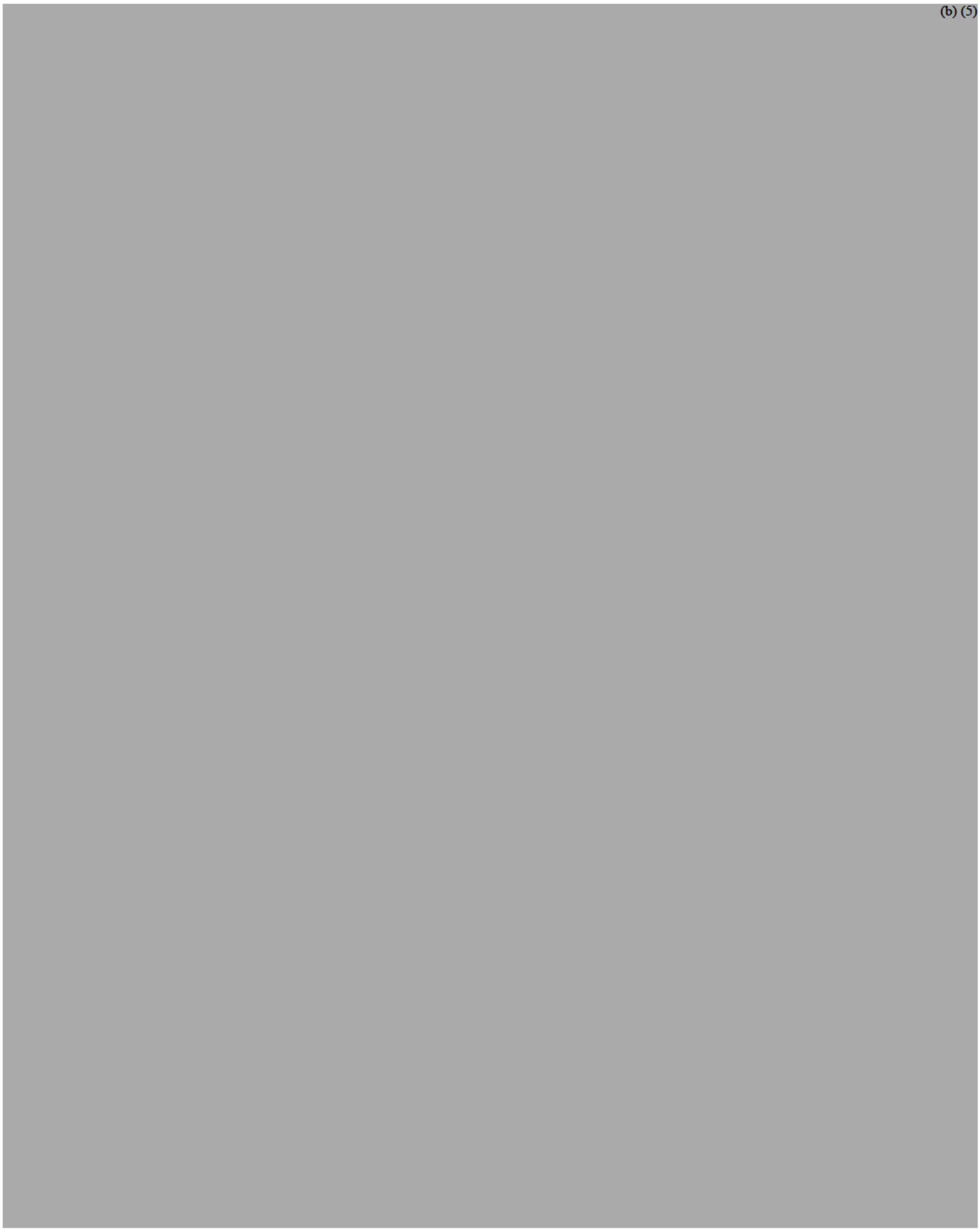
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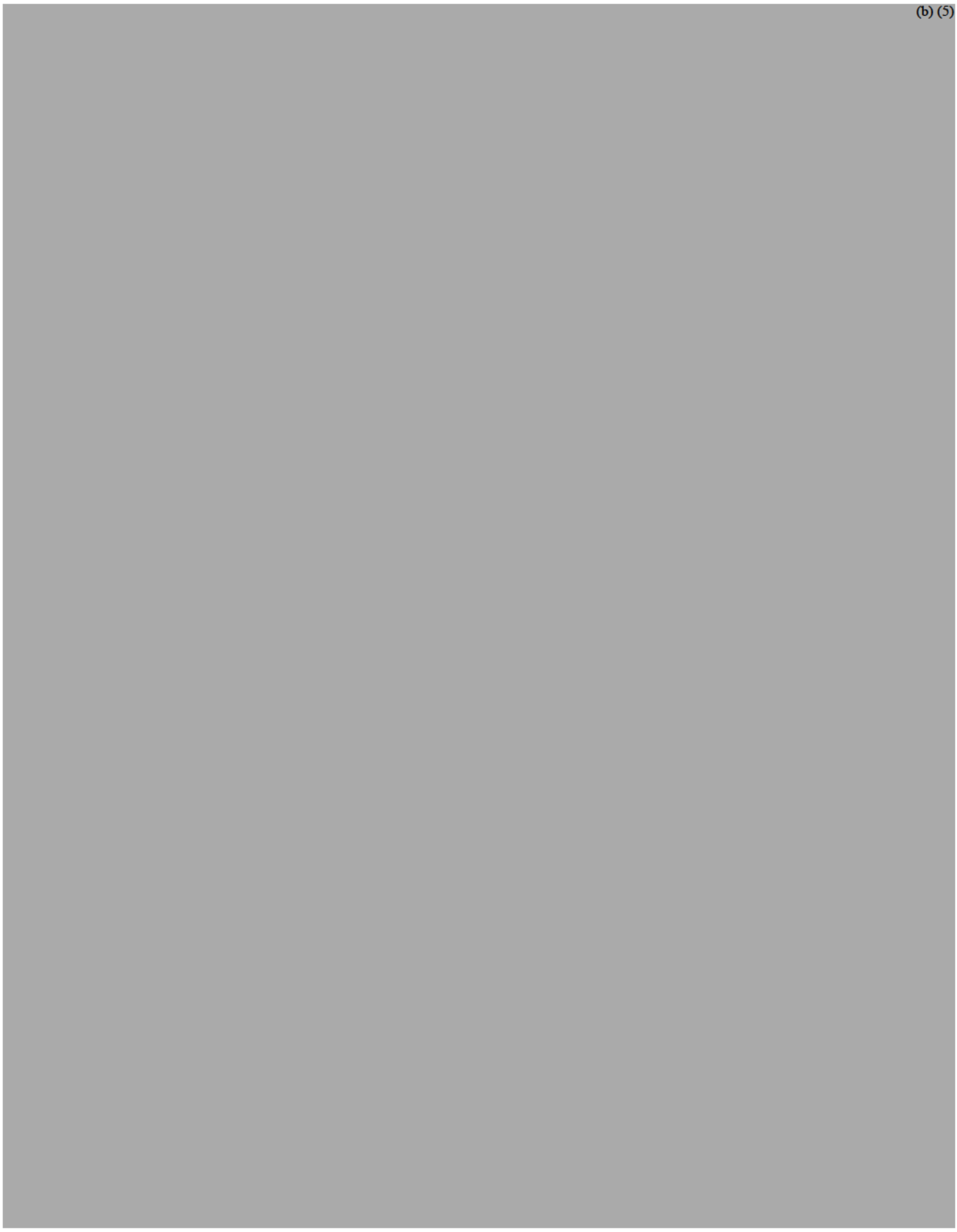
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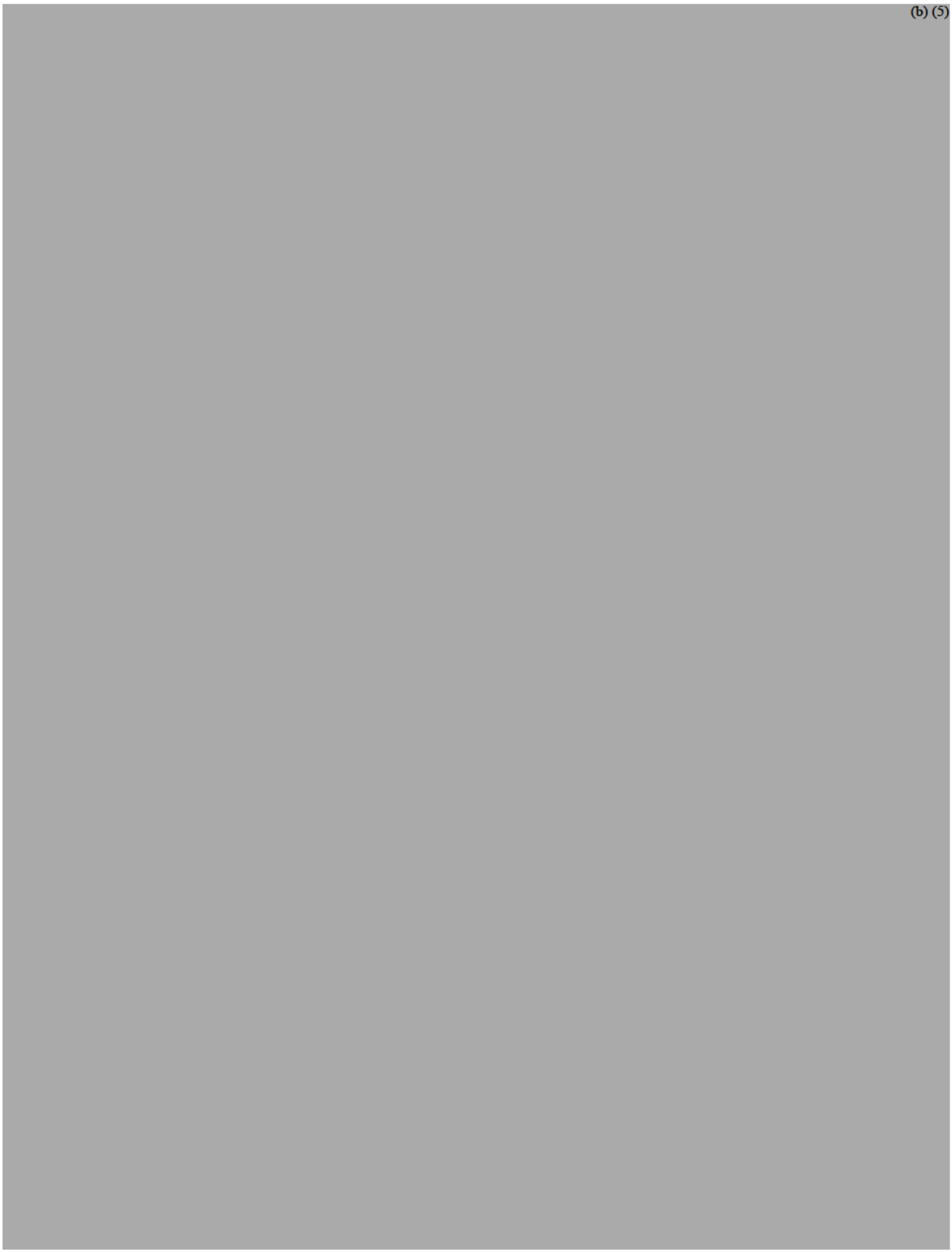
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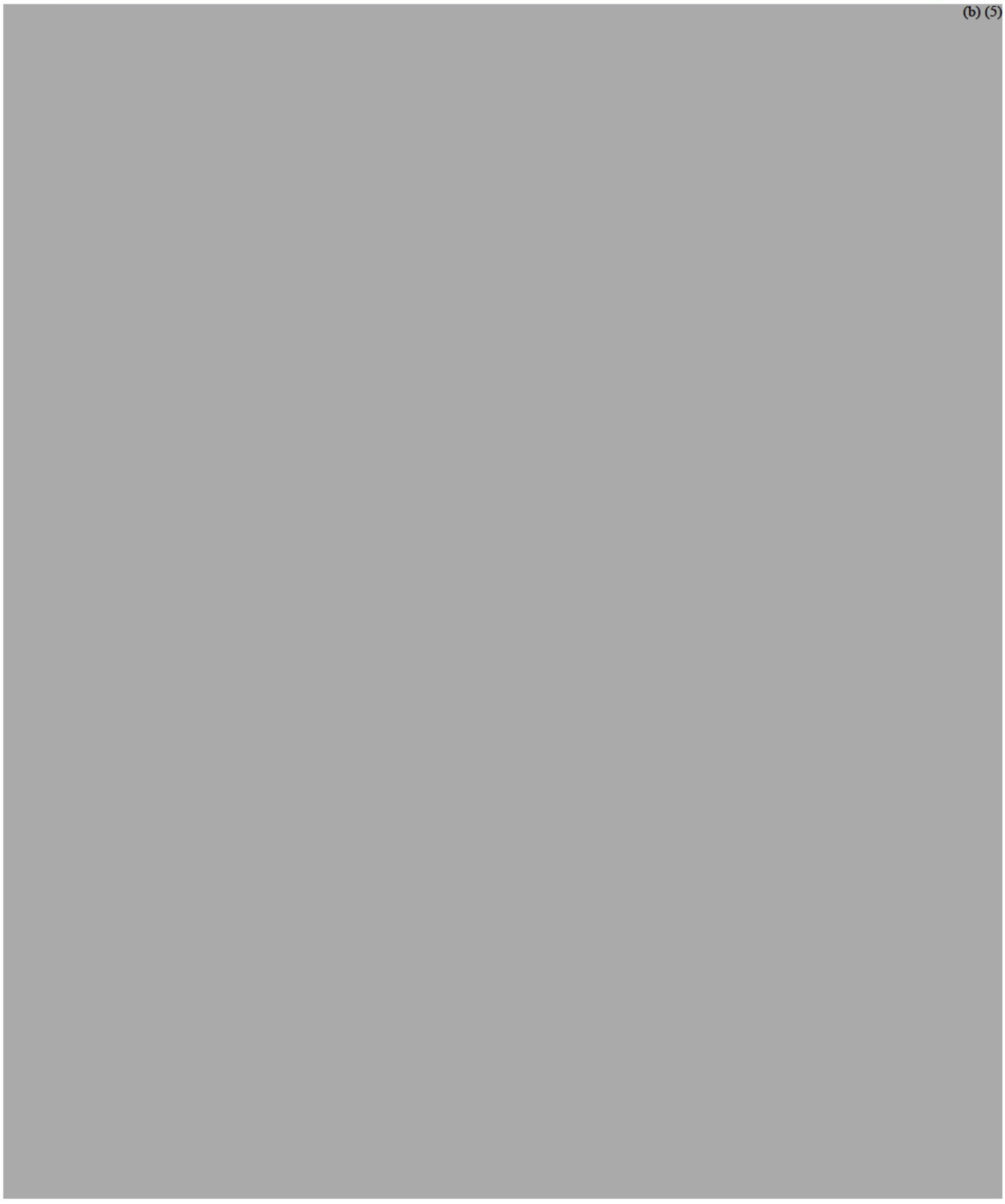
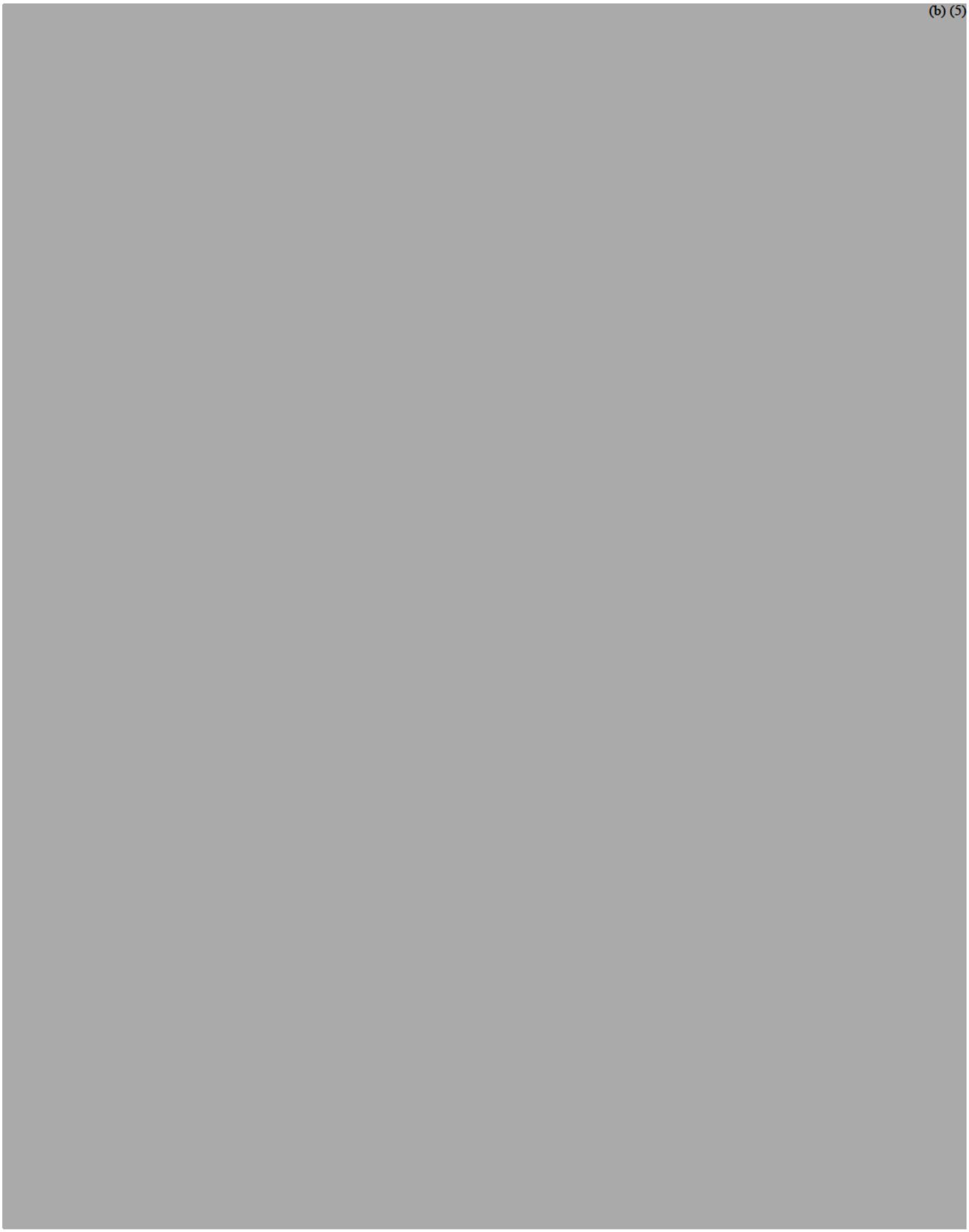
Rare Diseases Clinical Research Network

(b) (5)

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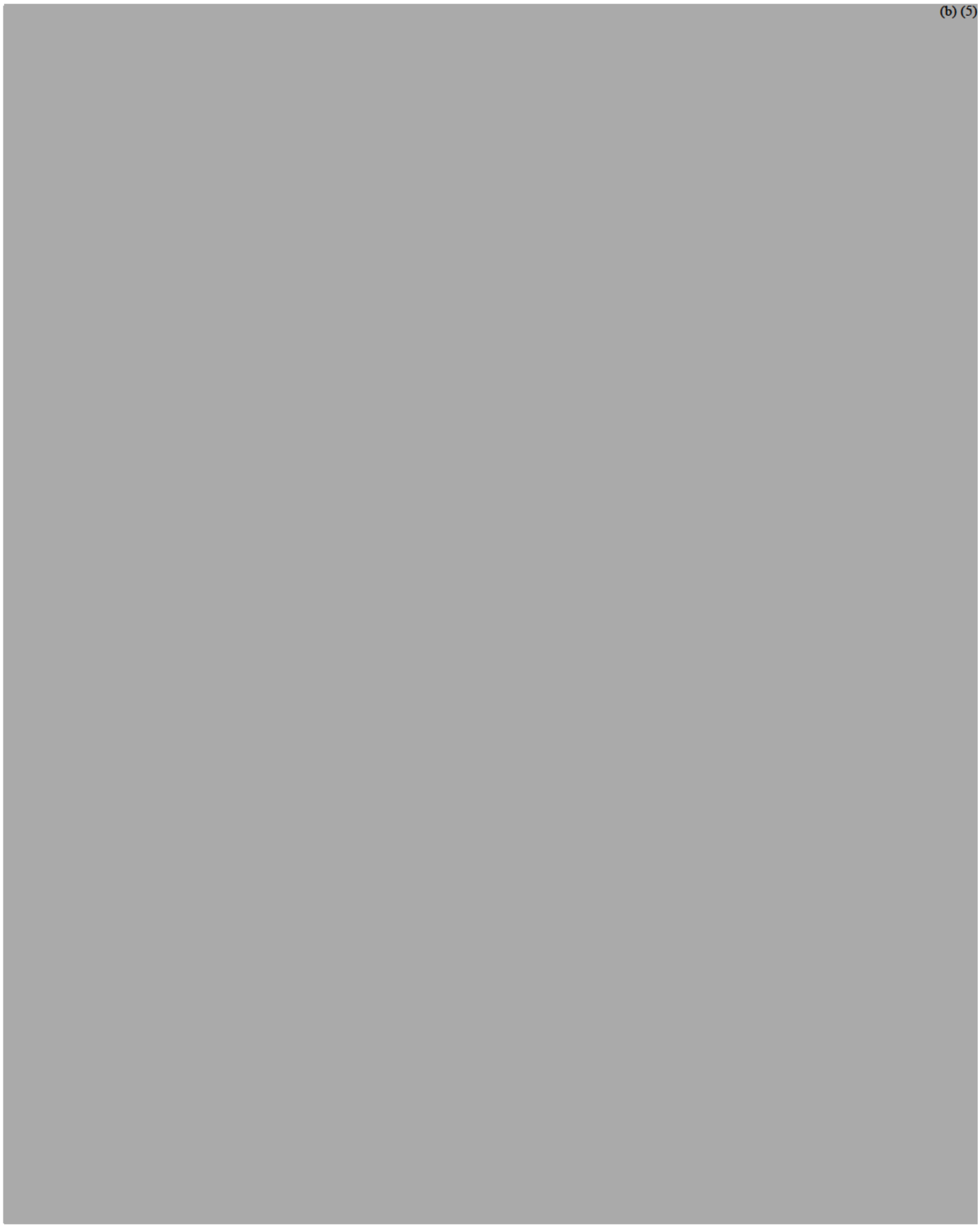
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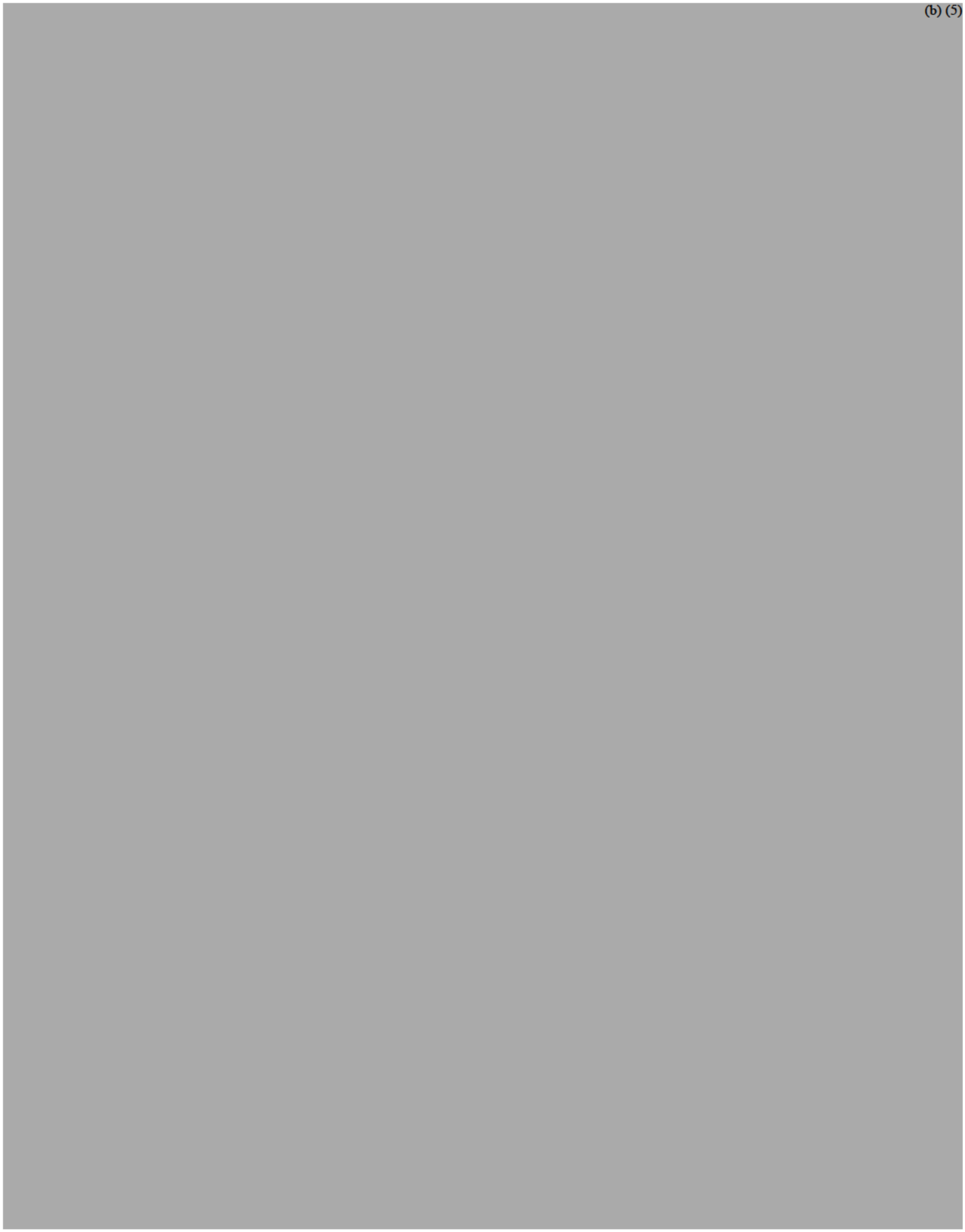
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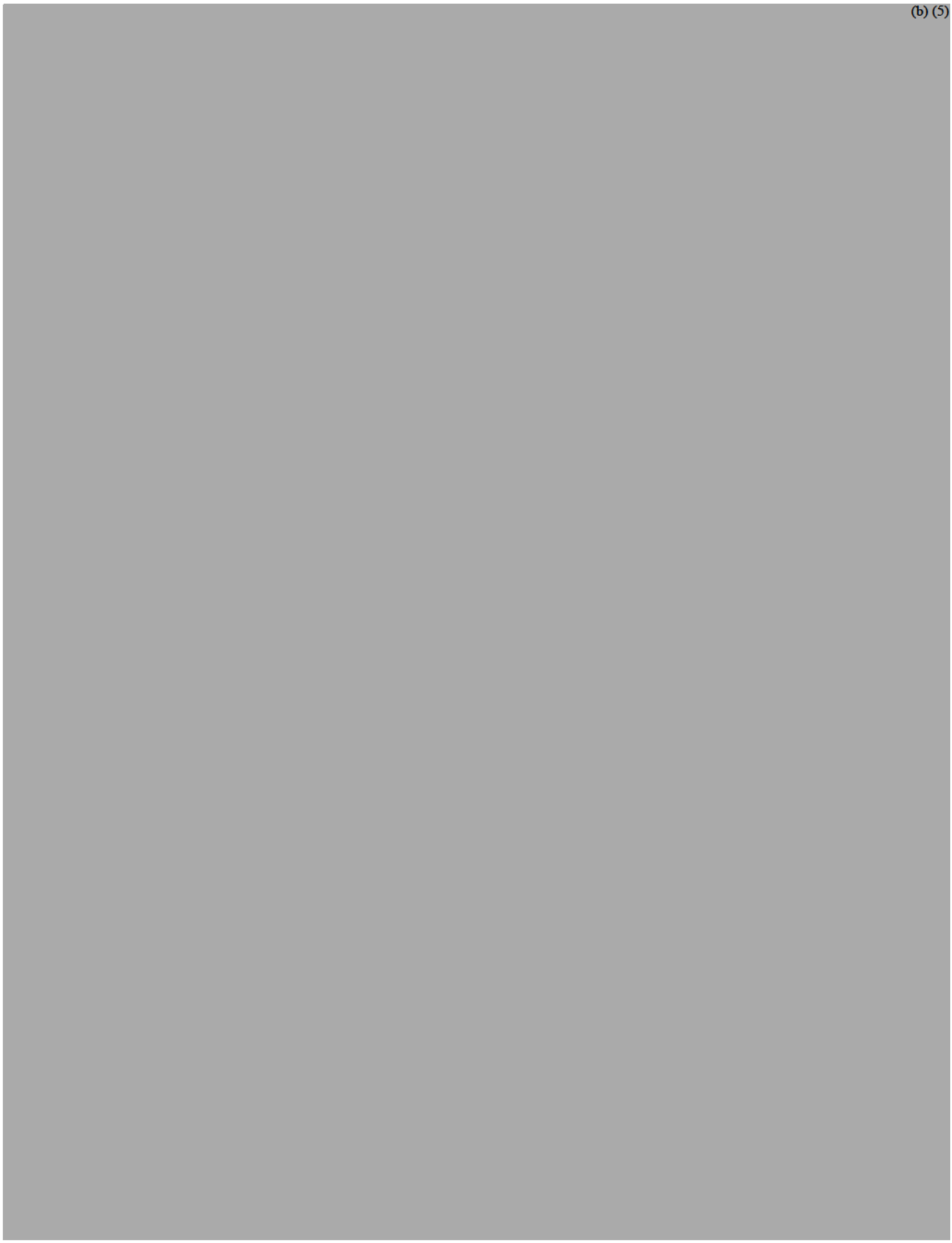
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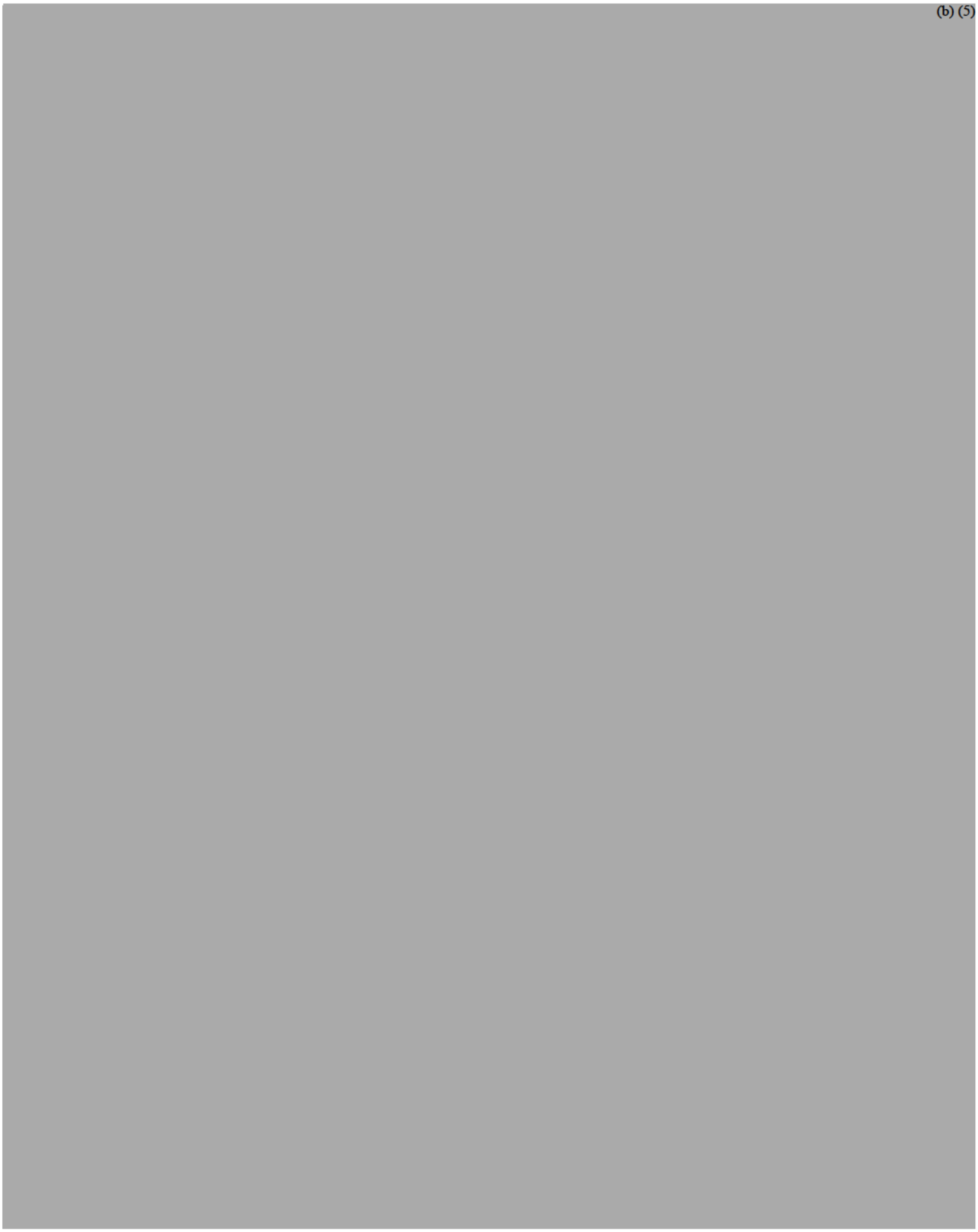
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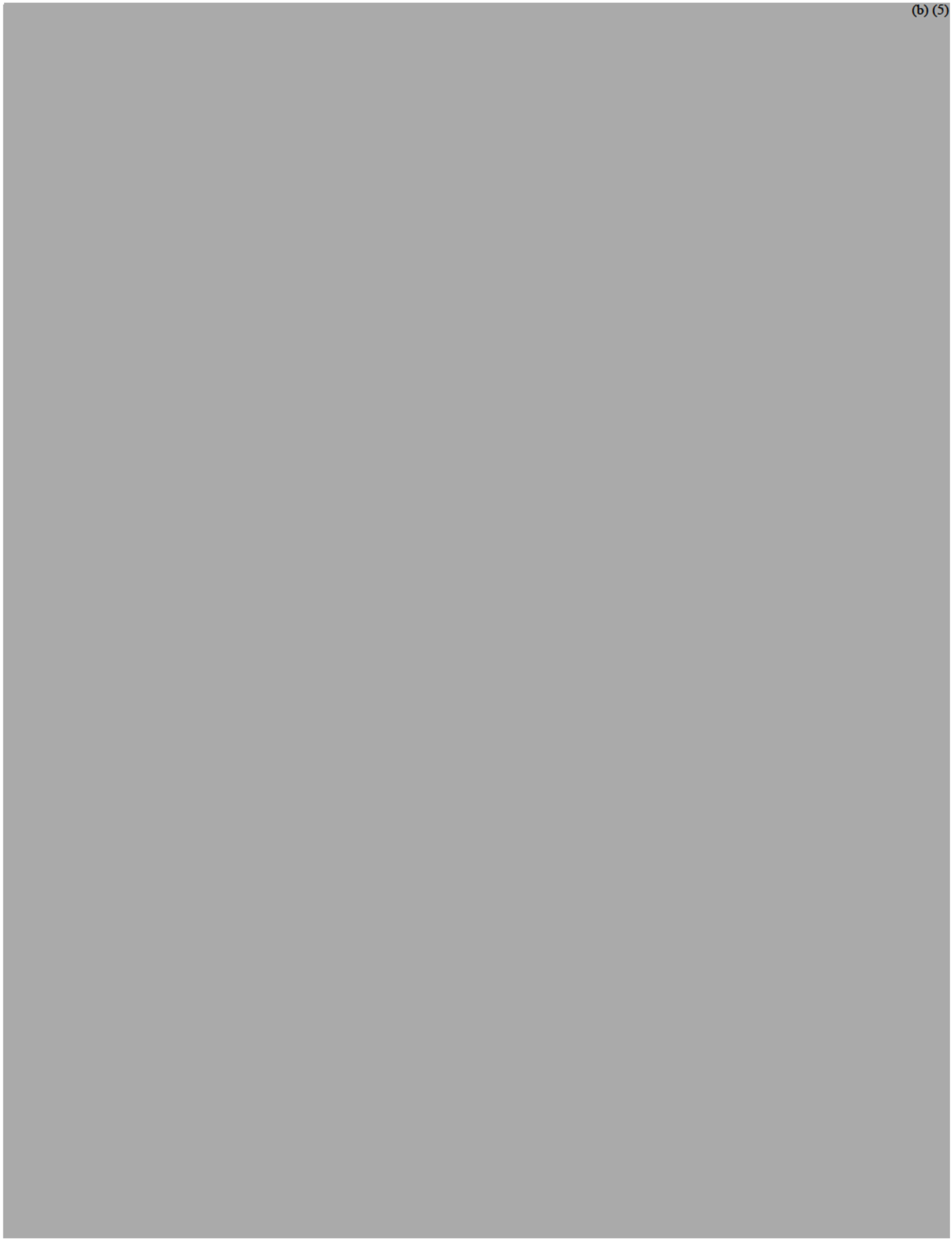
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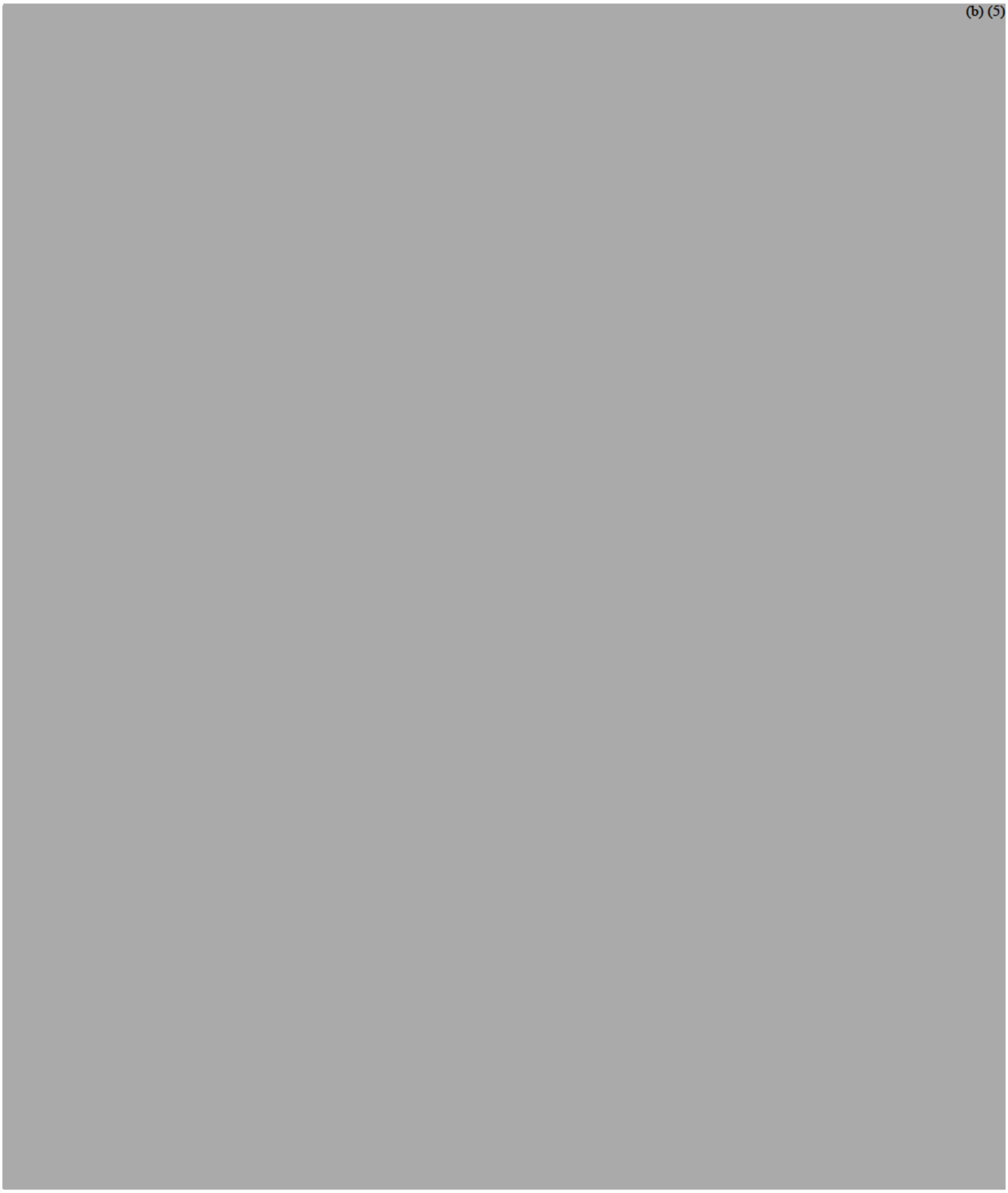
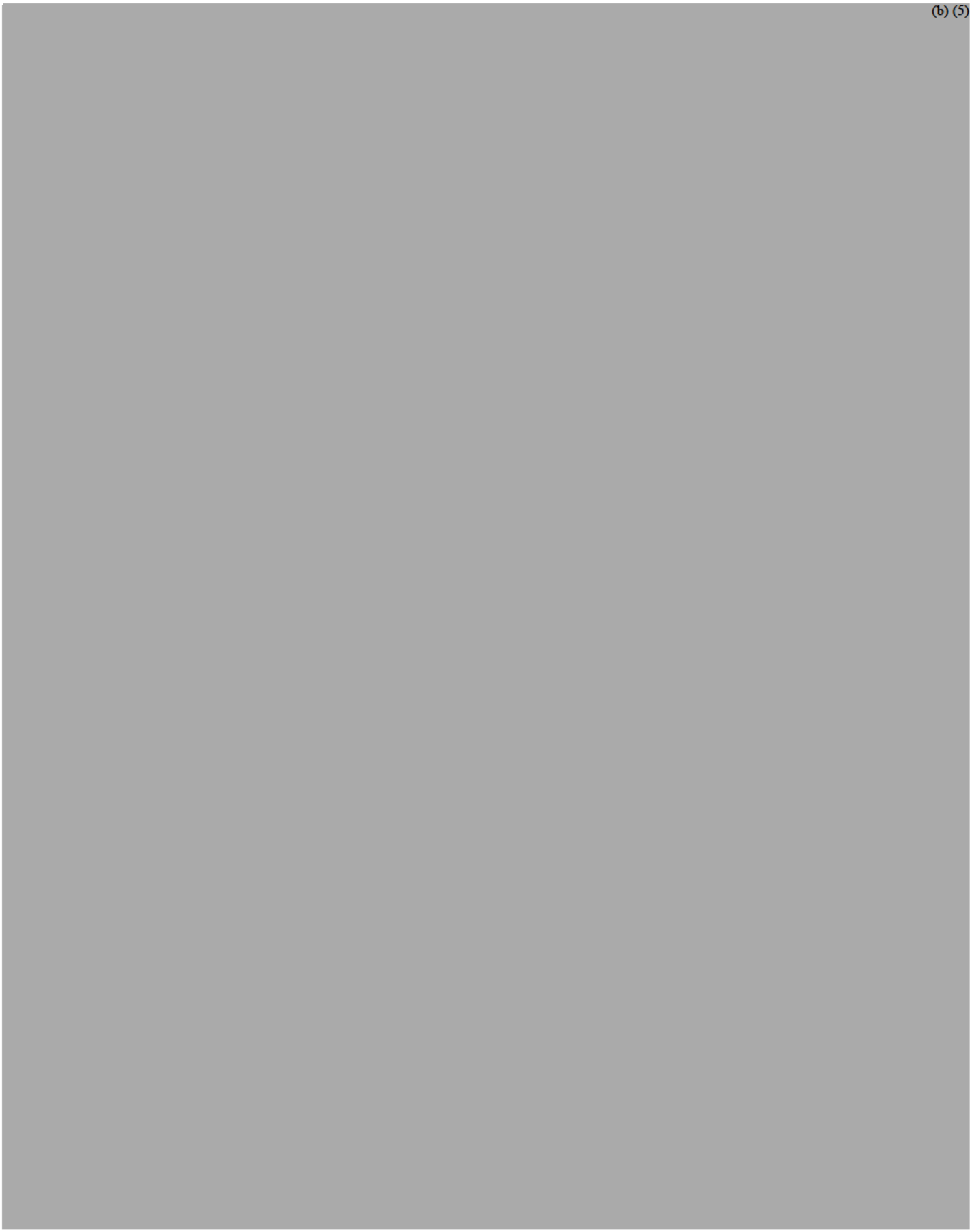
Autism Centers of Excellence

(b) (5)

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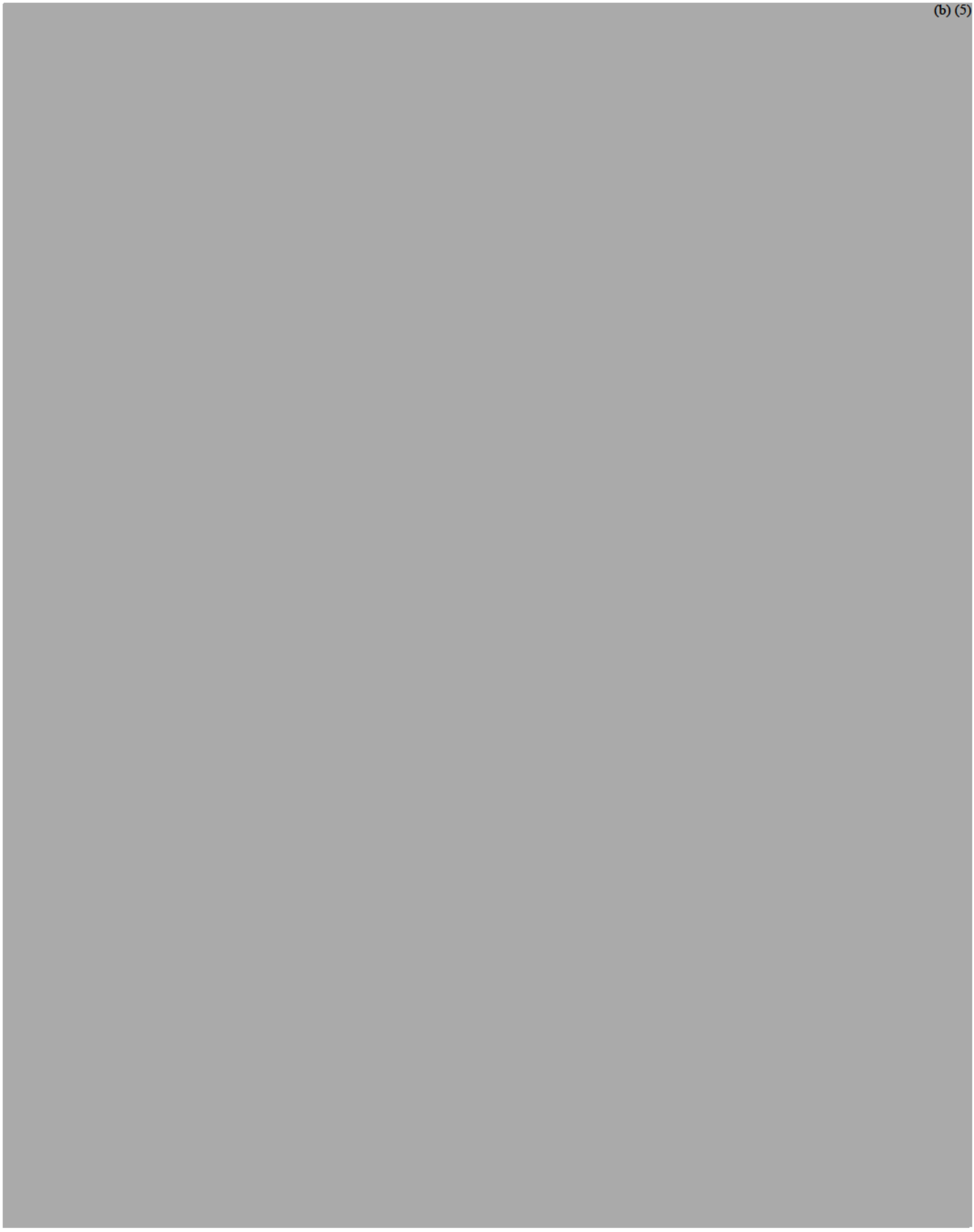

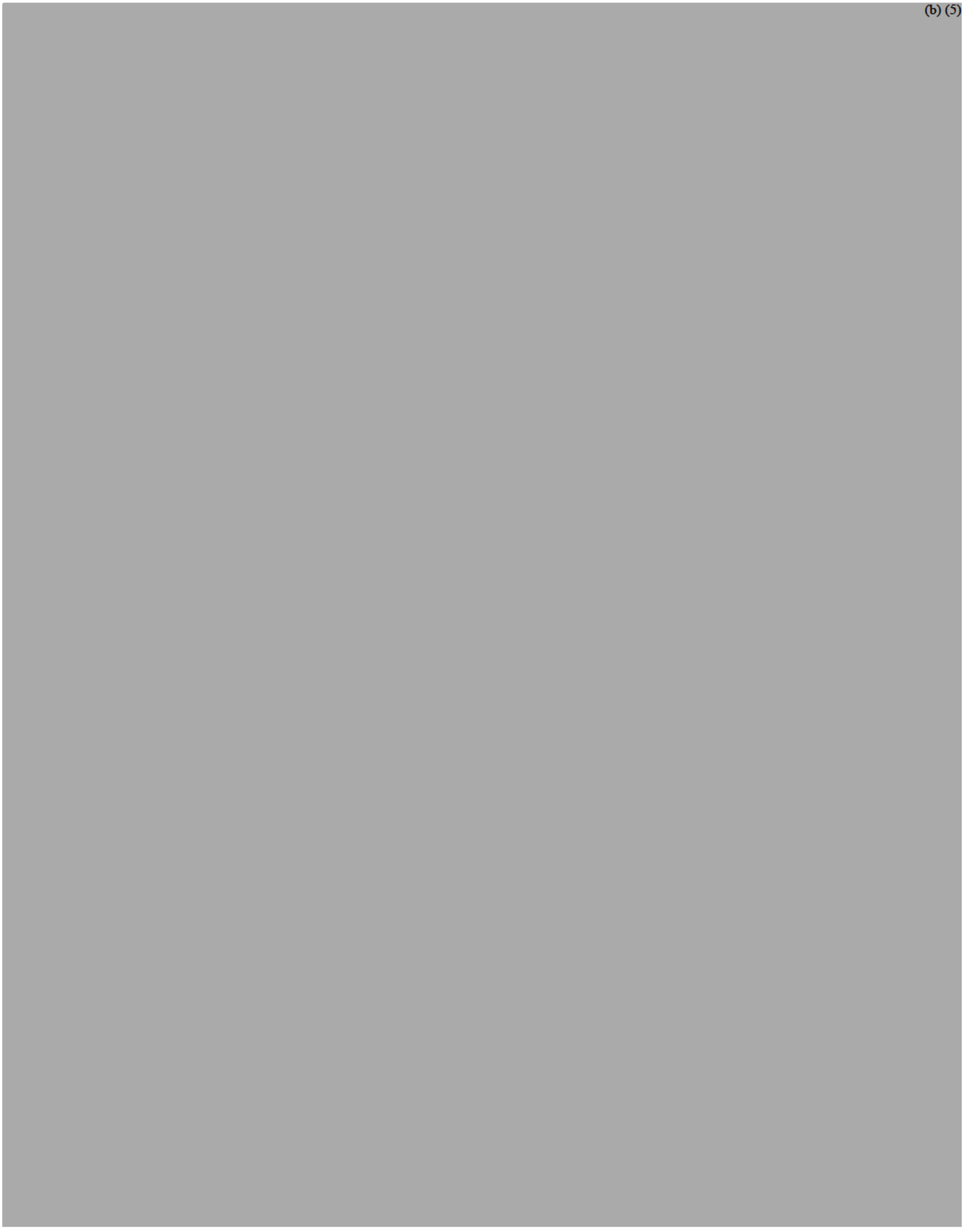
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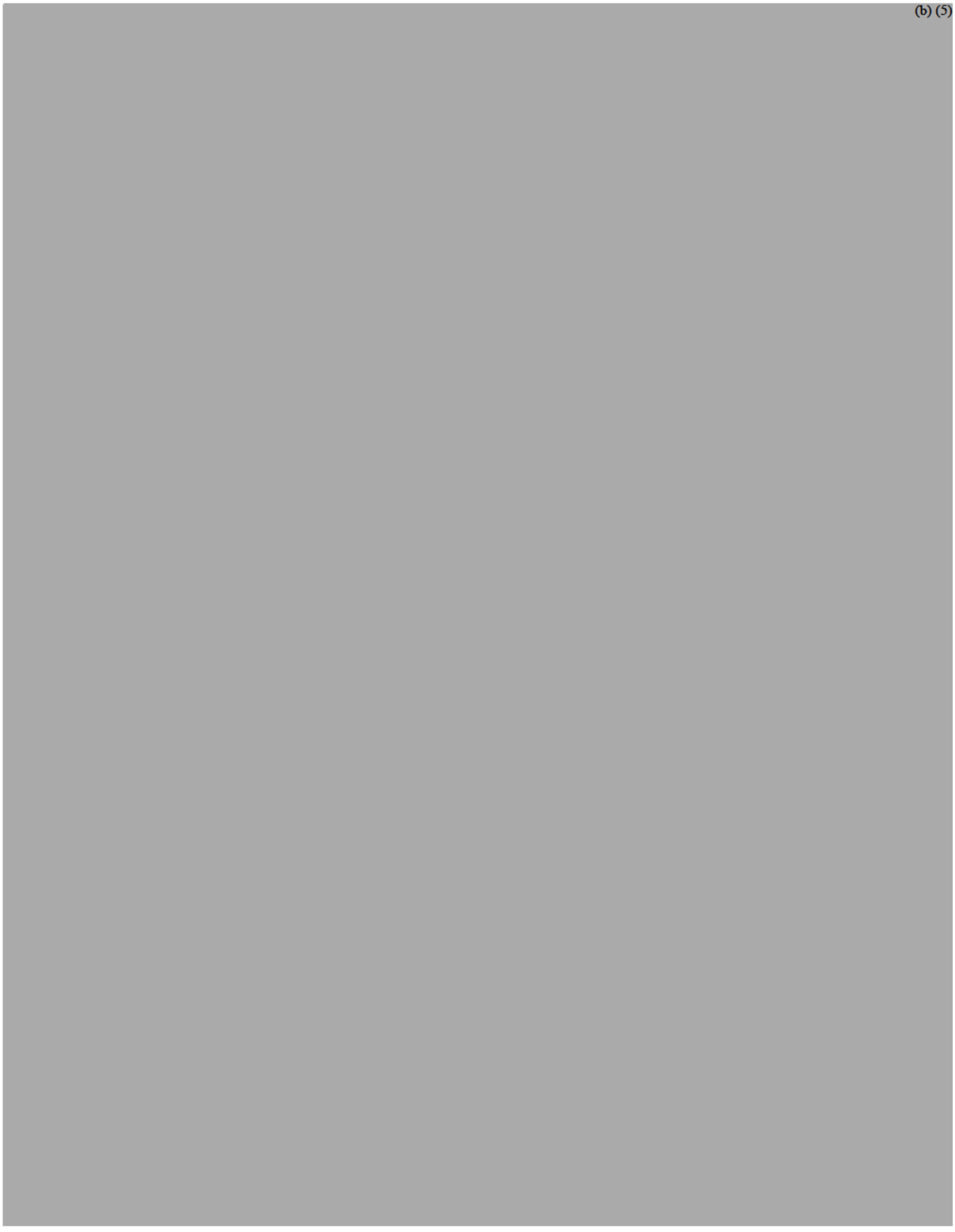
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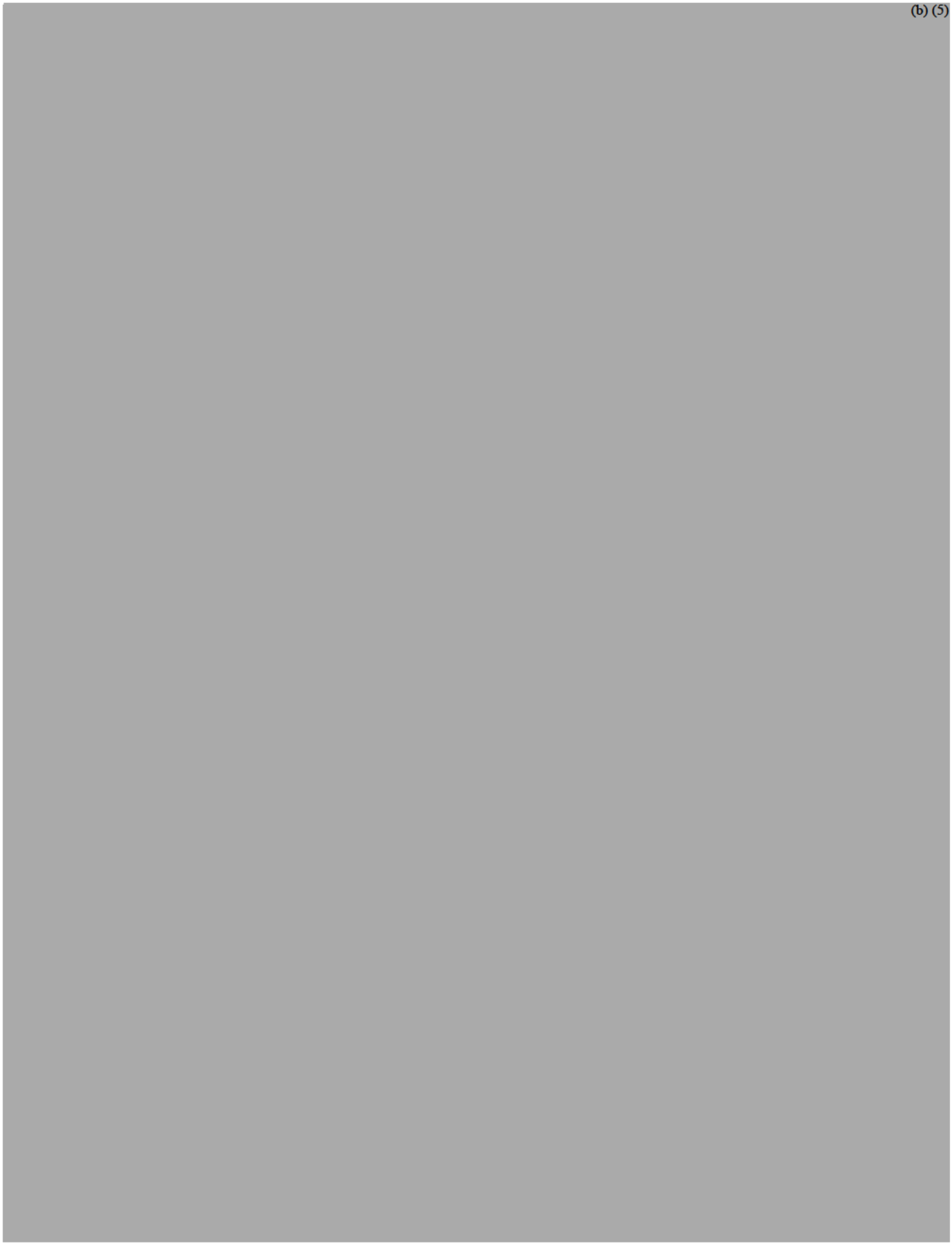
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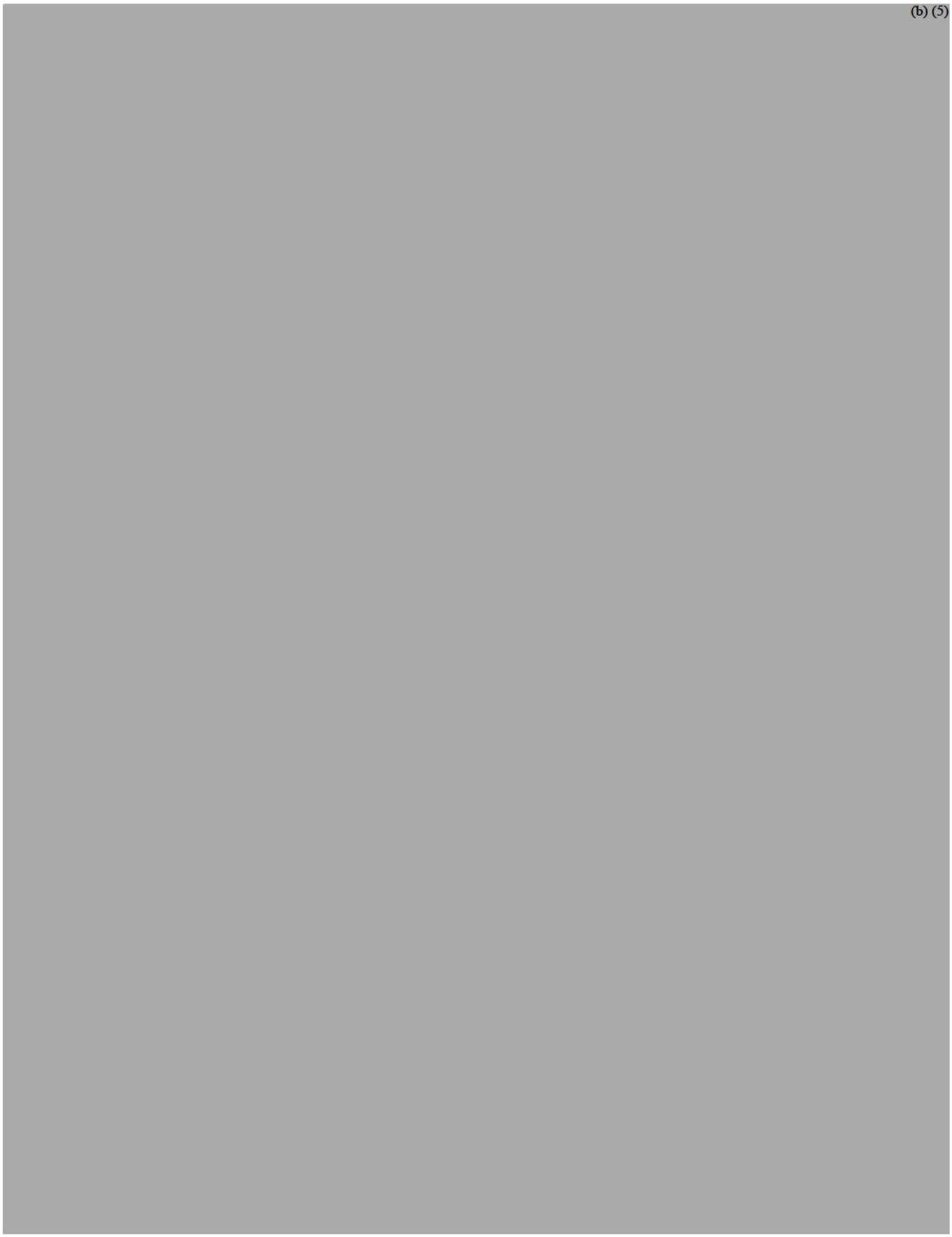
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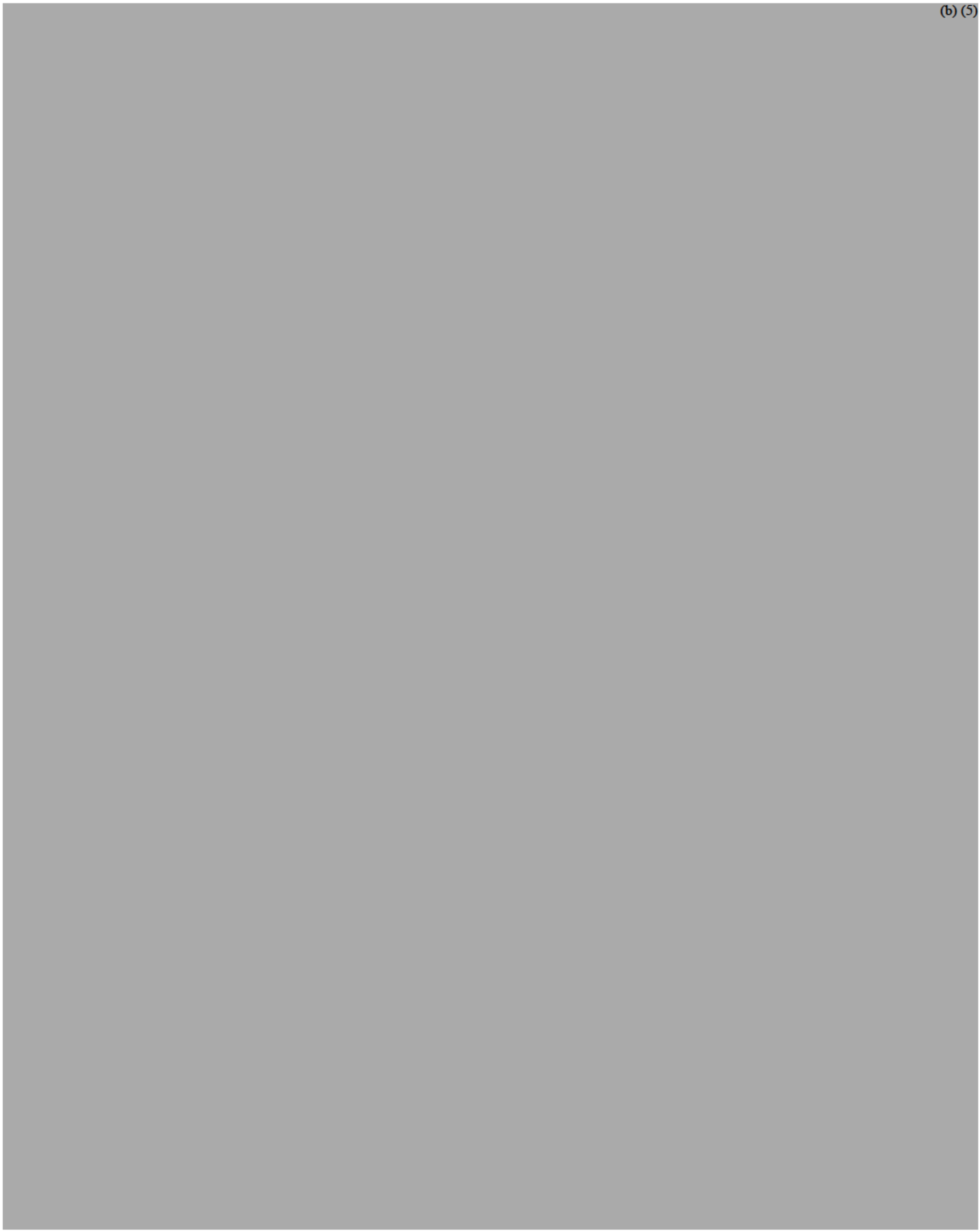
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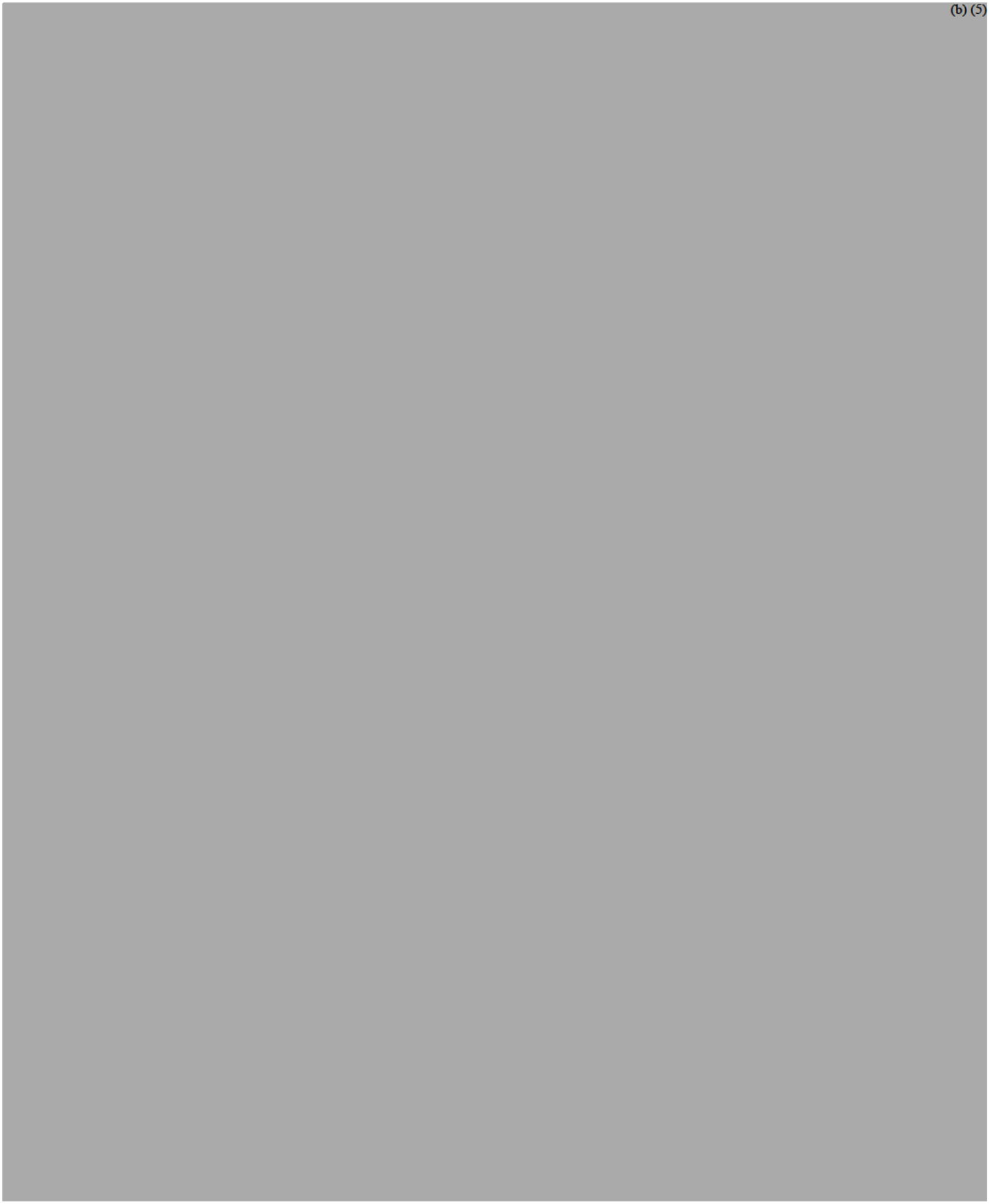
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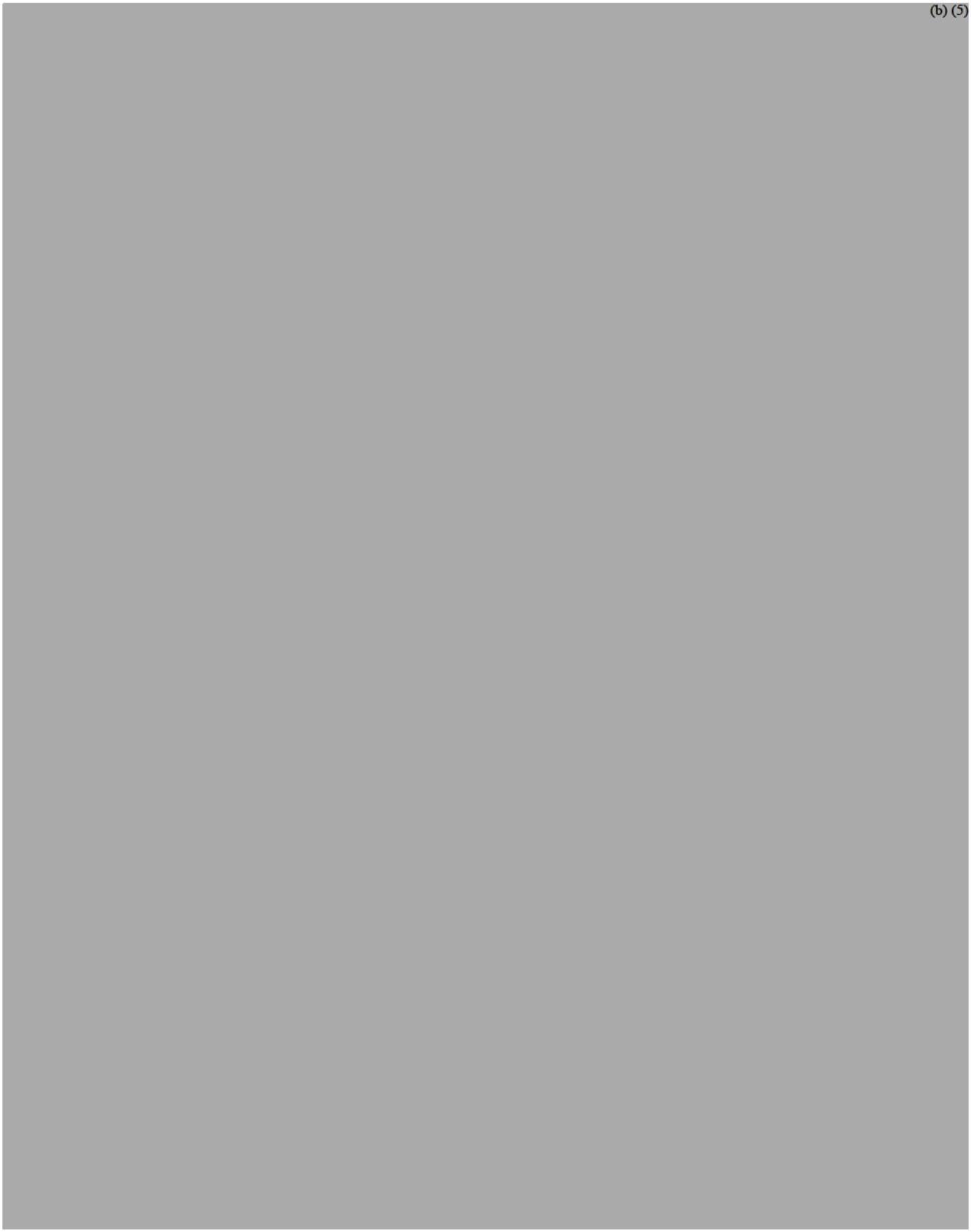
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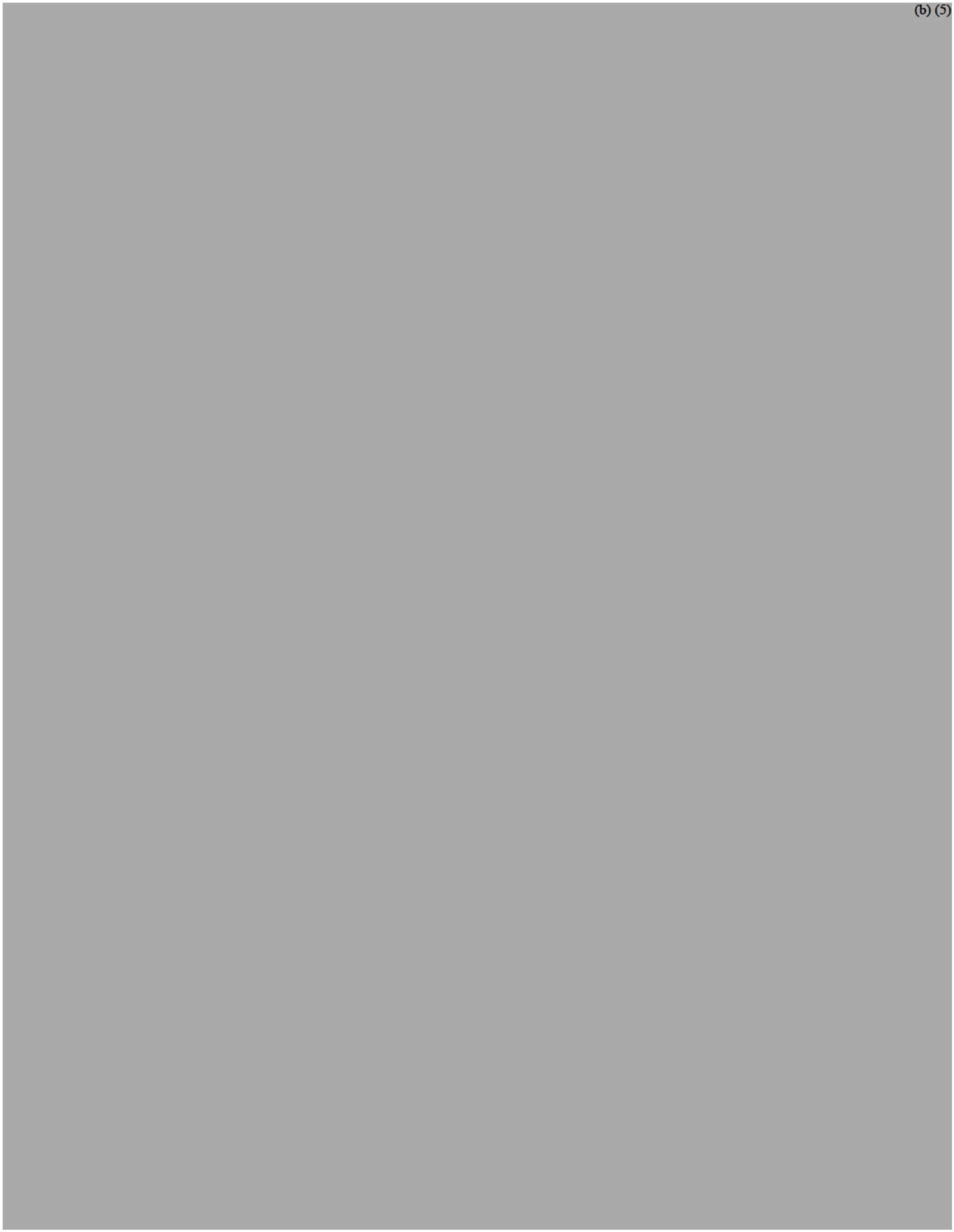
(b) (5)

Appendix A:

Excerpts of Legal Authorities Related to the NIH Director's Triennial Report to Congress

(b) (5)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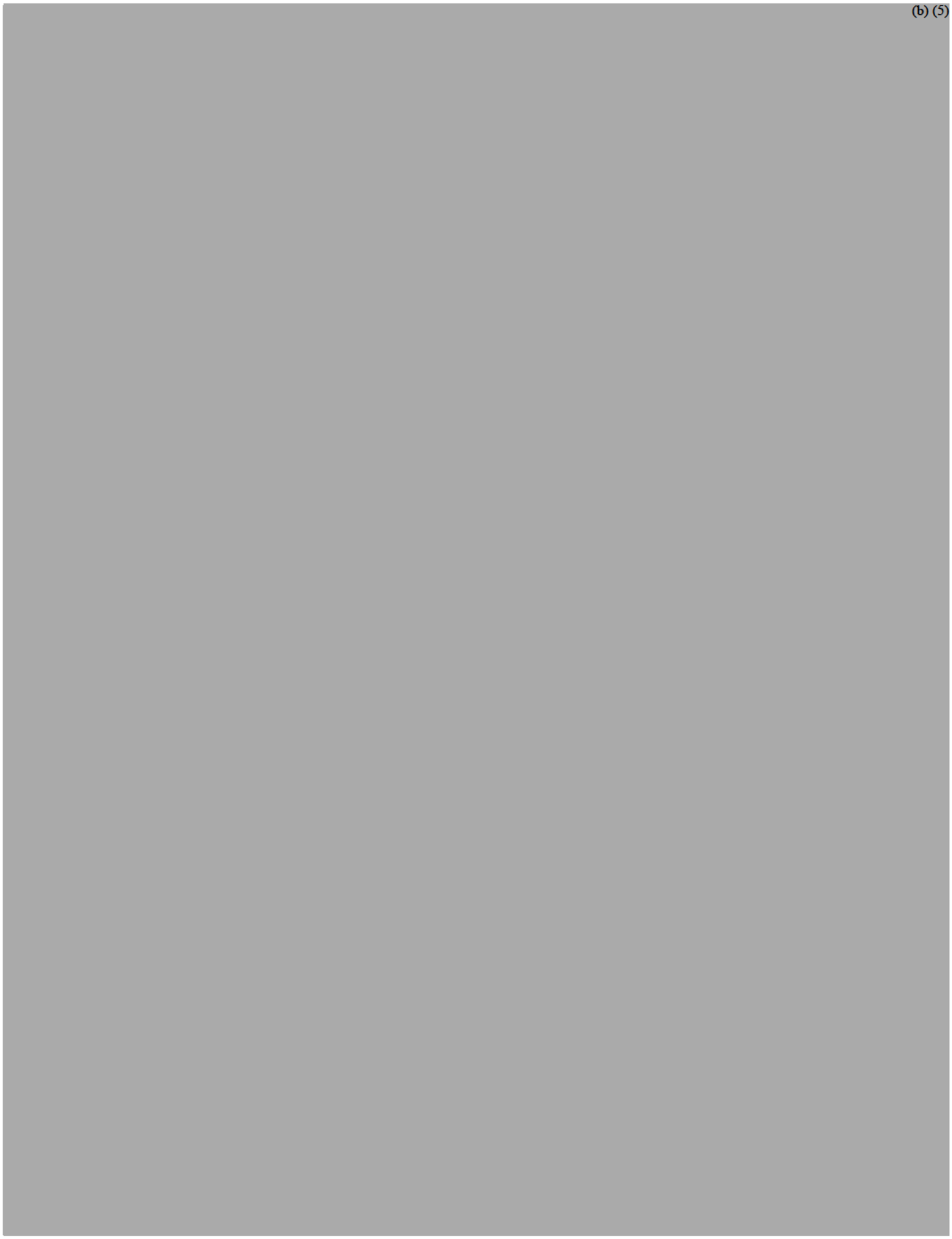
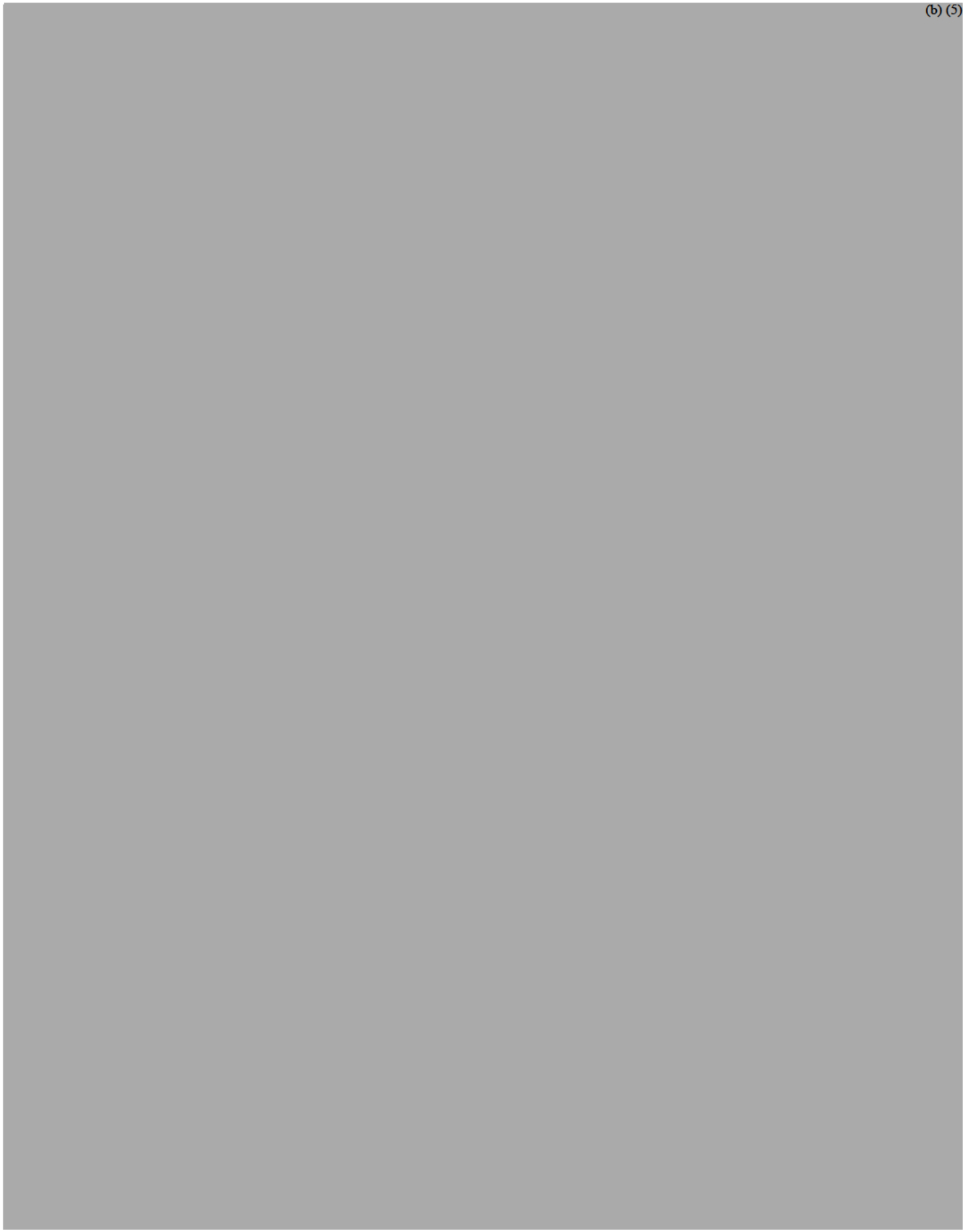
(b) (5)

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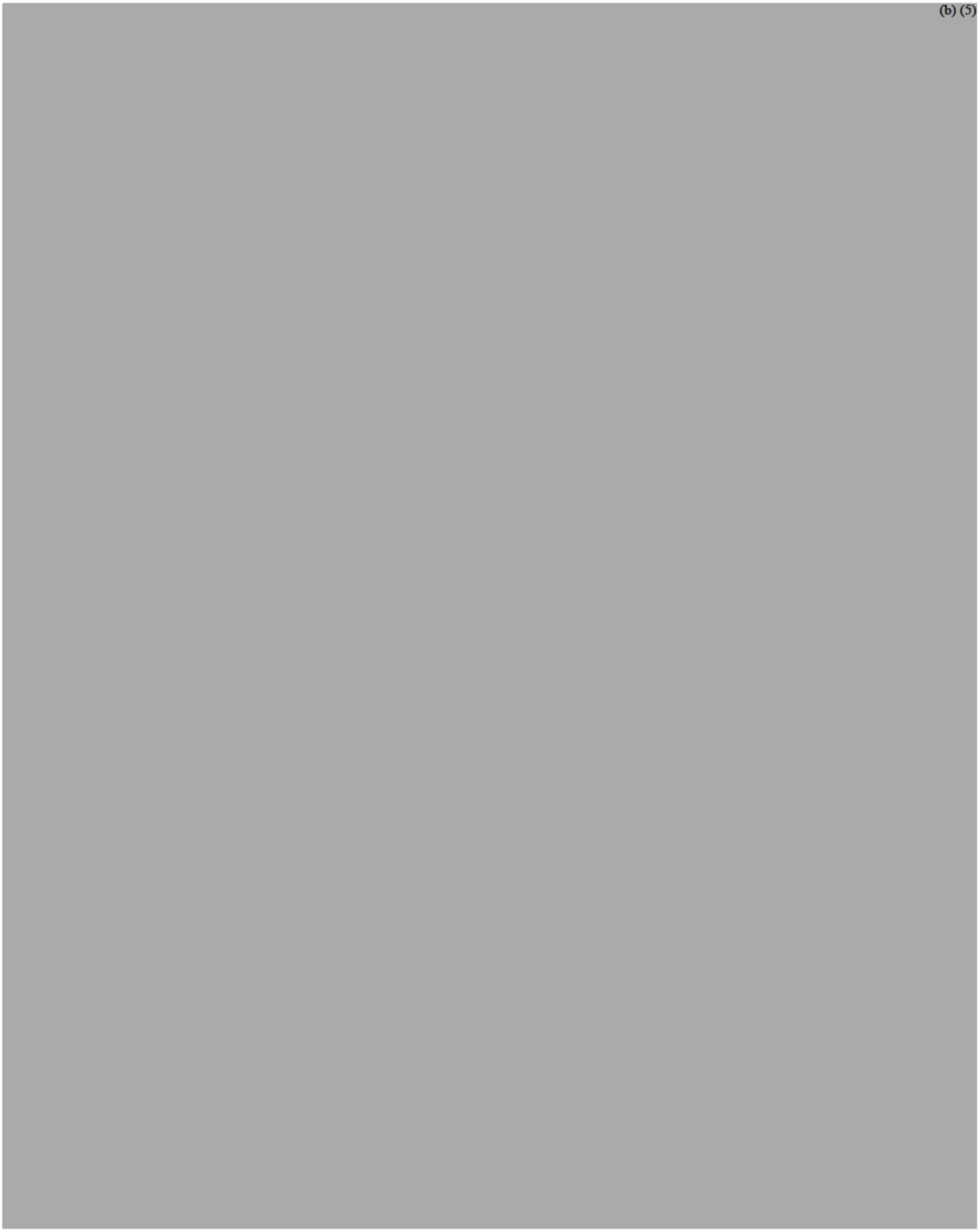
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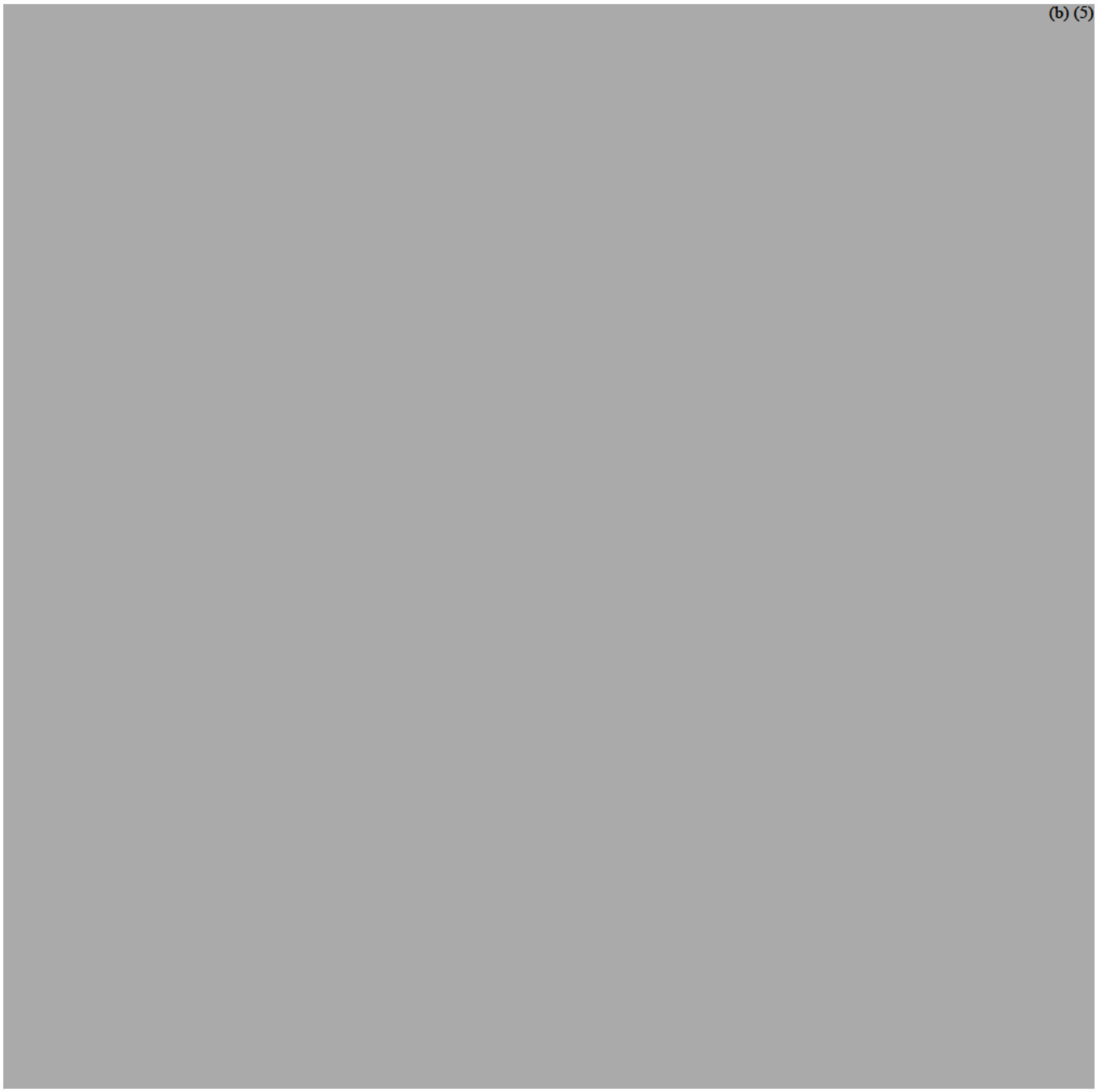
(b) (5)

Appendix B:

Report of the Advisory Committee on Research on Women's Health



Appendix C:

Actions Undertaken to Conduct or Support Research Related to Vector-Borne Diseases

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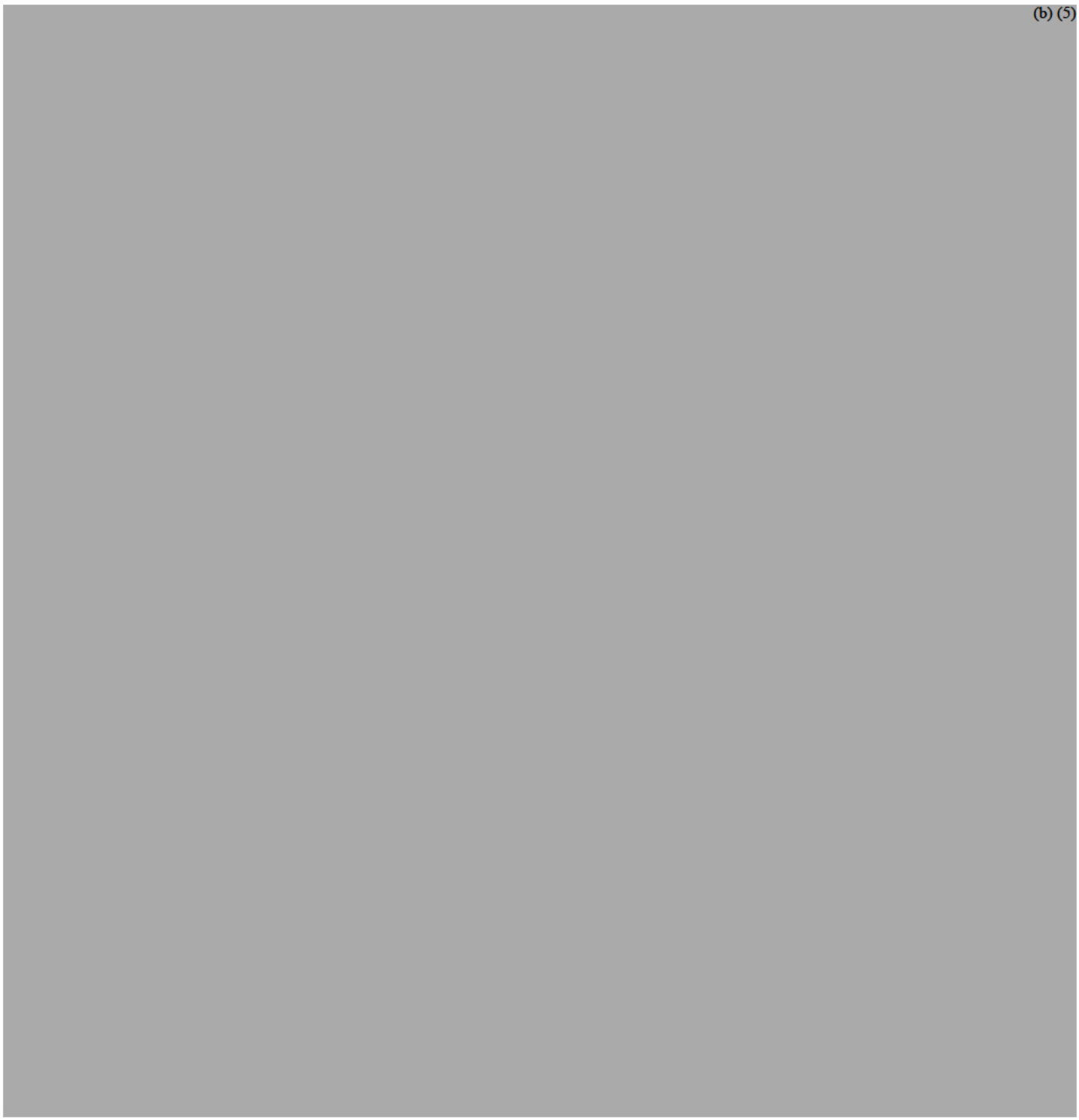

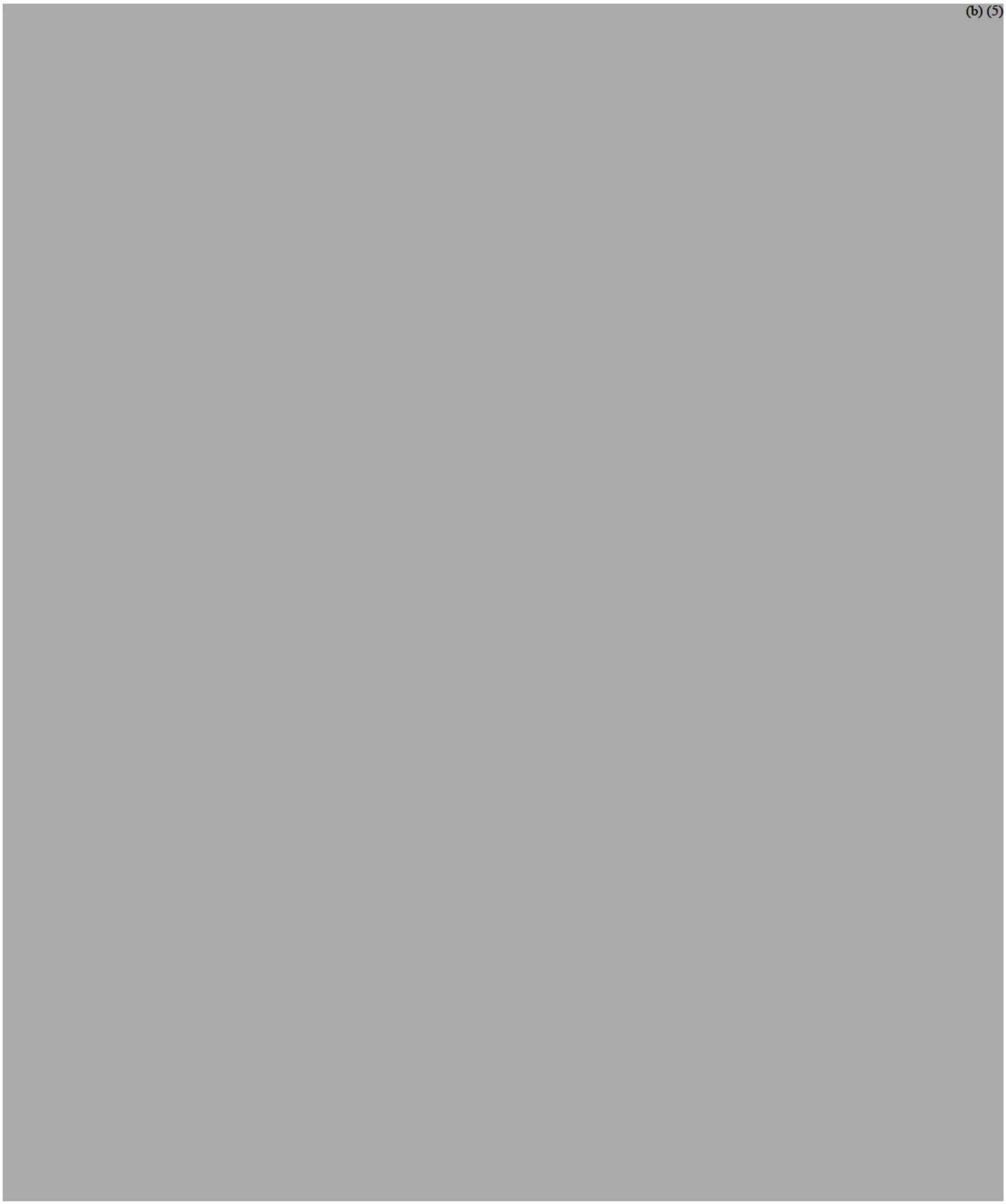
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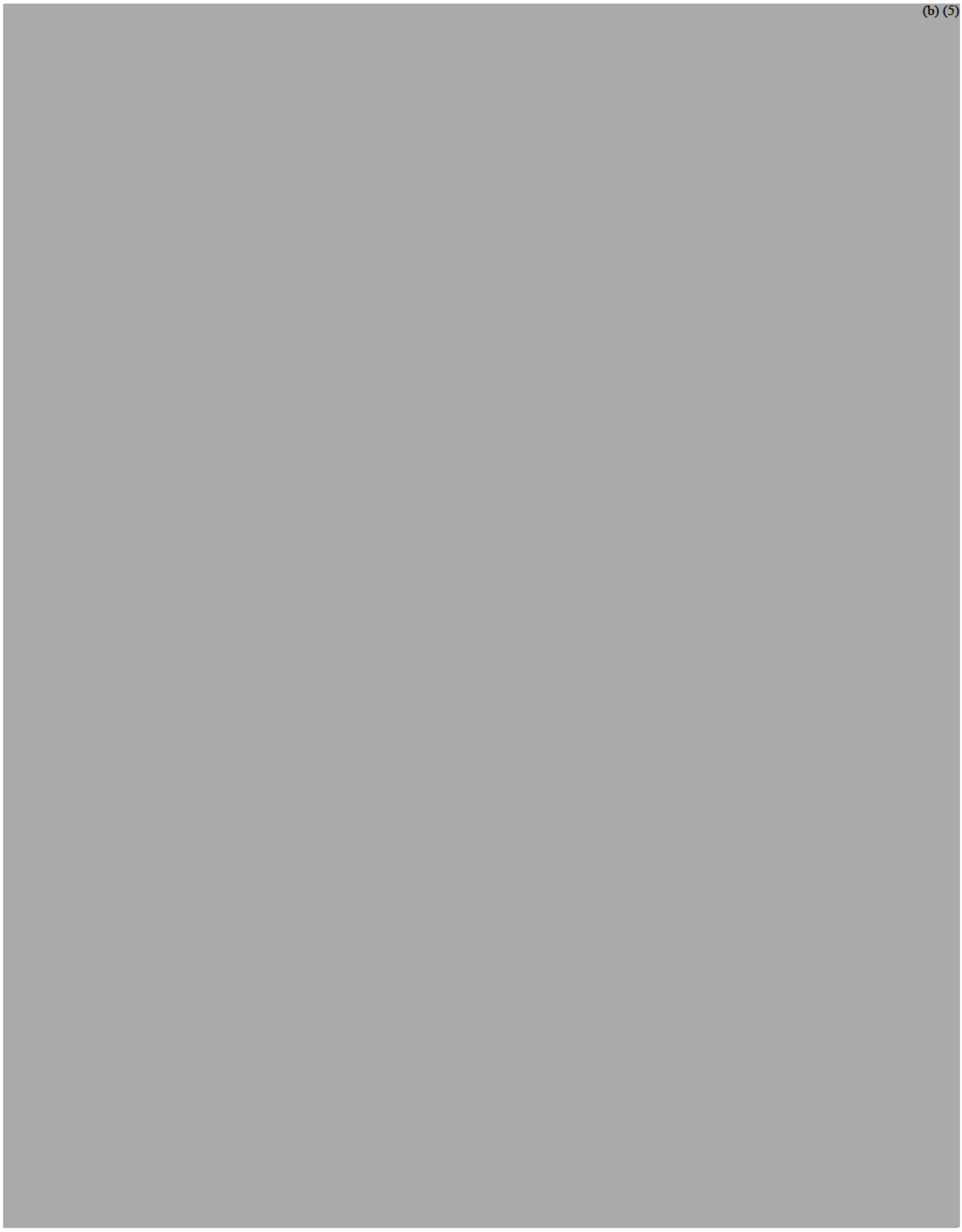
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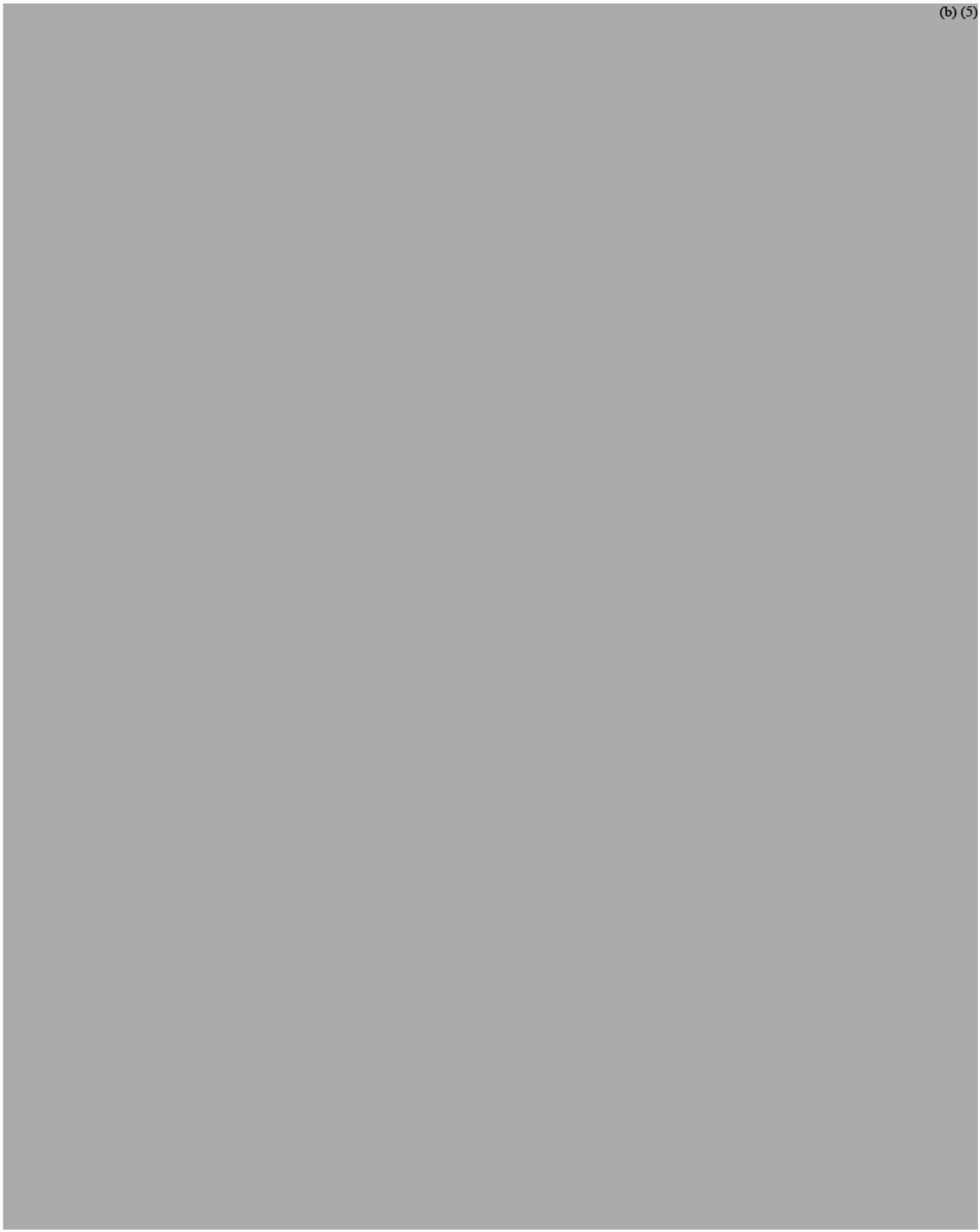
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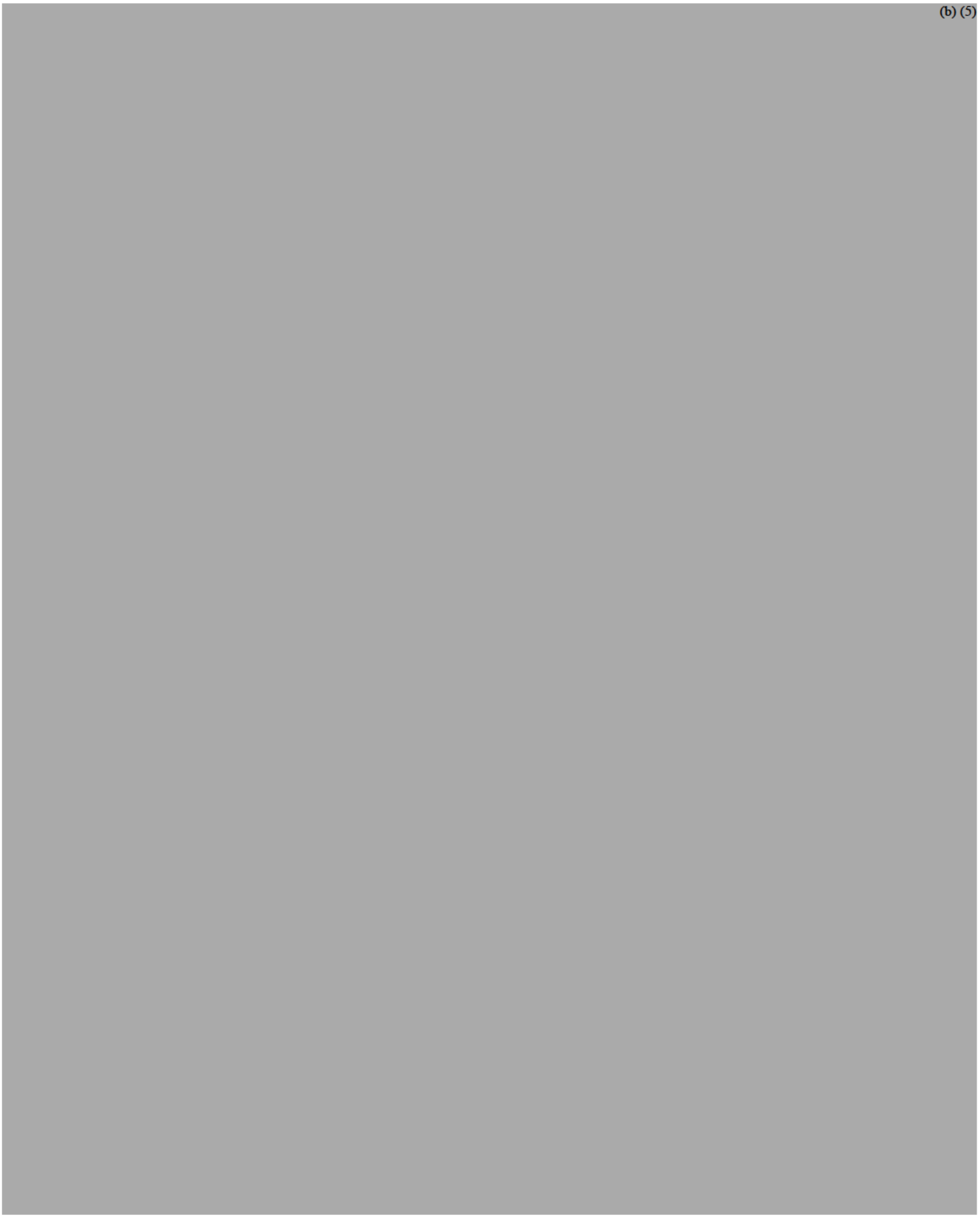

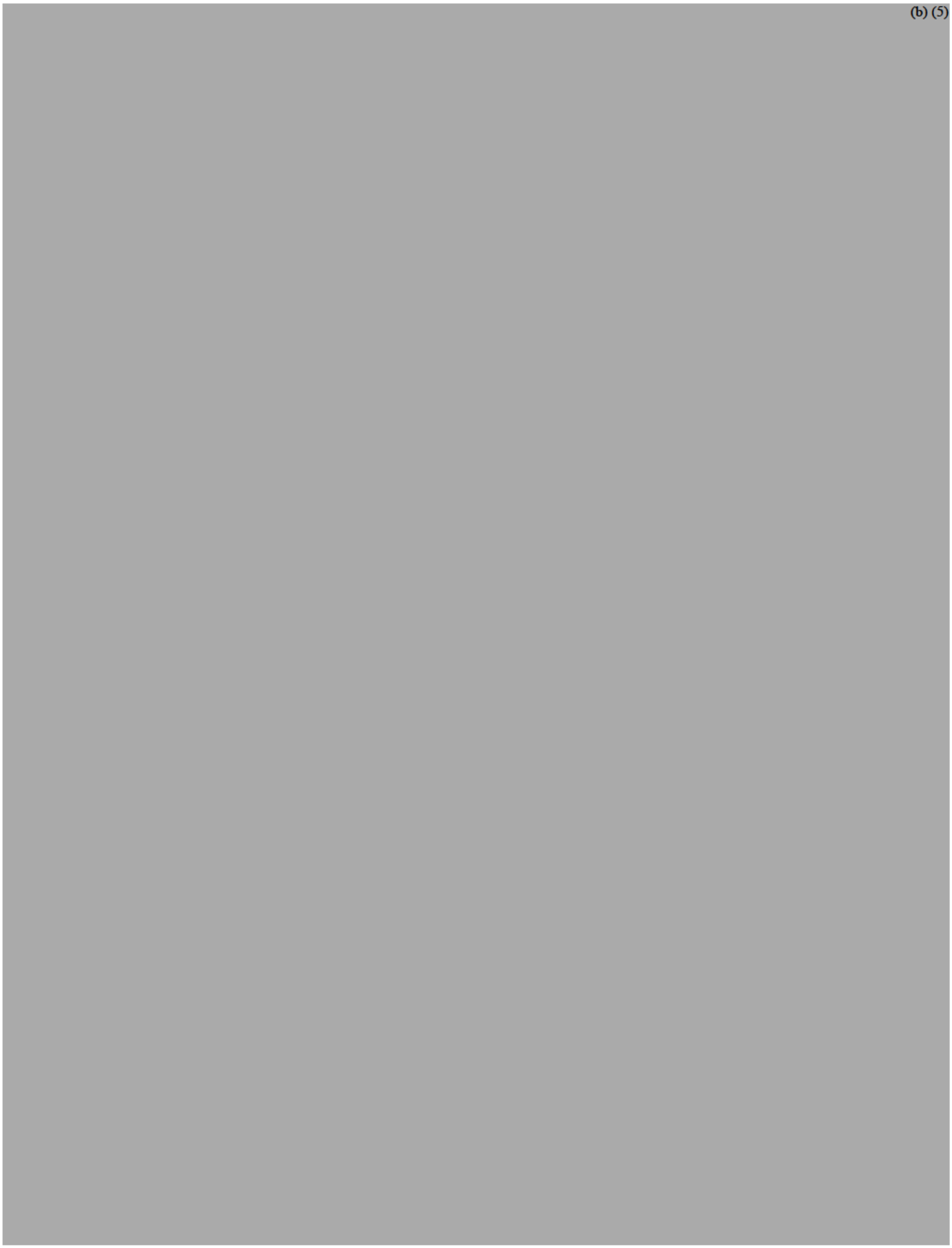
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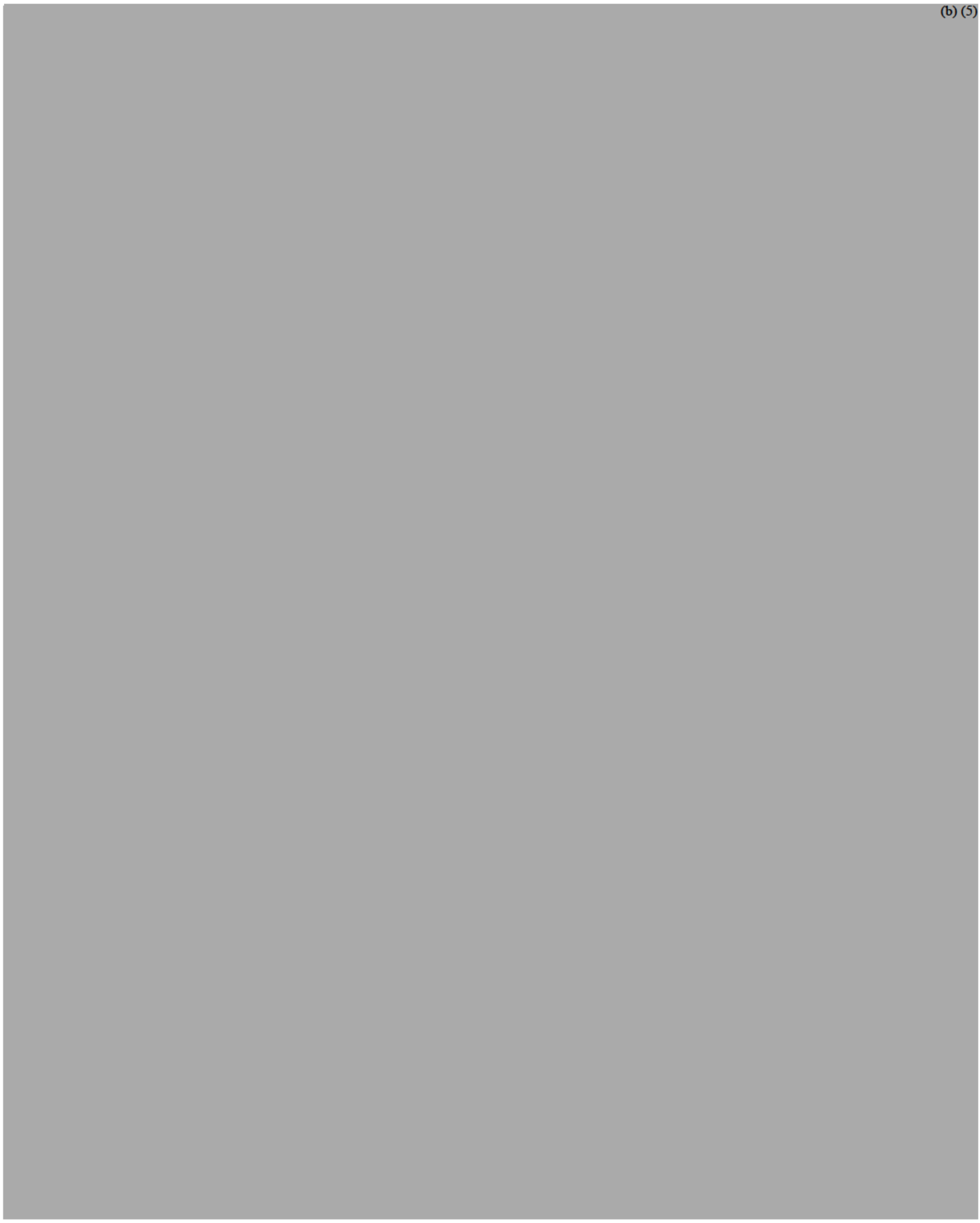
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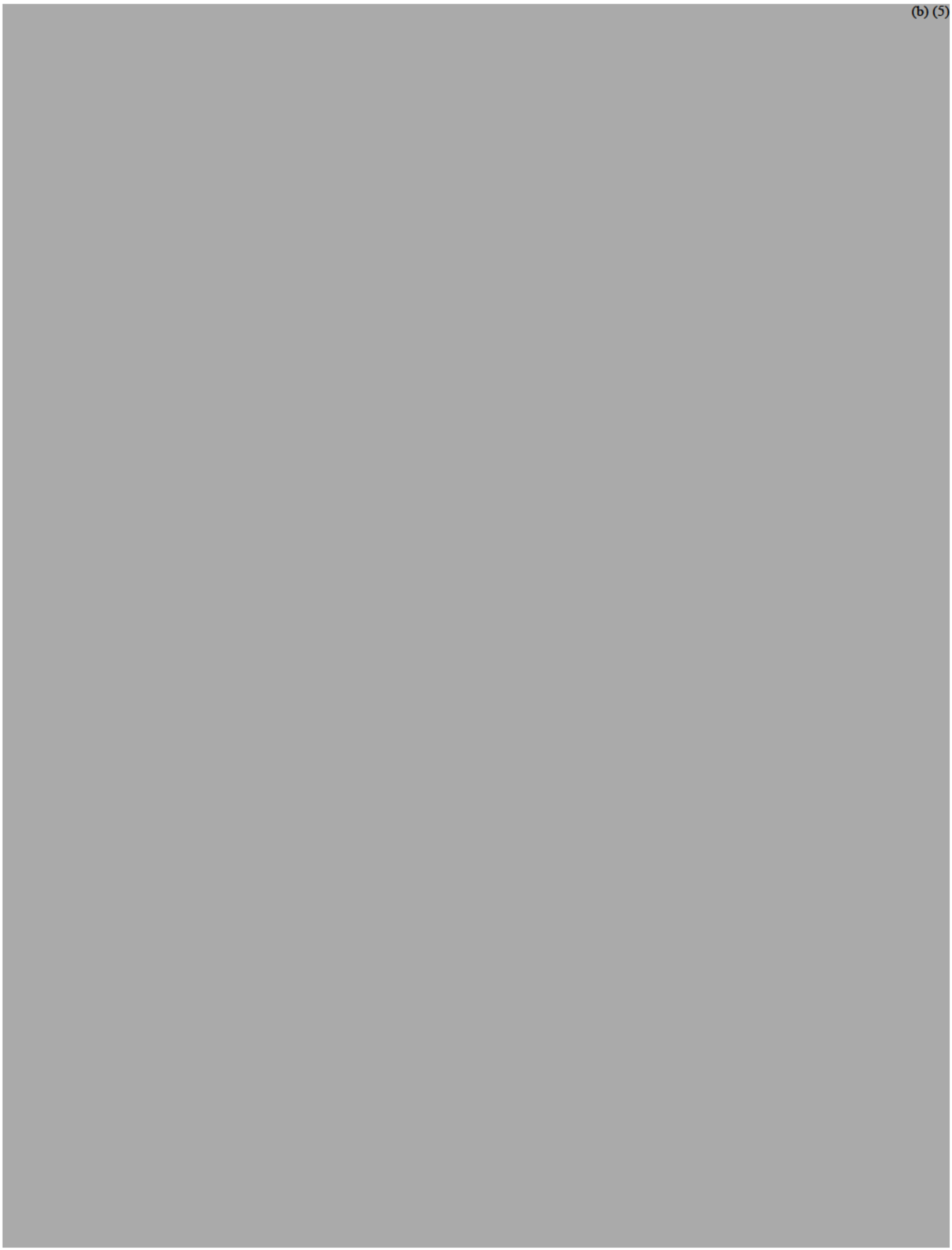
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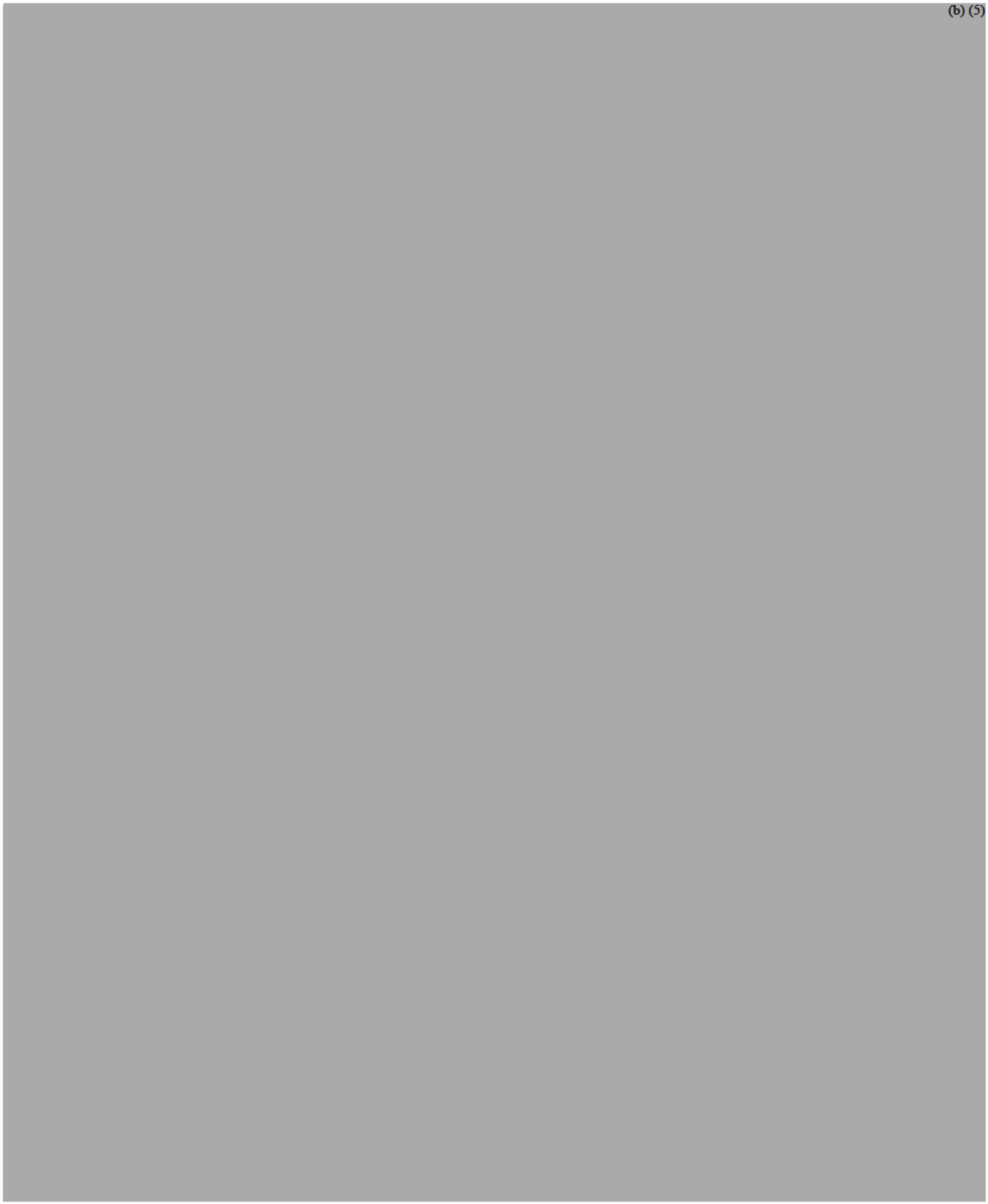
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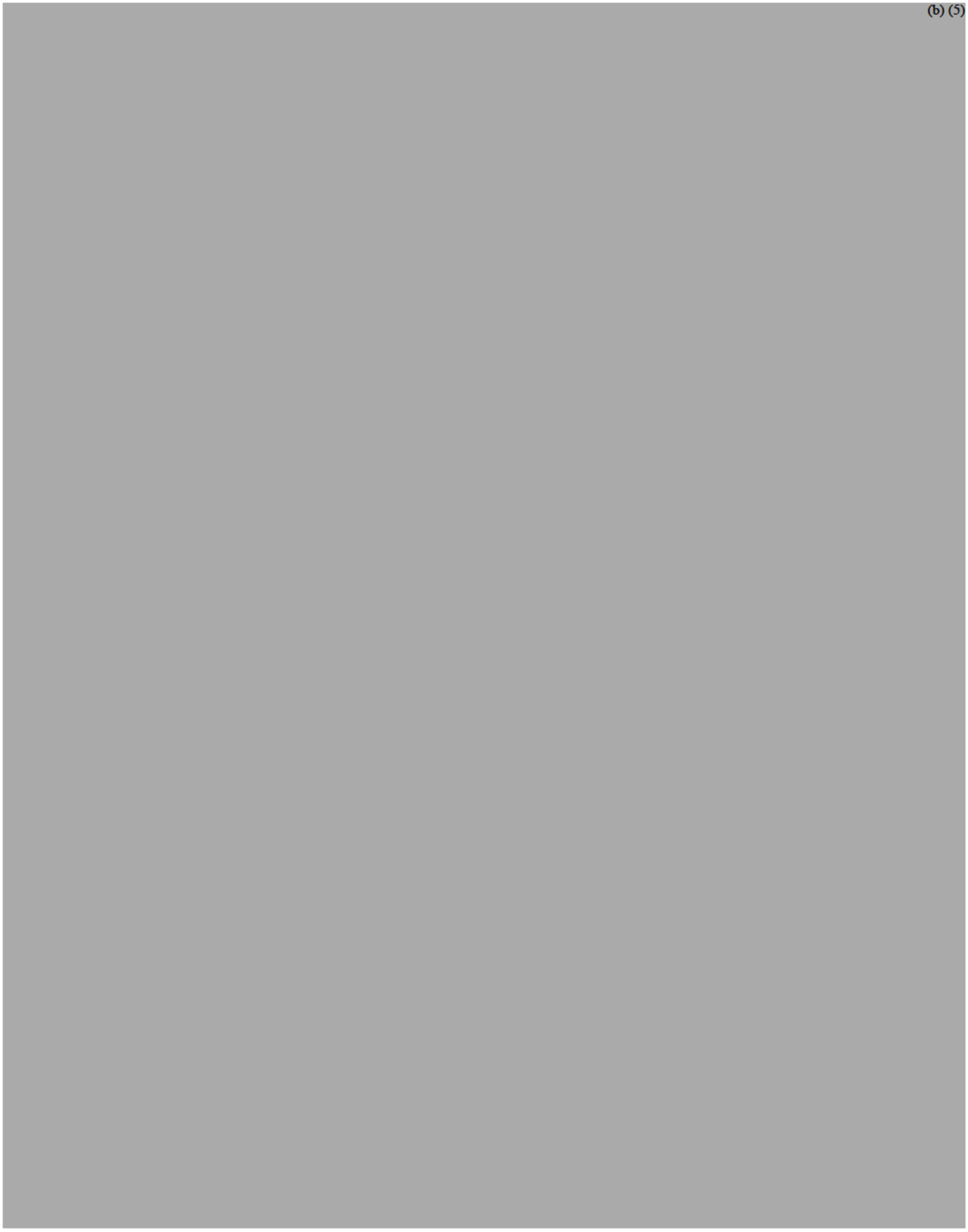
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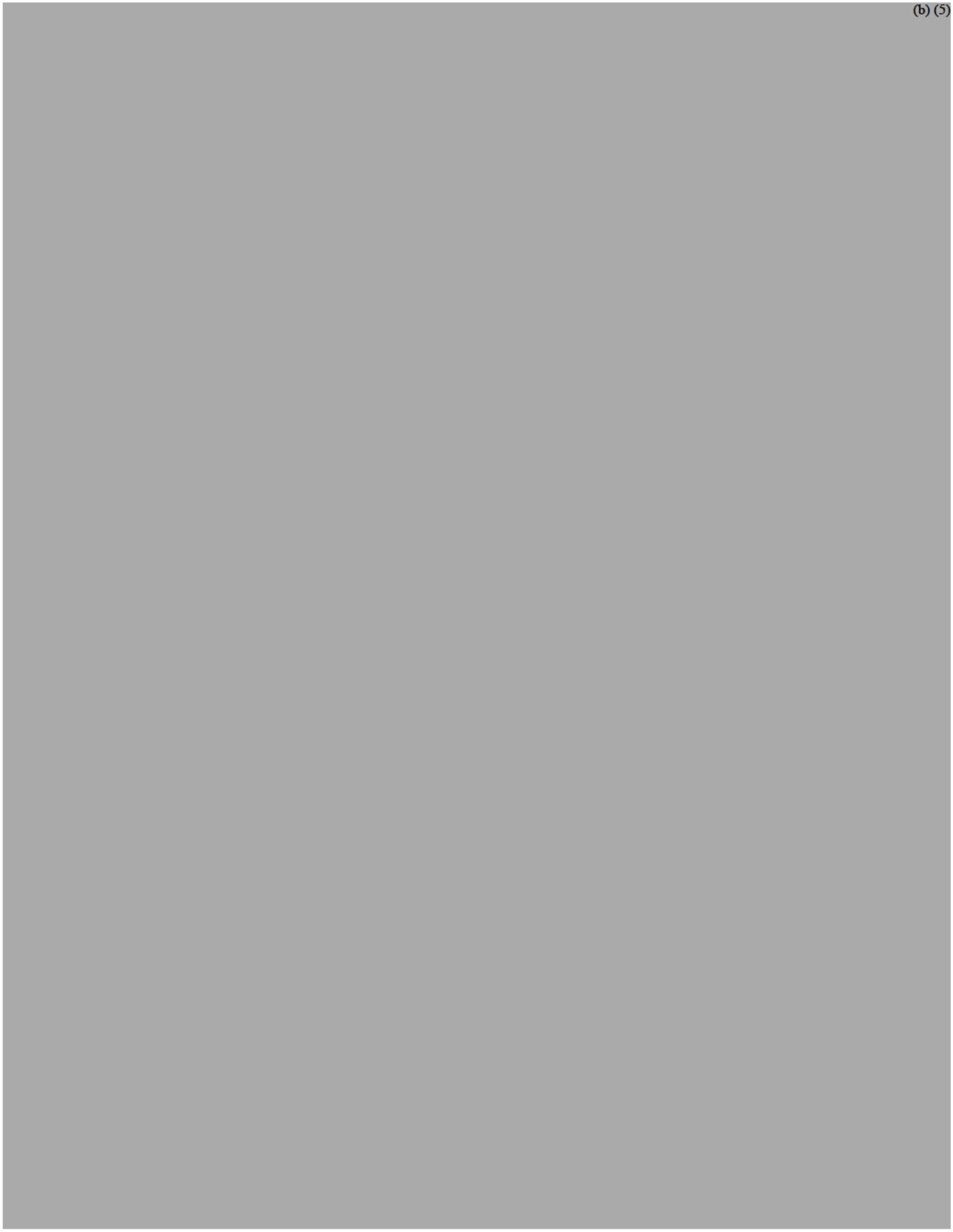
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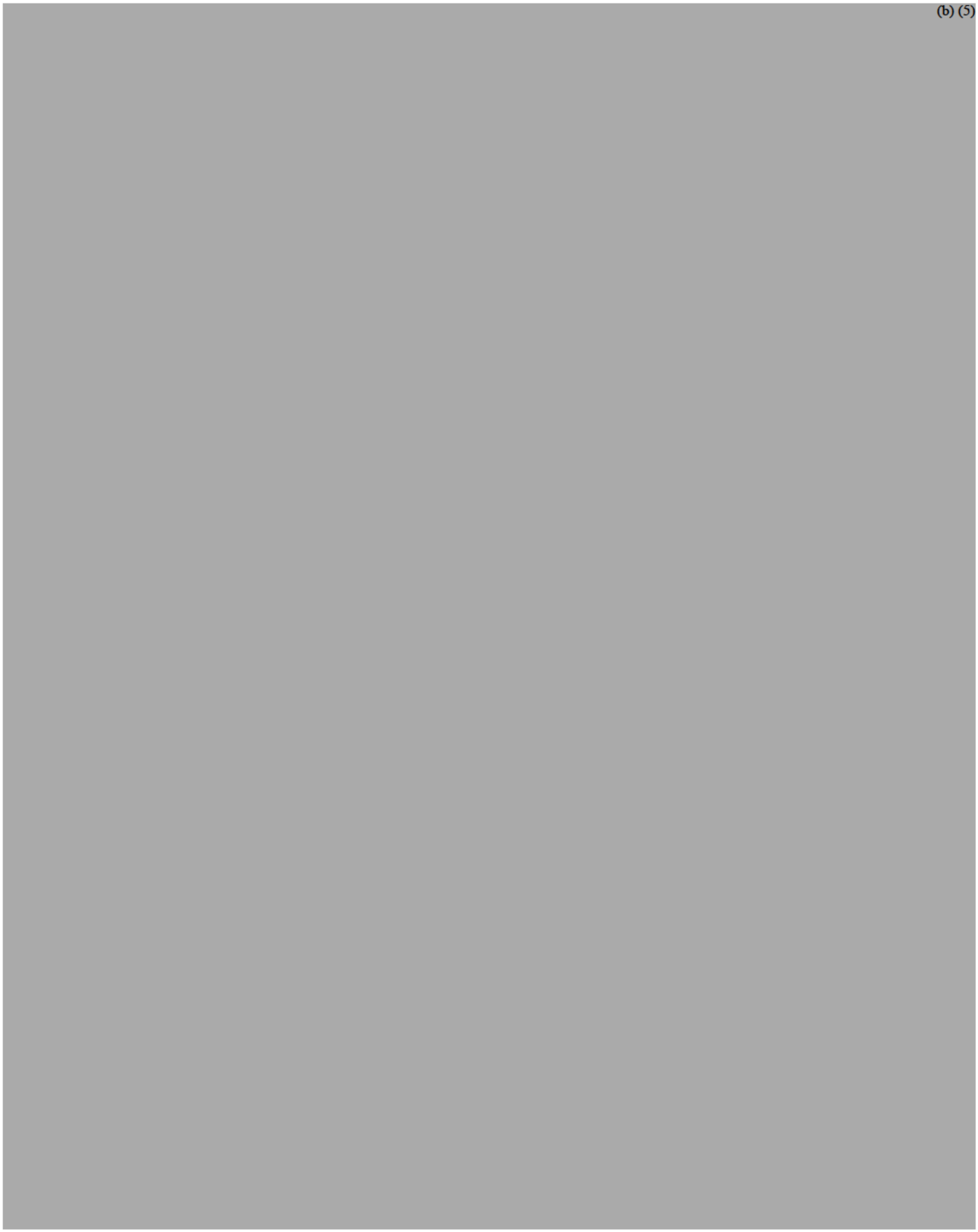
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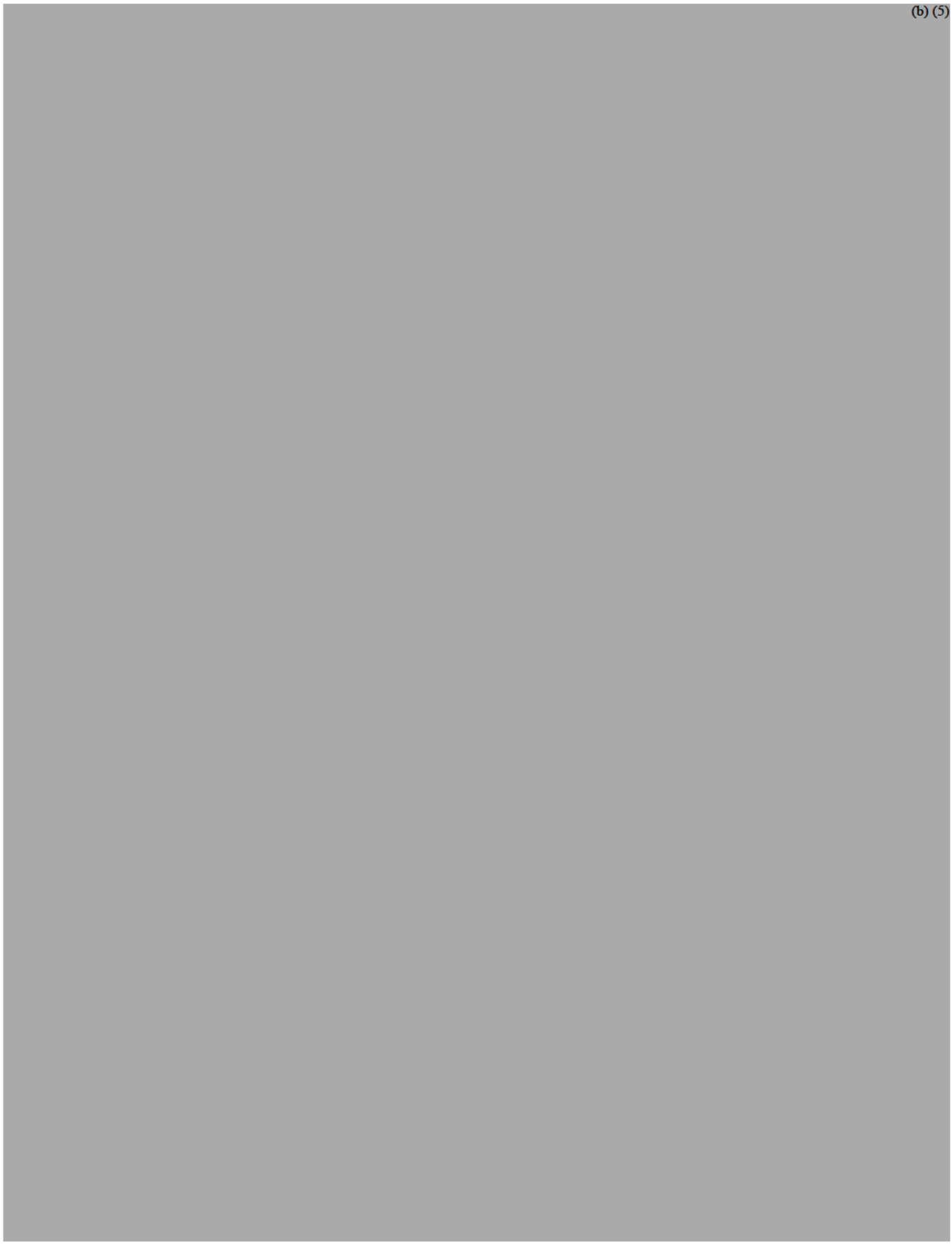
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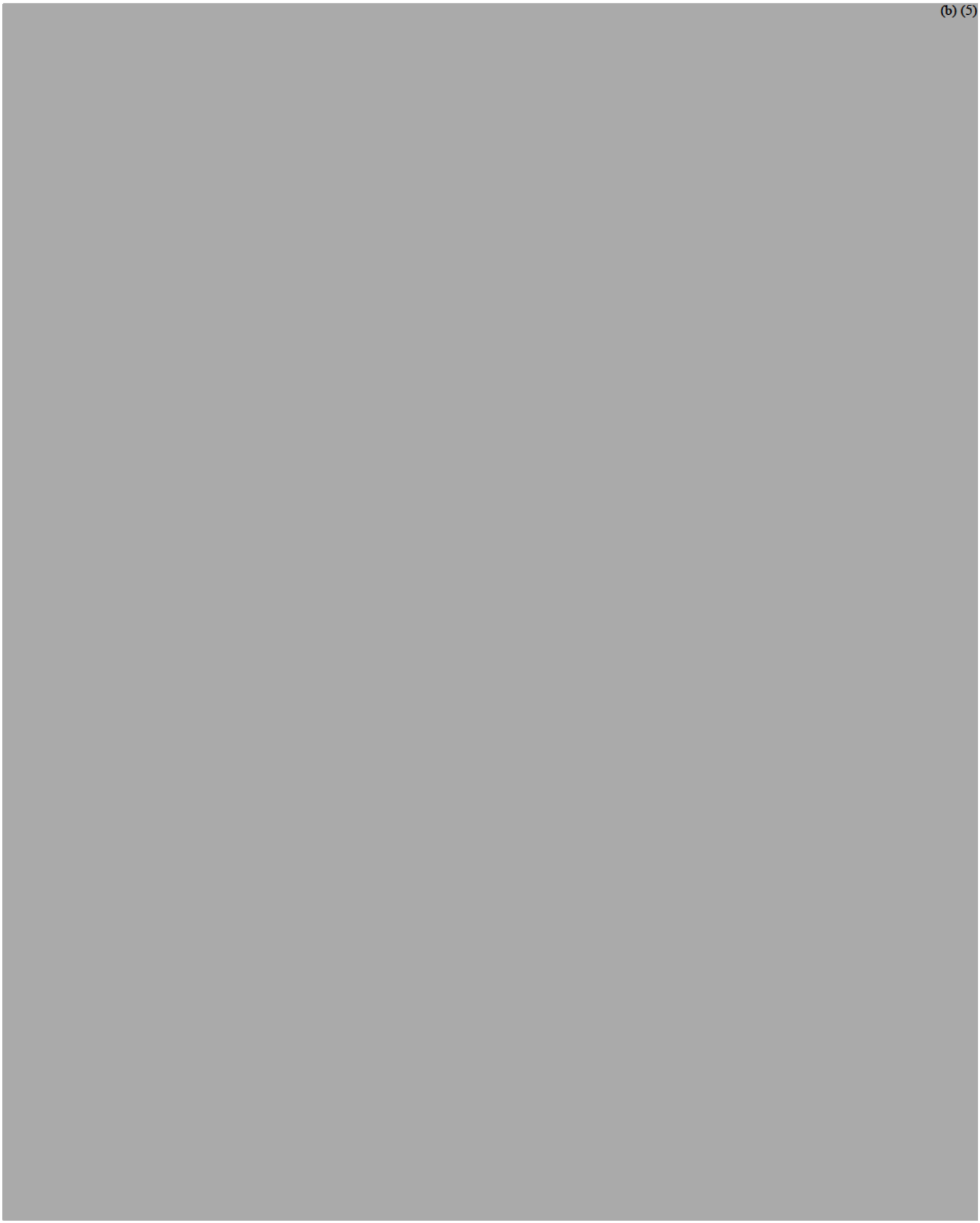
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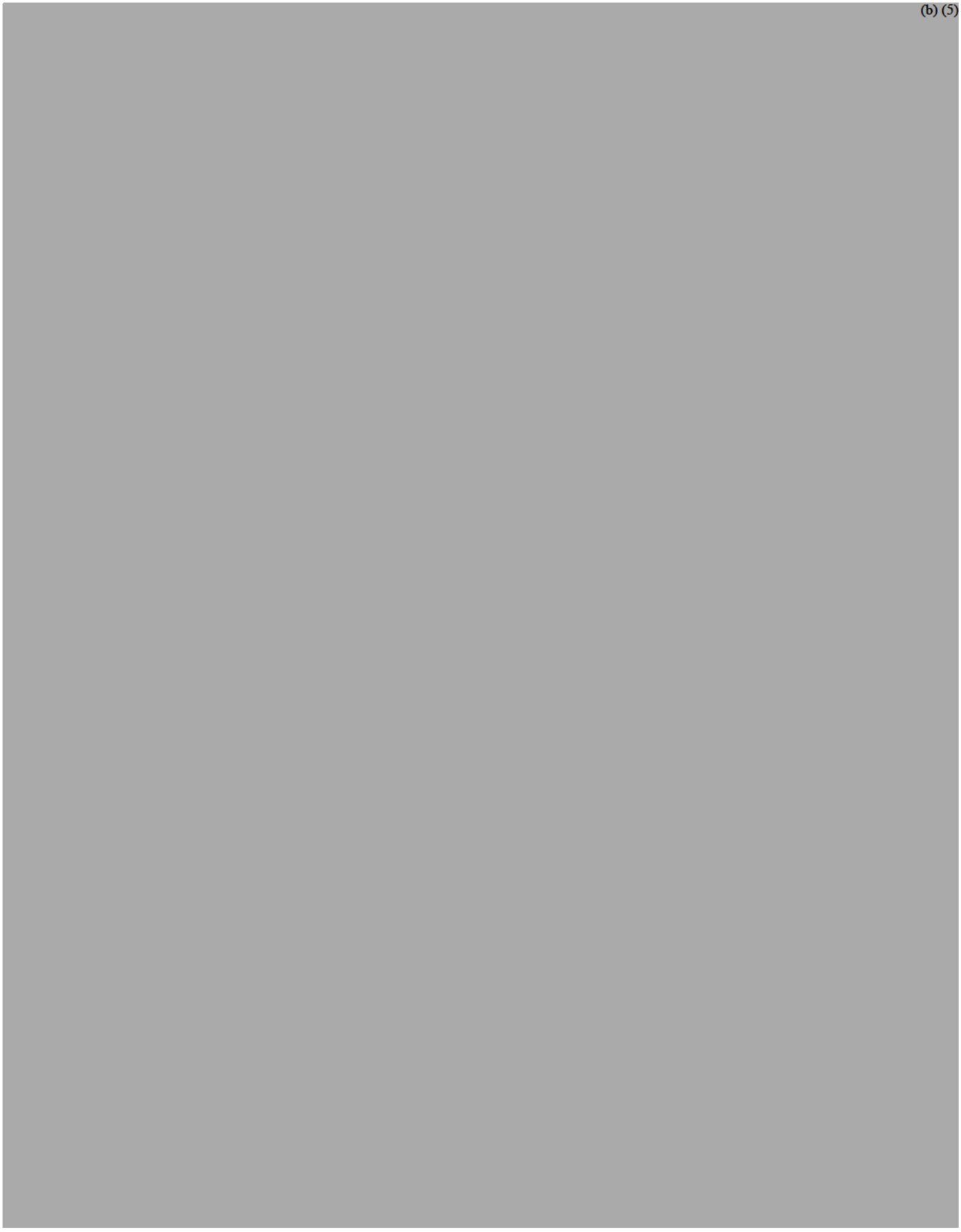
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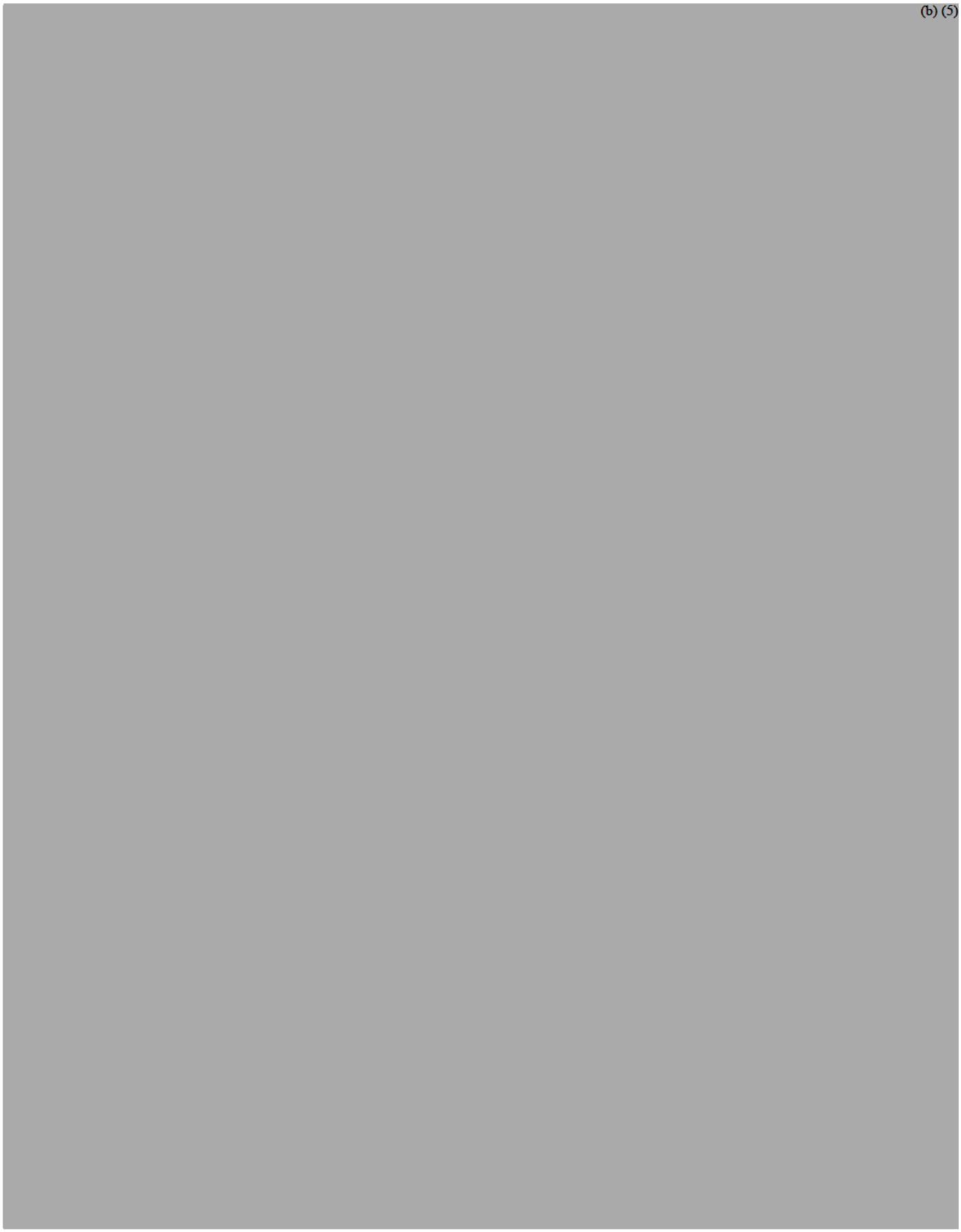
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Appendix D:

Report of Trans-NIH Research

Appendix E:

Research Training and Graduate Medical Education Data

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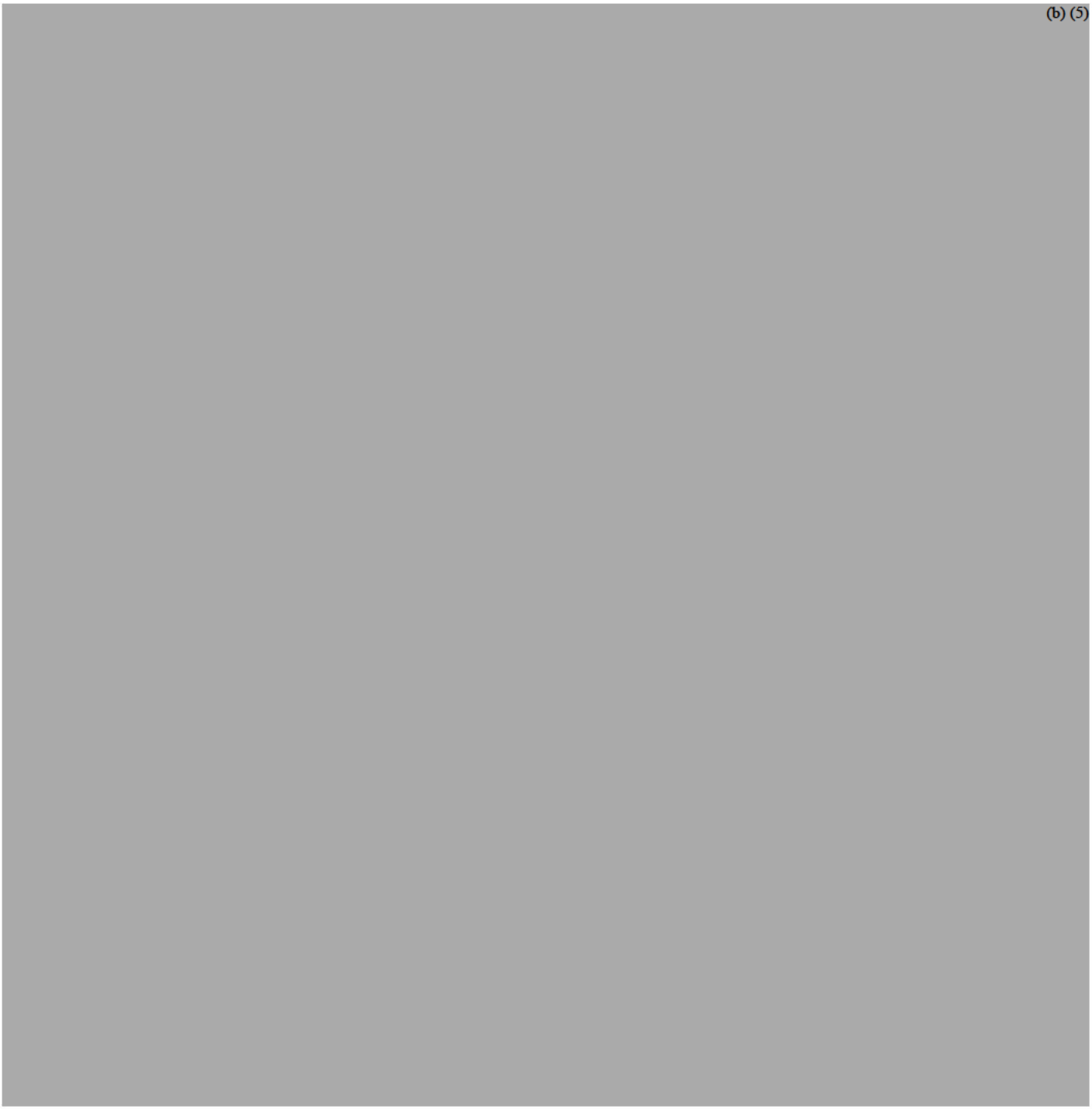

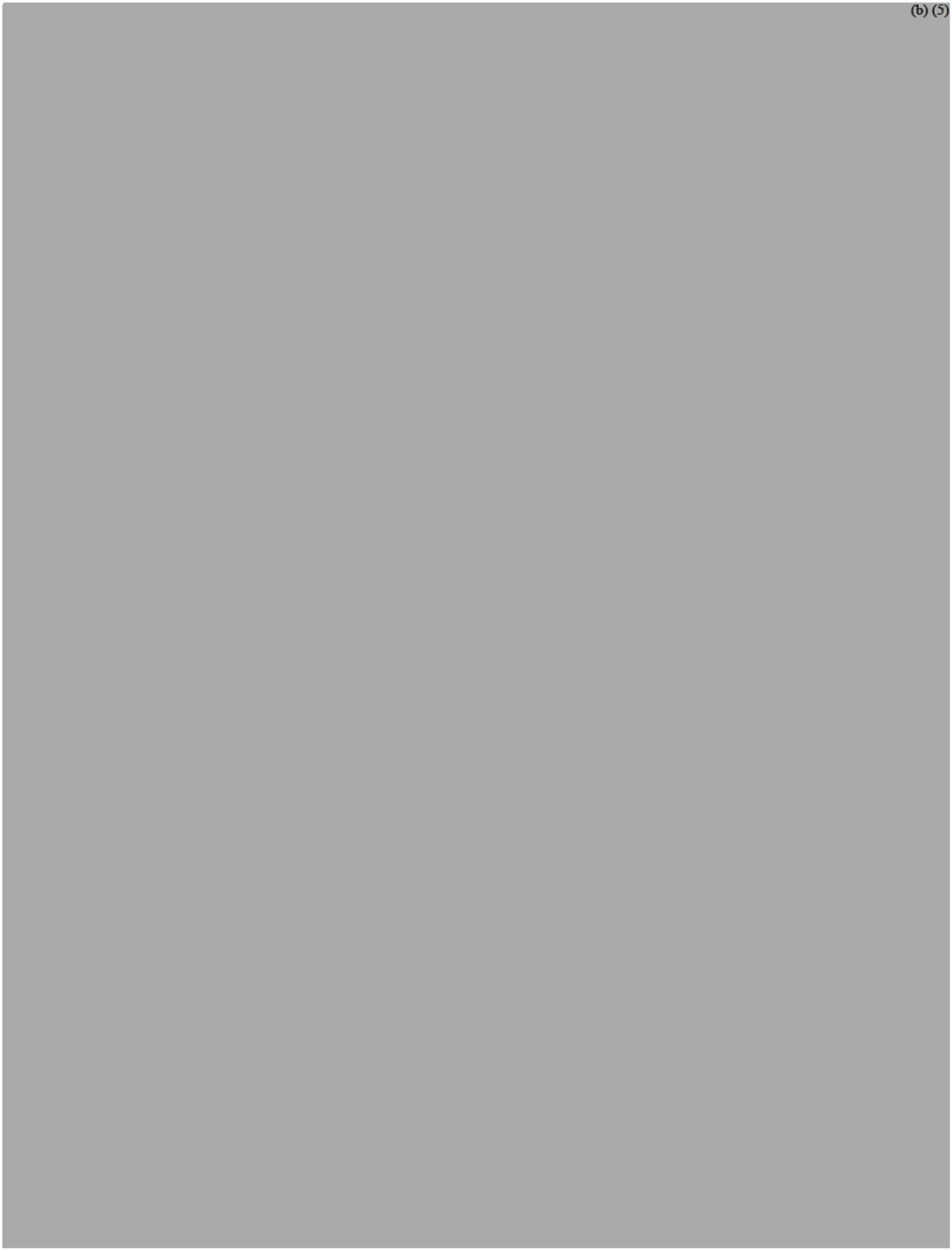
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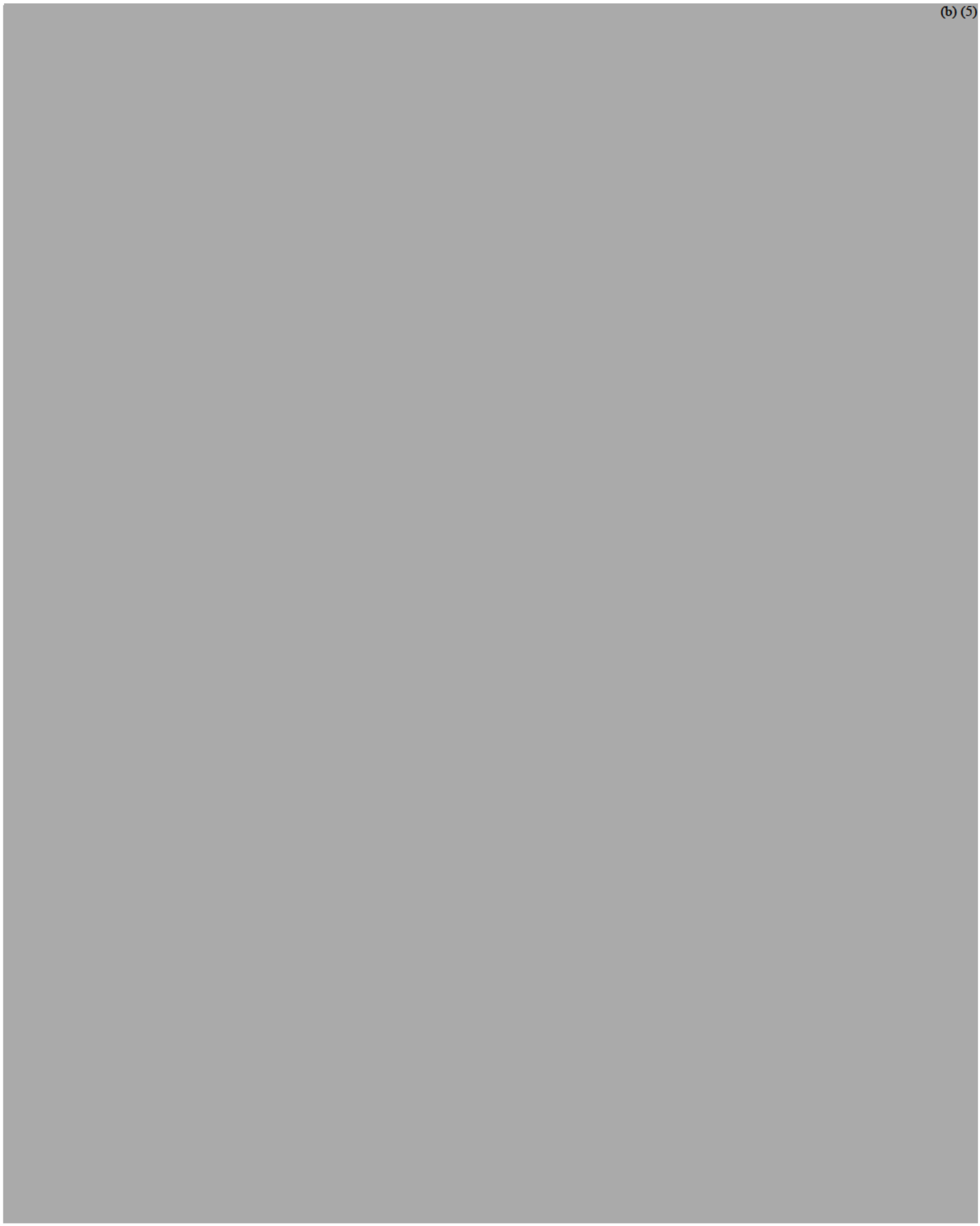
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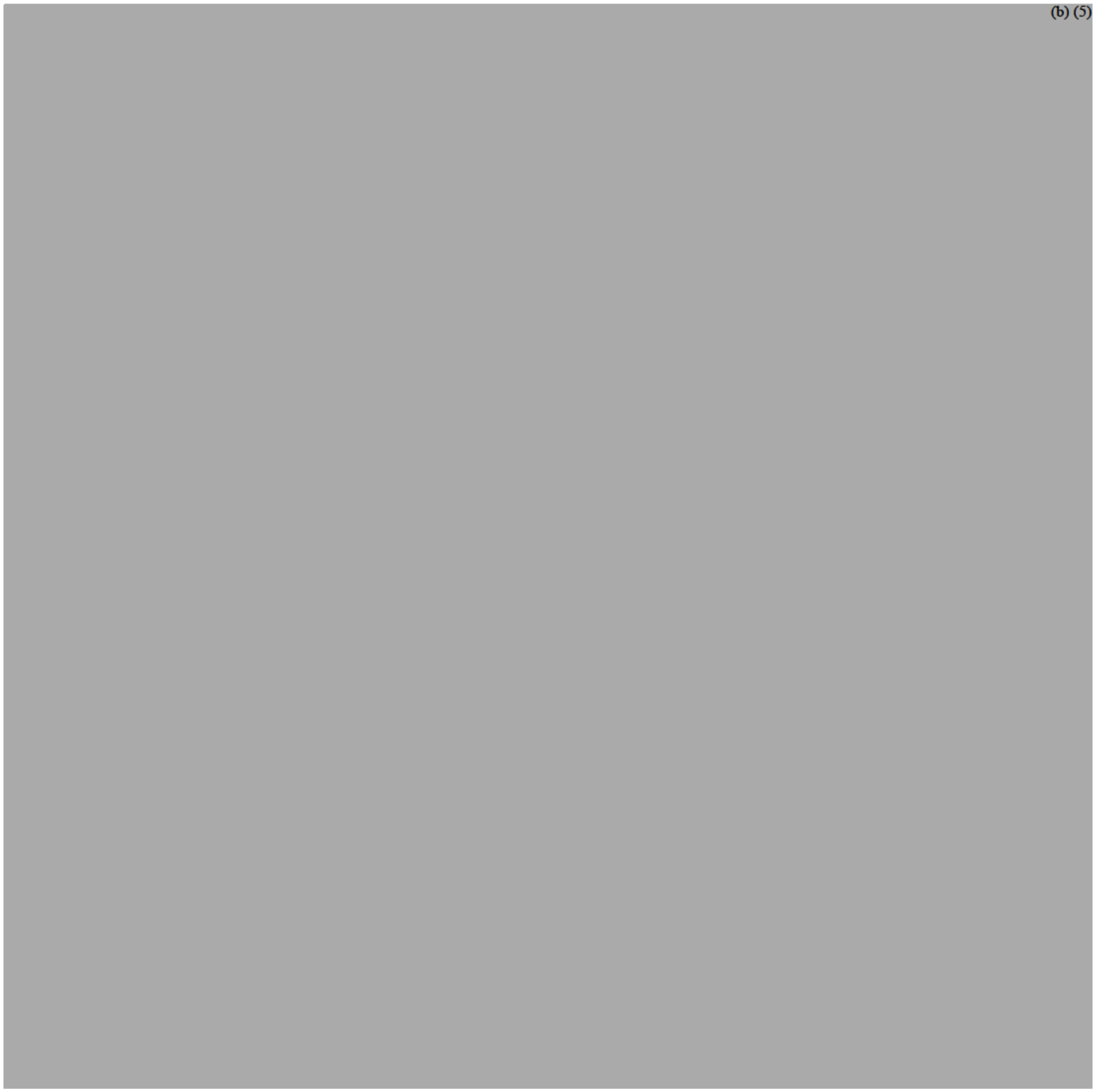
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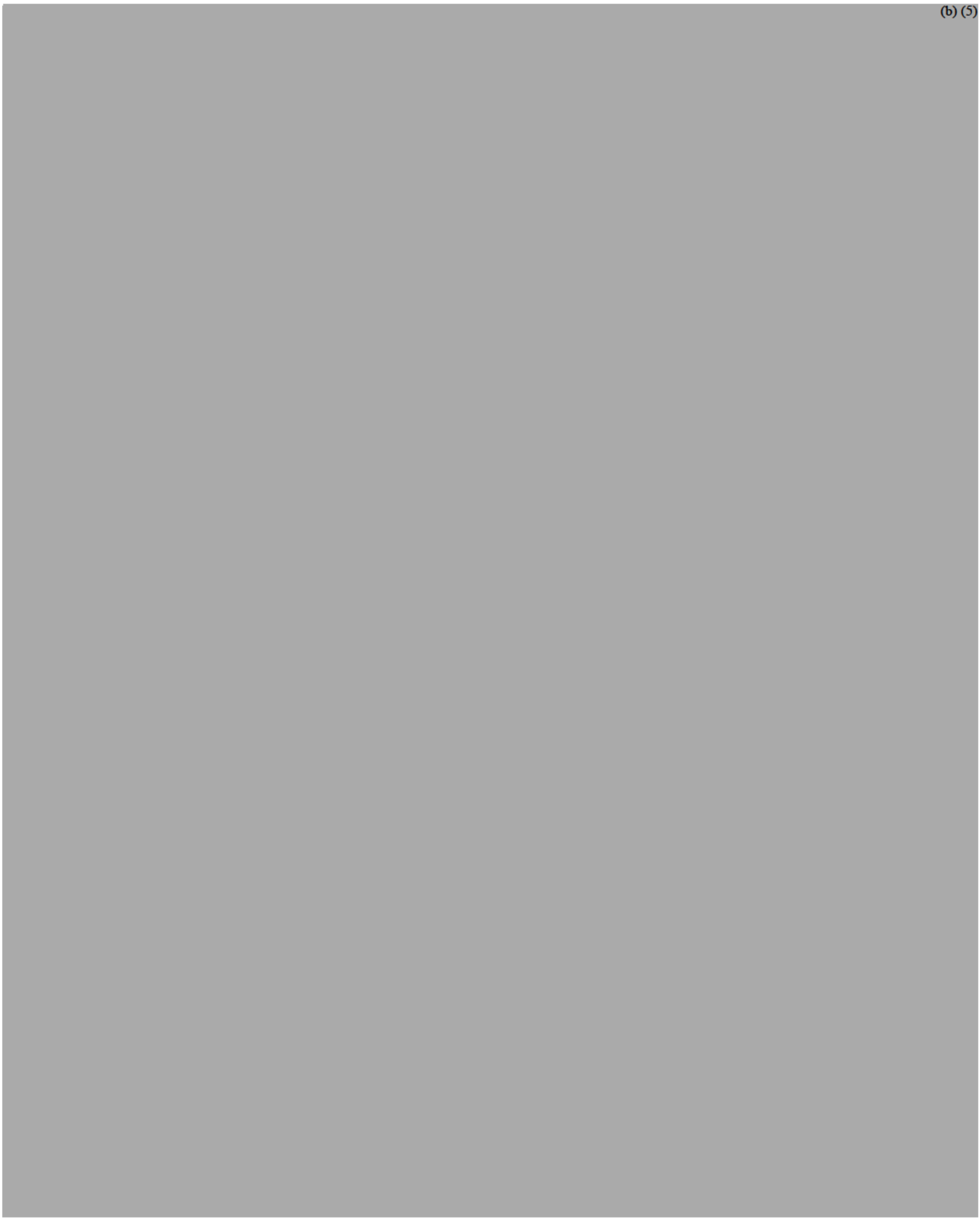
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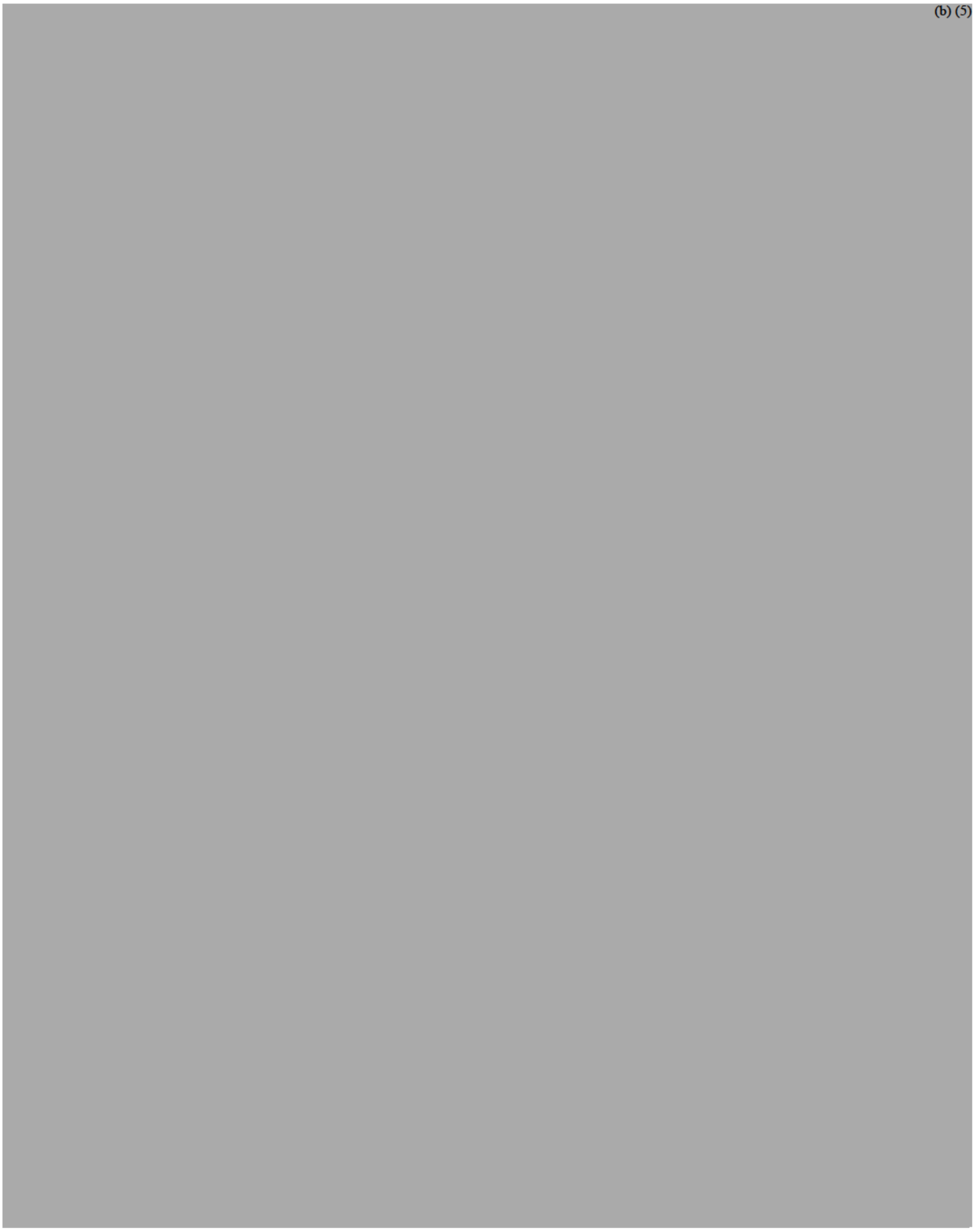
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Appendix F:

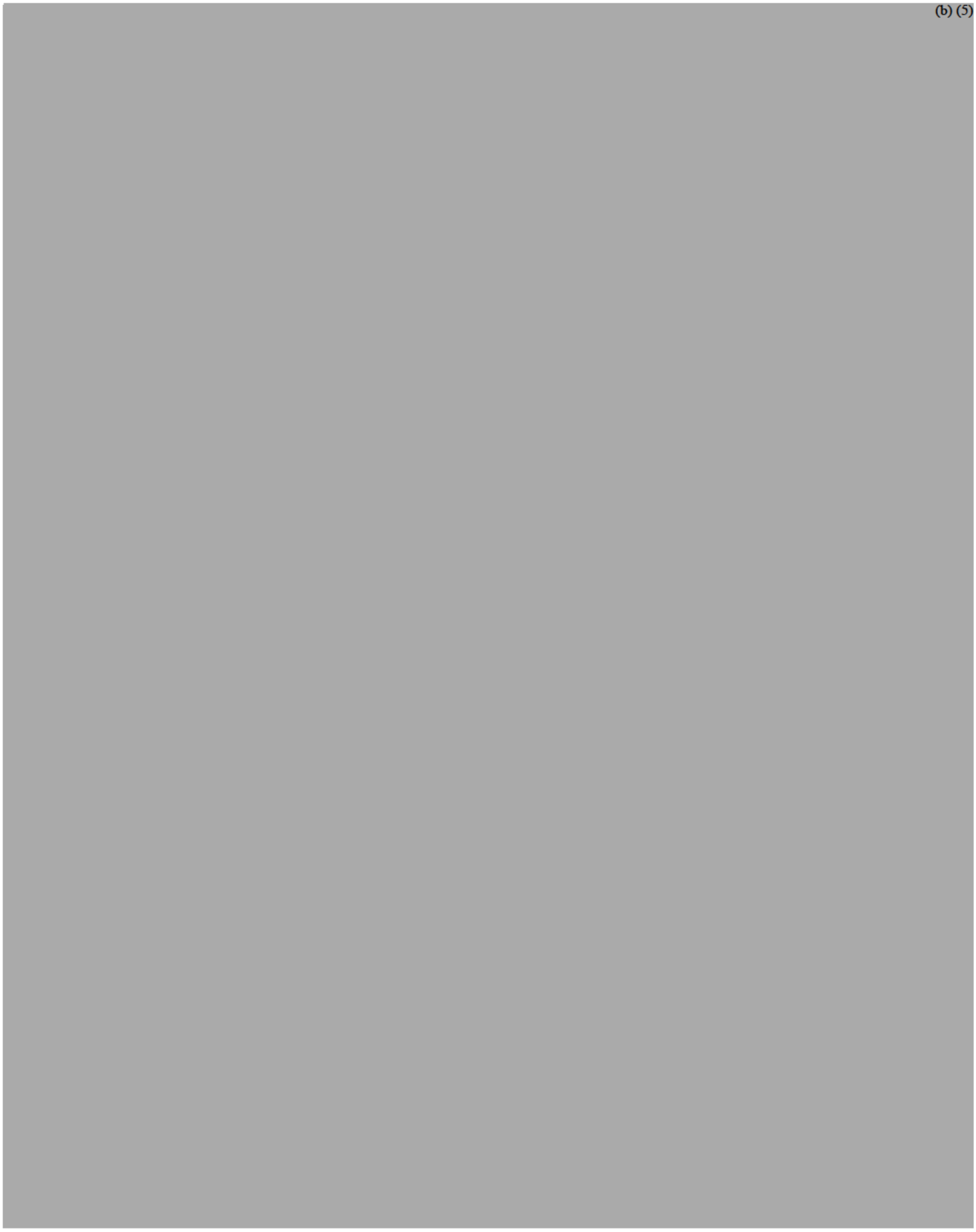
Monitoring Adherence to the NIH Policy on the Inclusion of Women and Minorities as Subjects in Clinical Research

(b) (5)

Appendix G:

Catalog of Disease Registries, Databases, and Biomedical Information Systems

(b) (5)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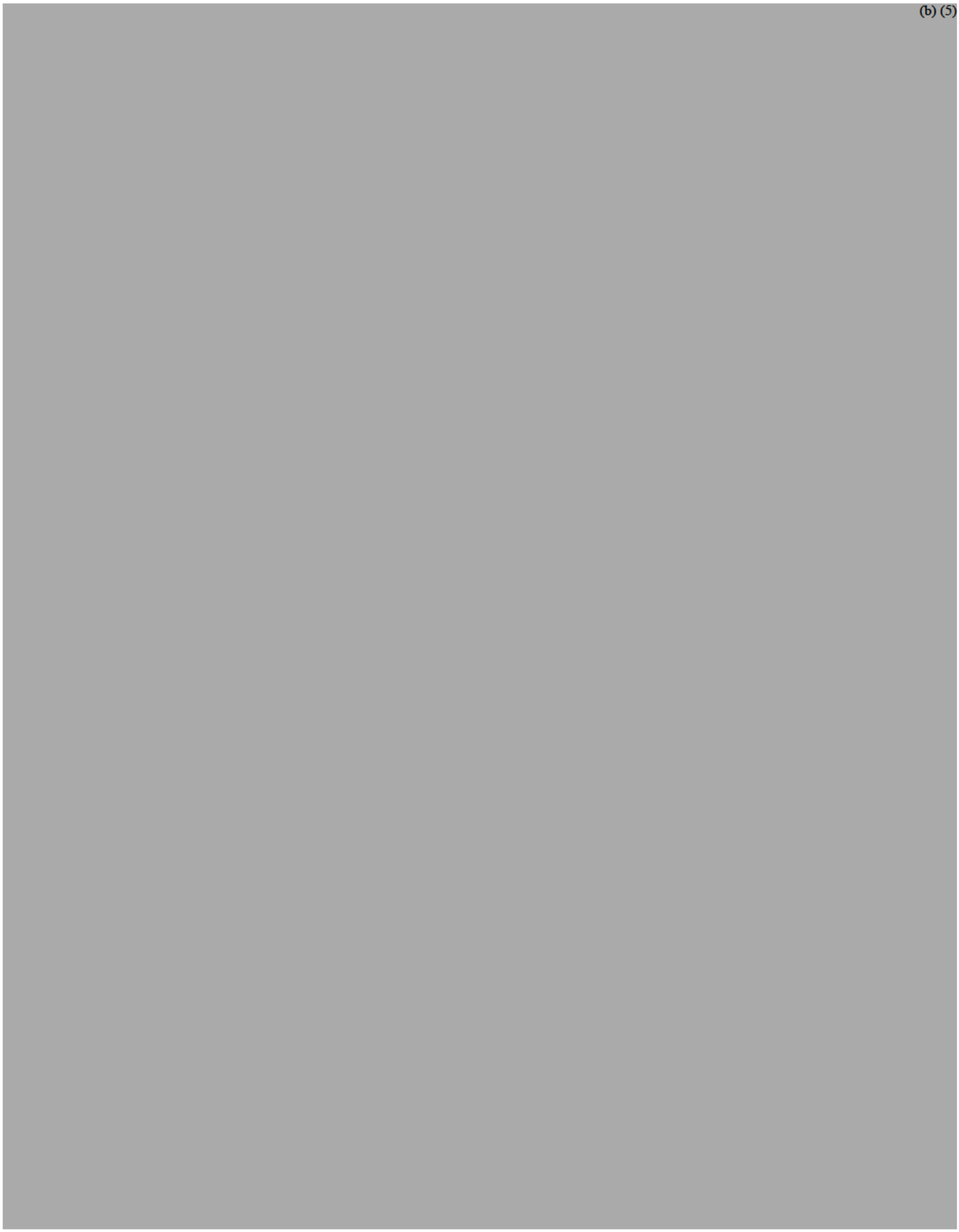
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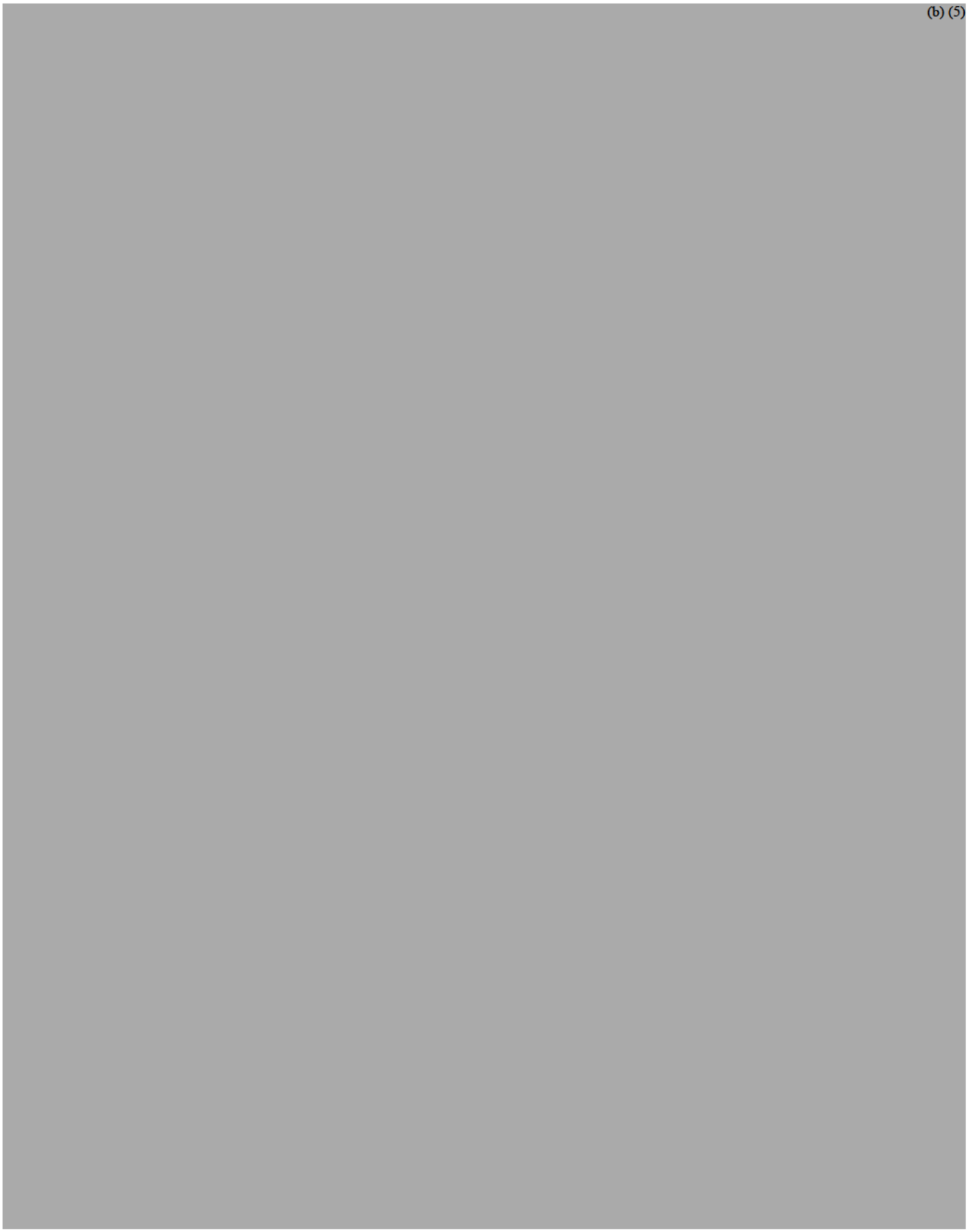
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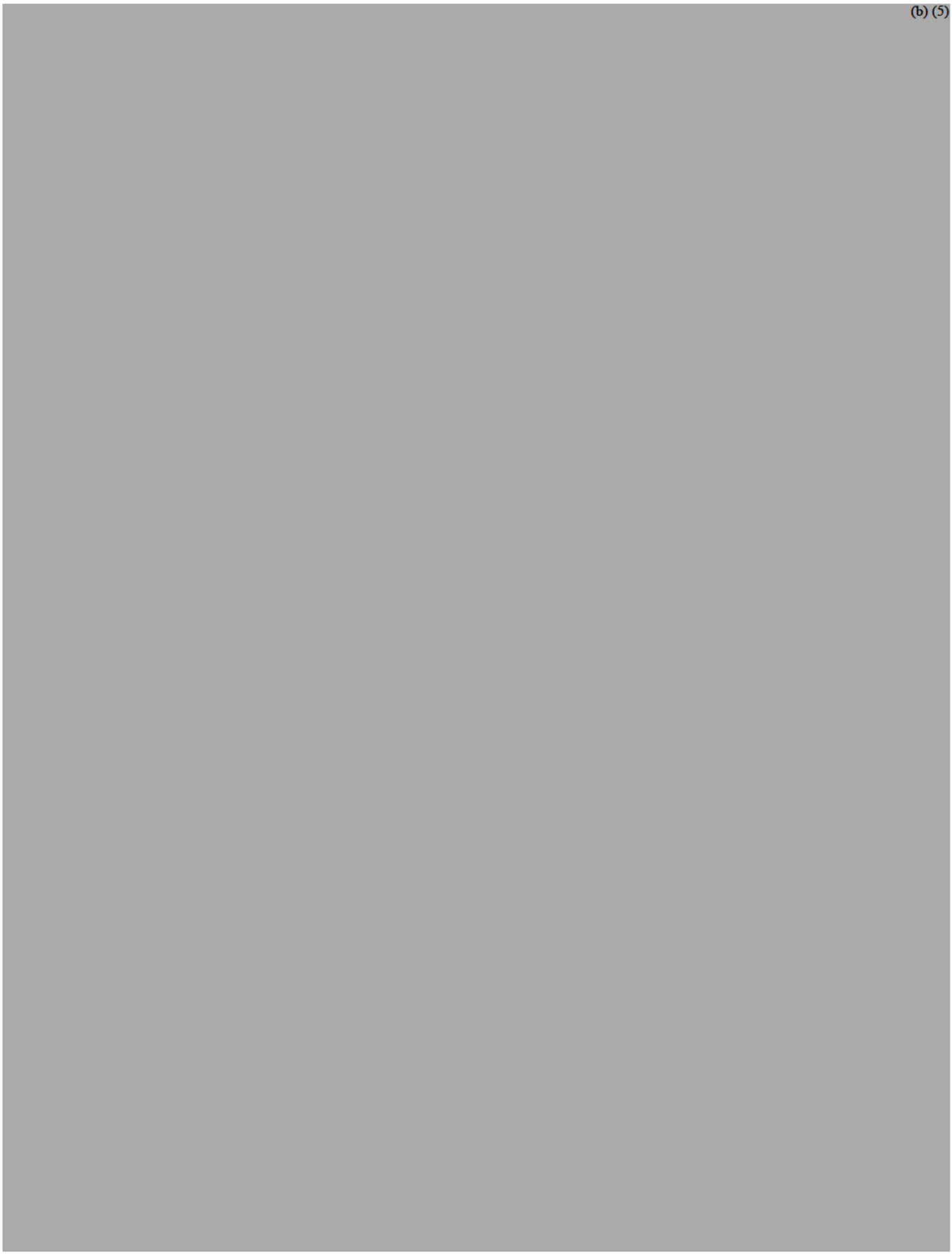
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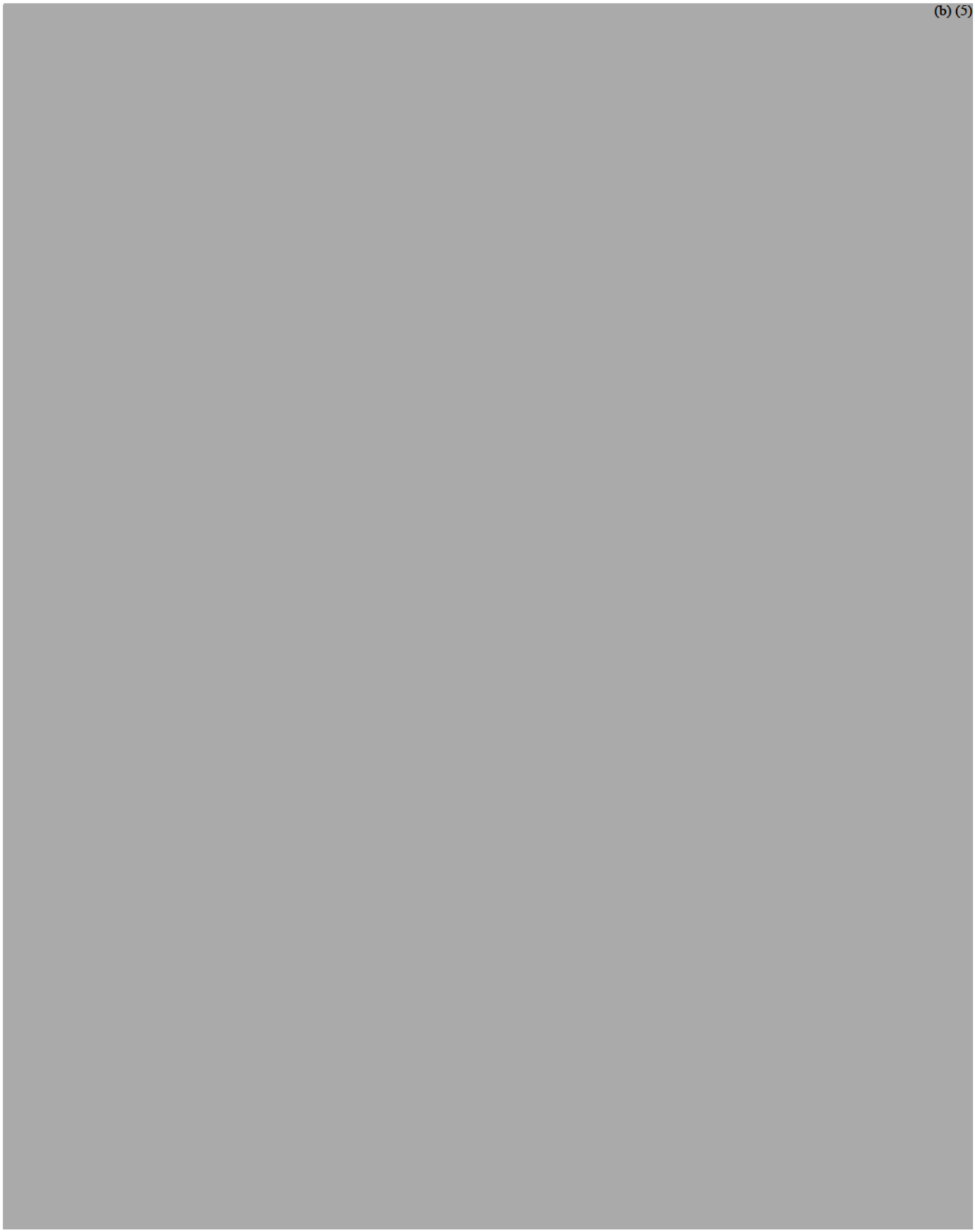
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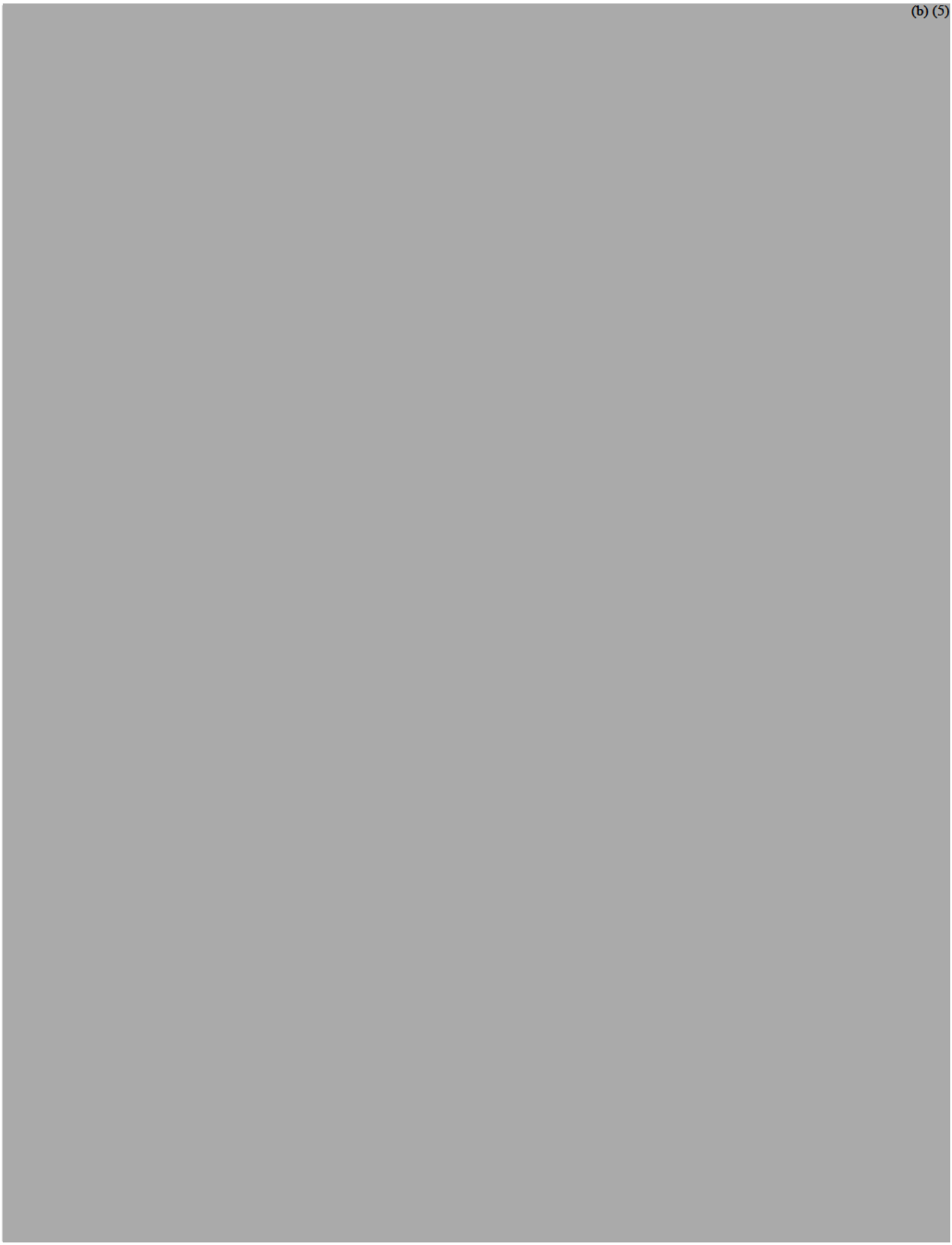
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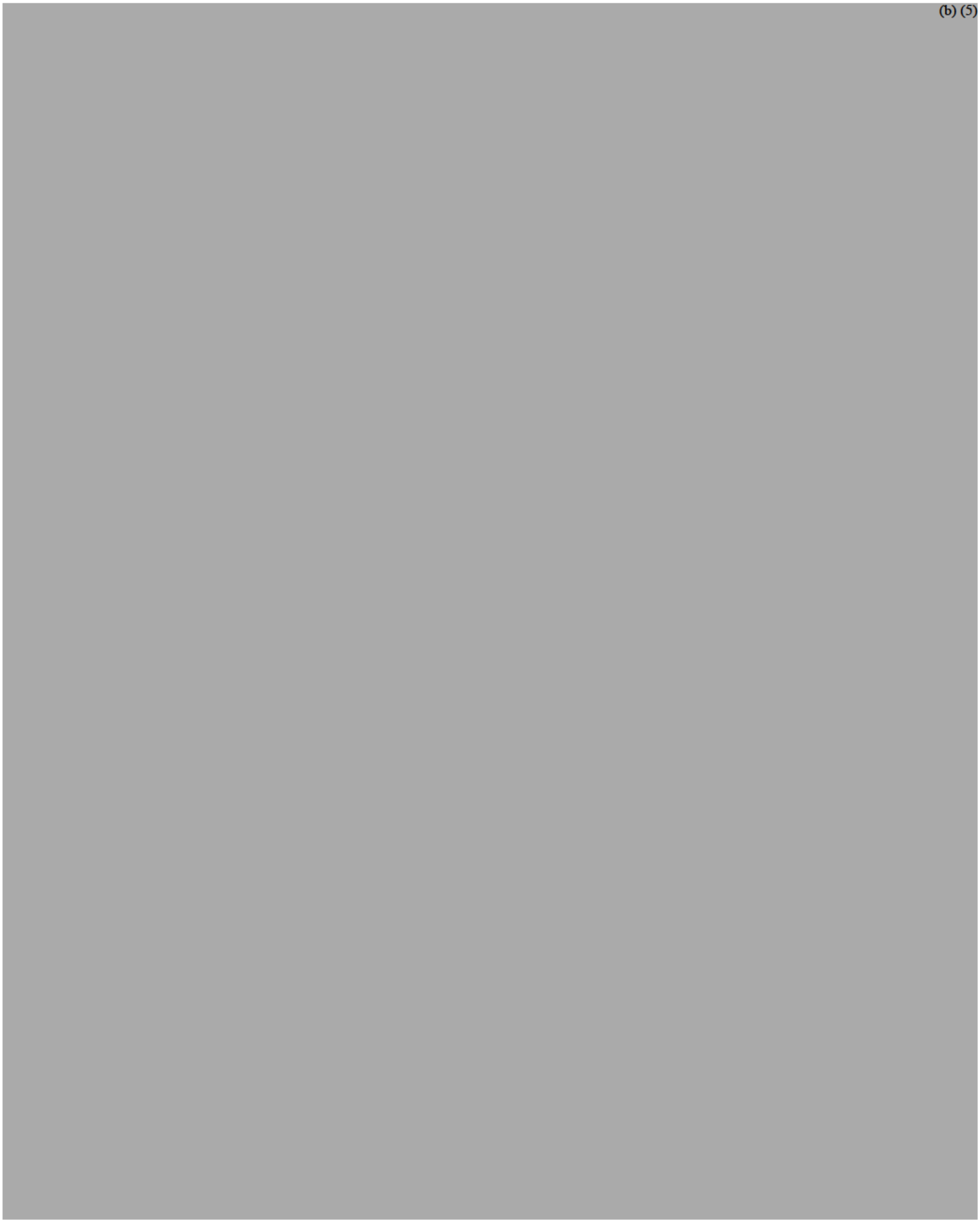
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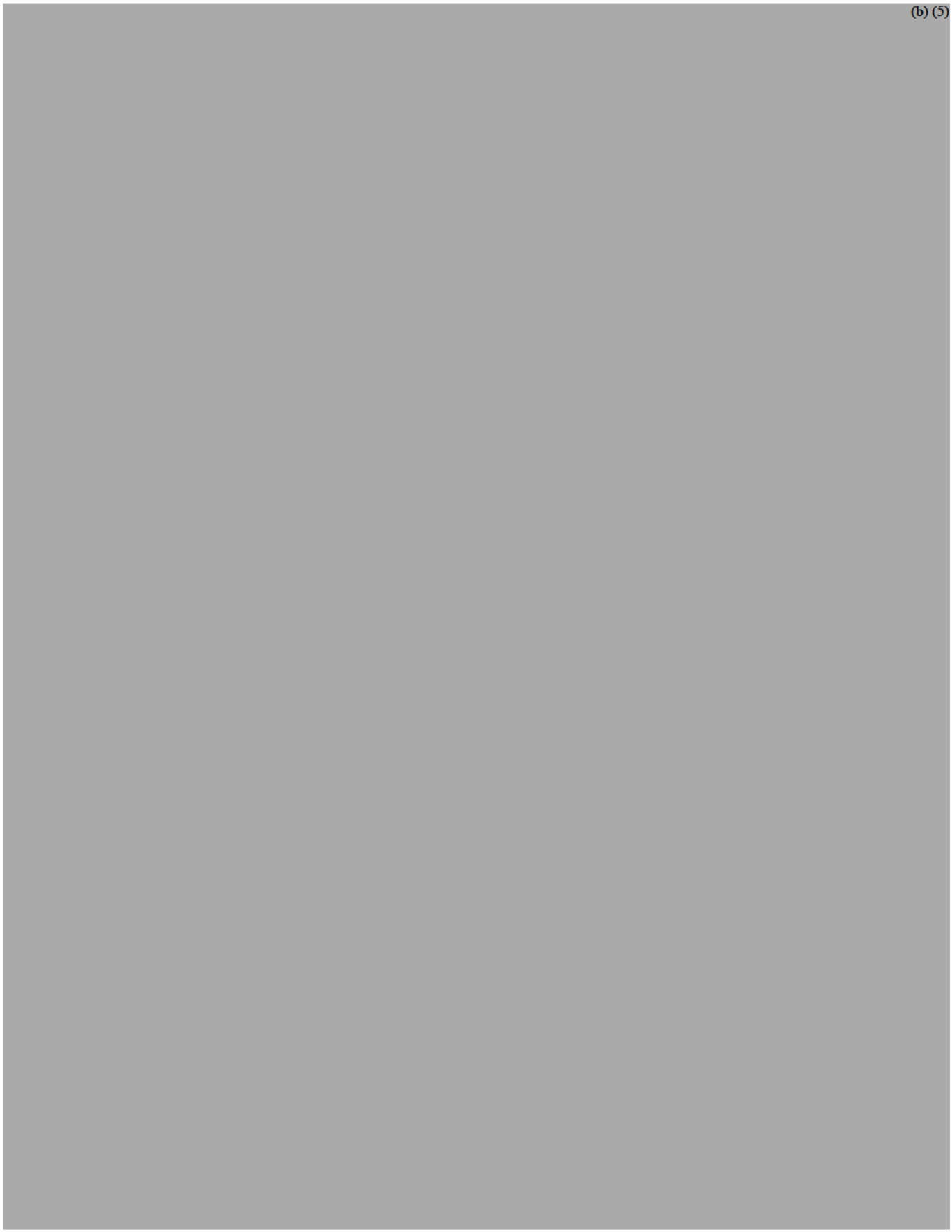
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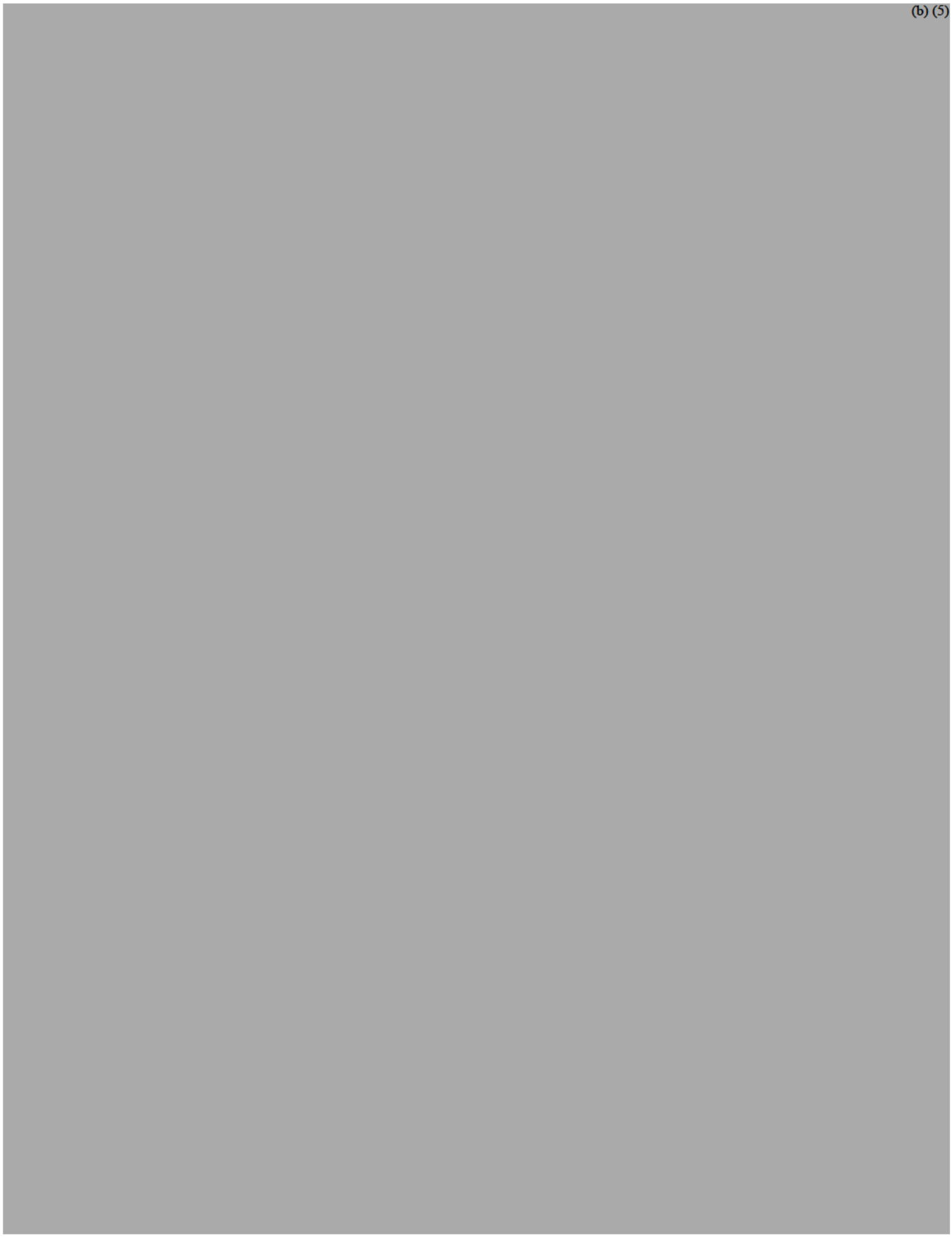
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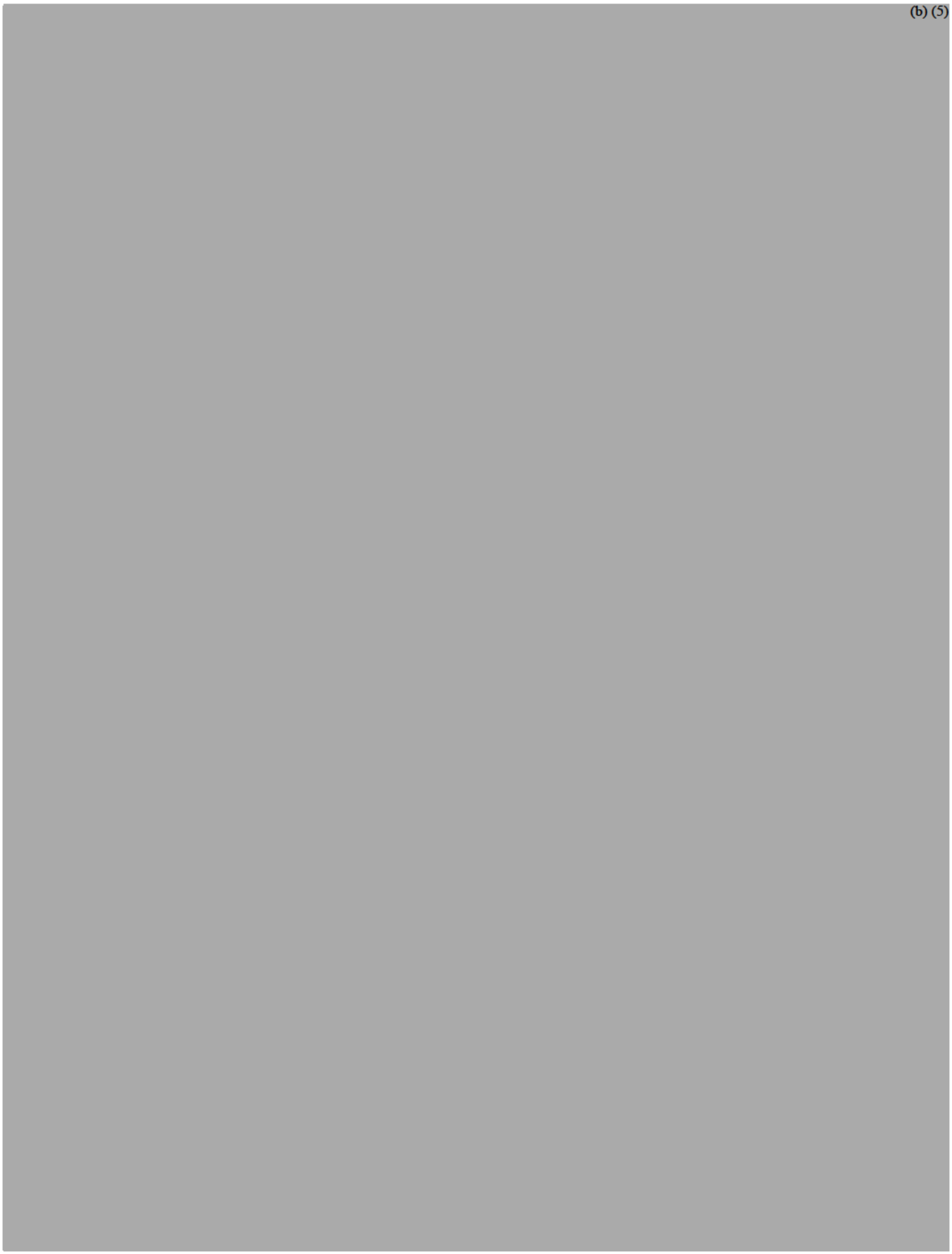
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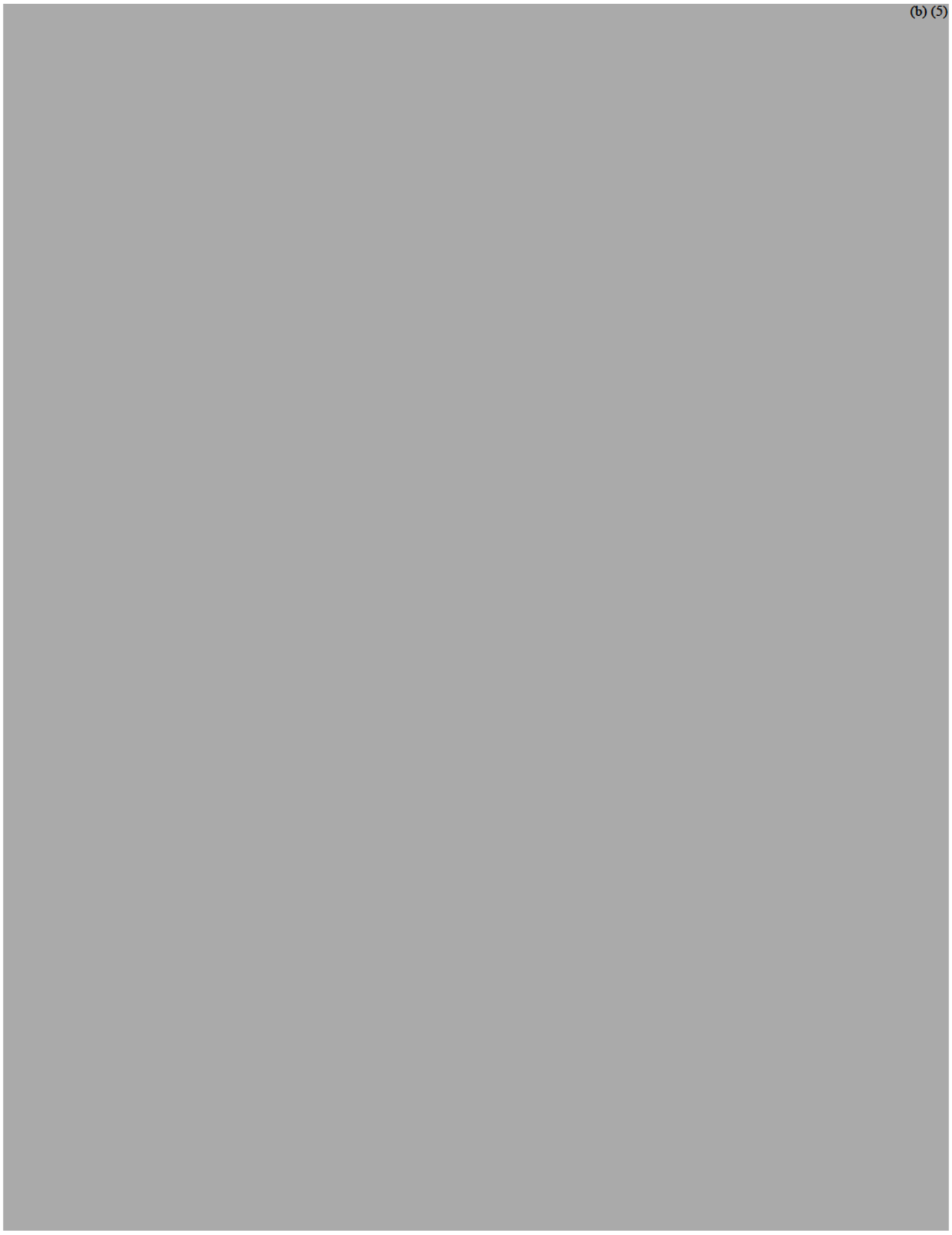
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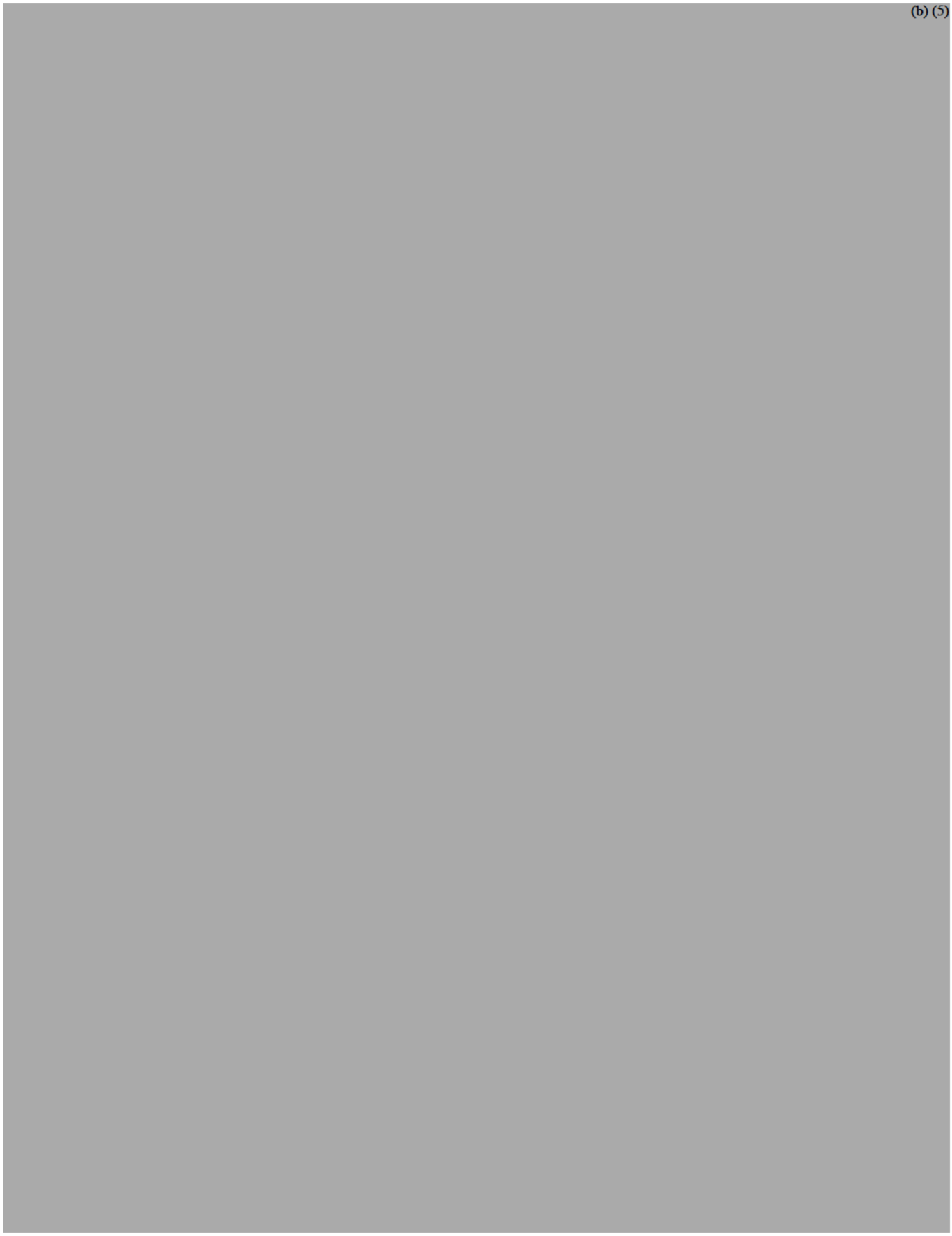
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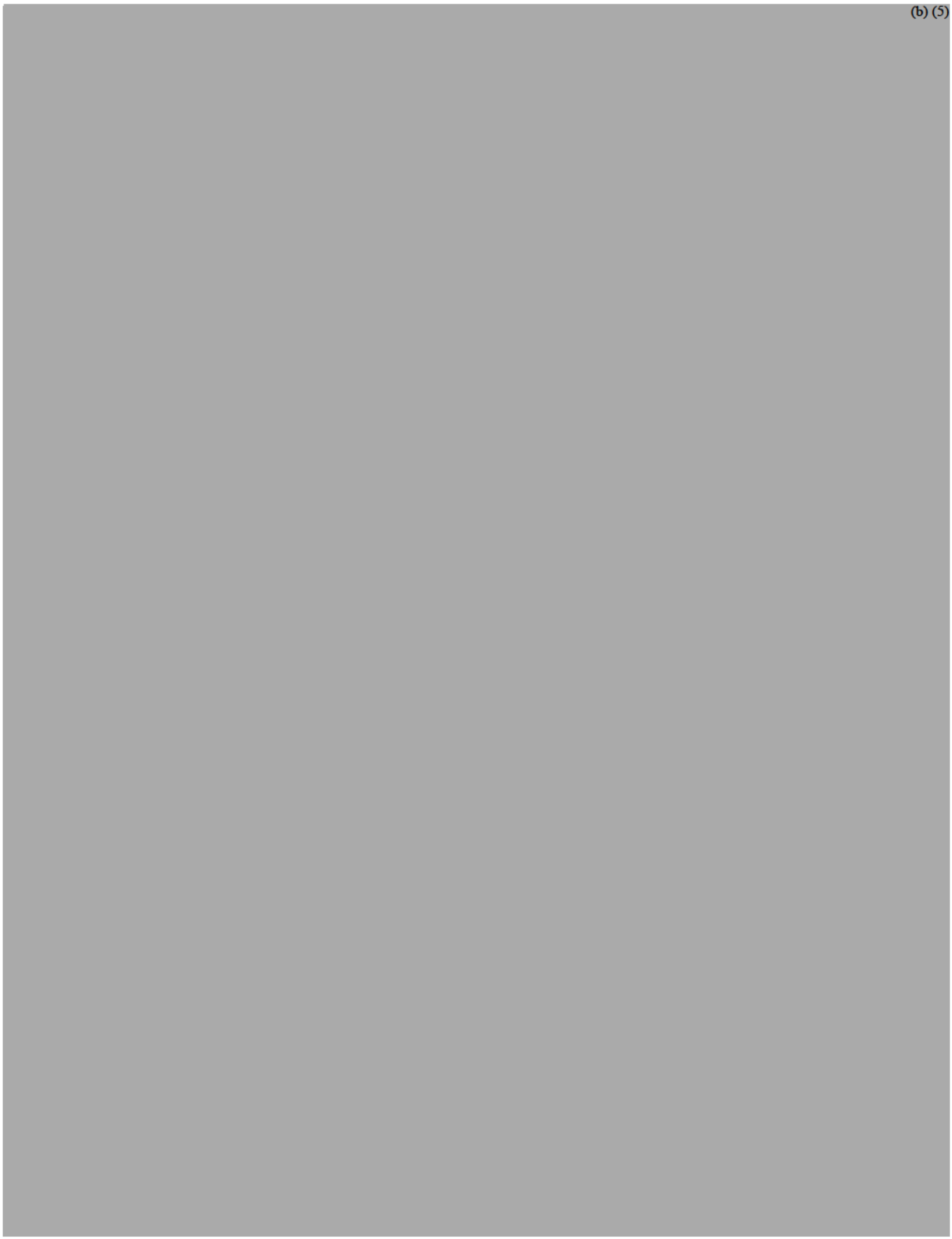
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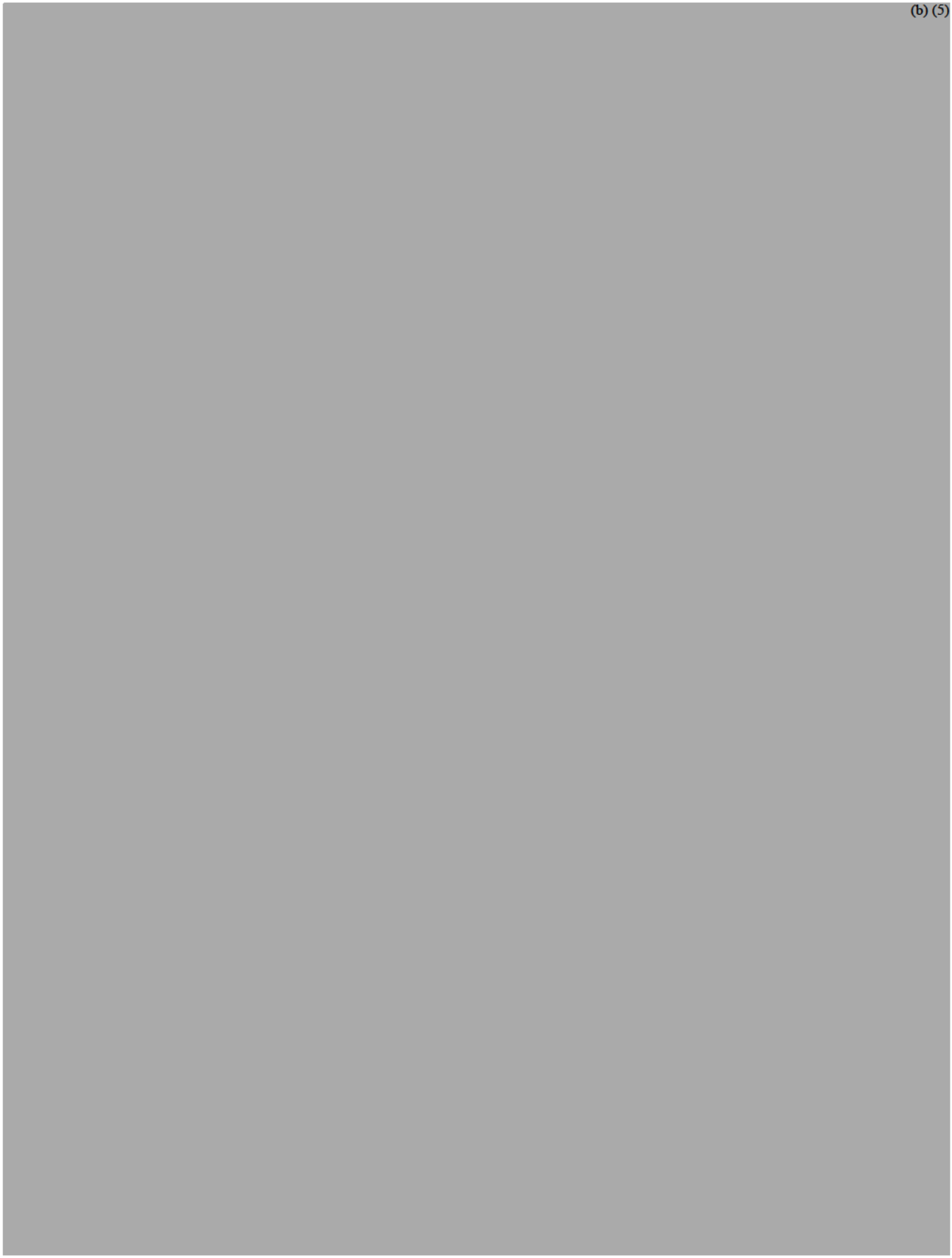
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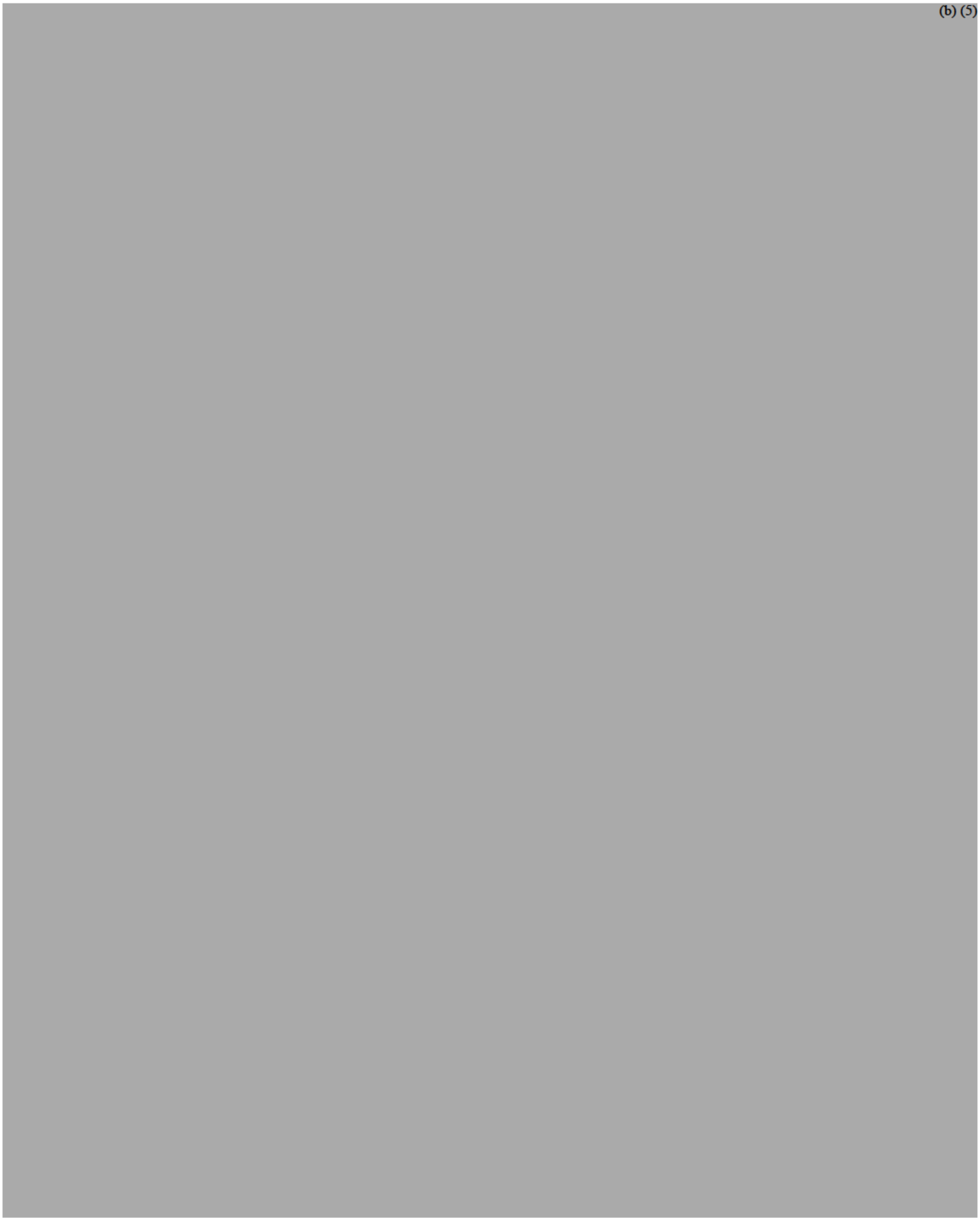
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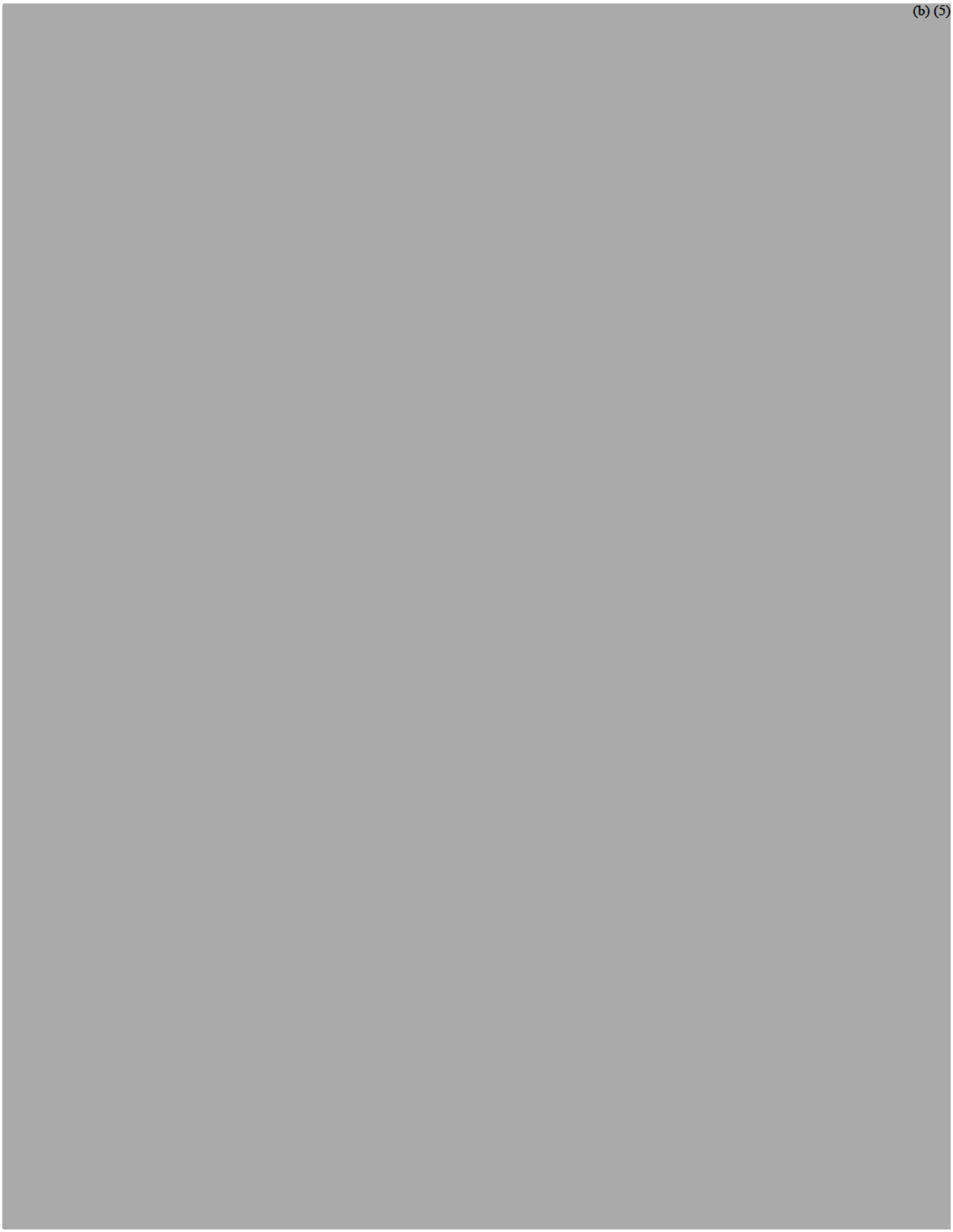
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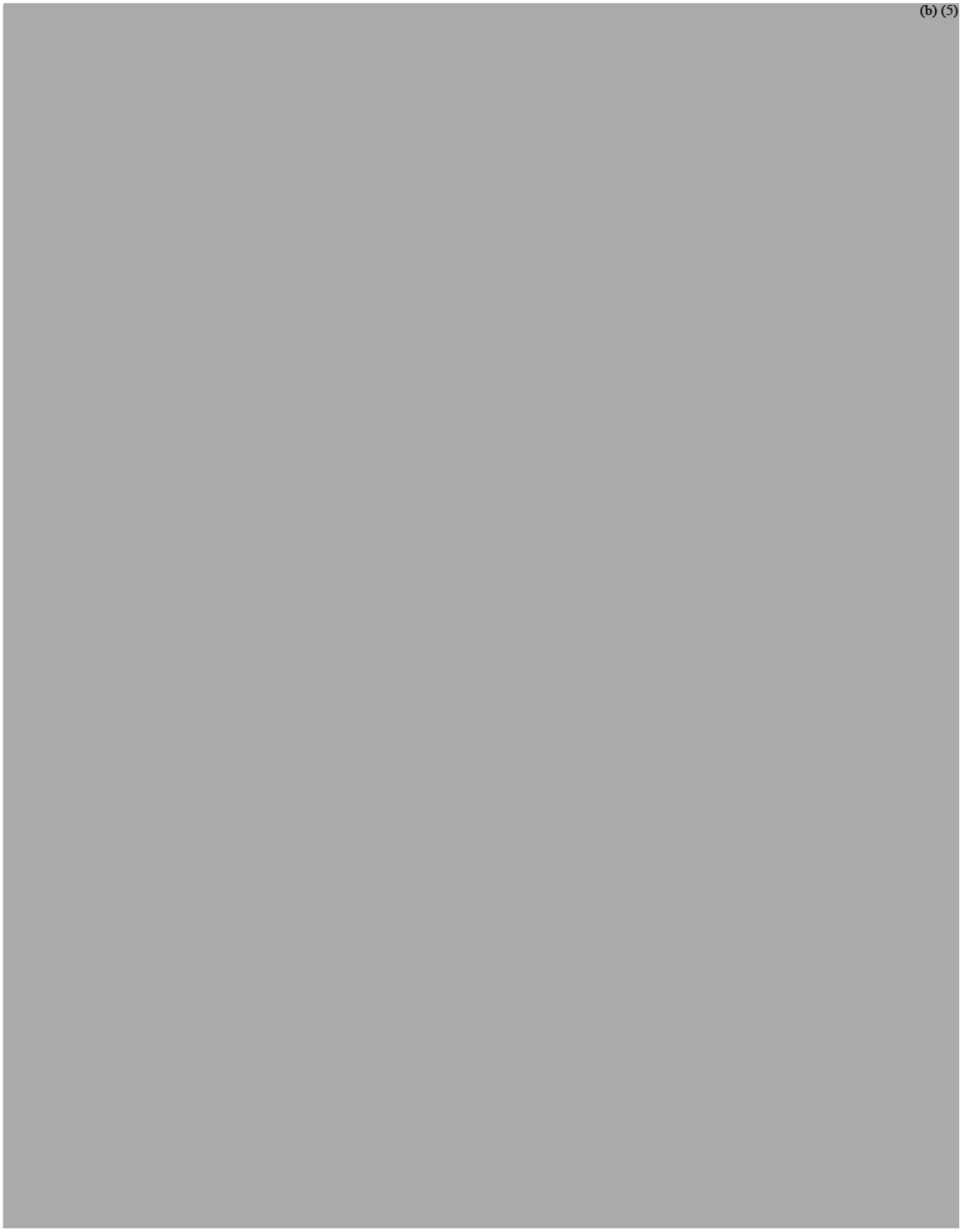
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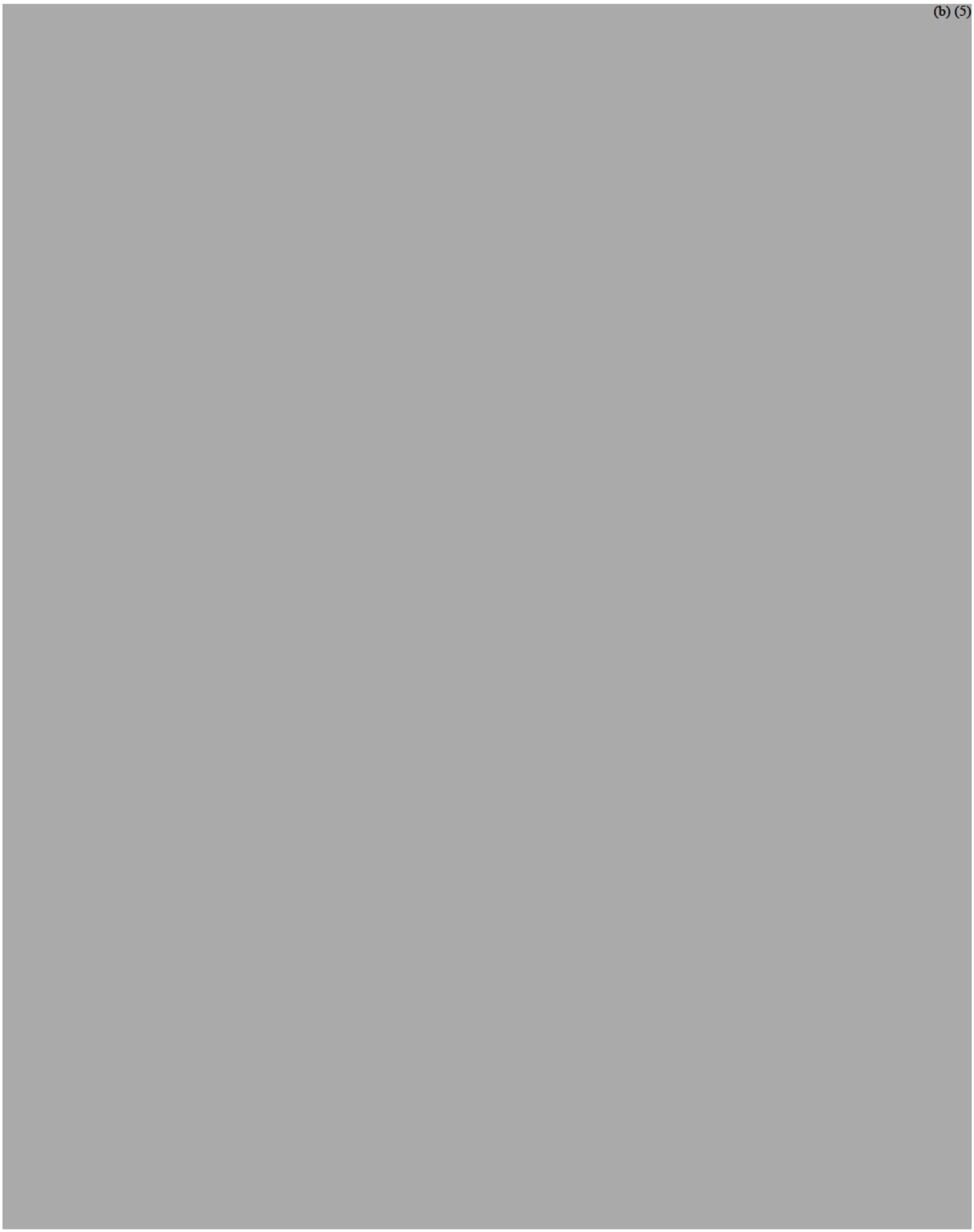
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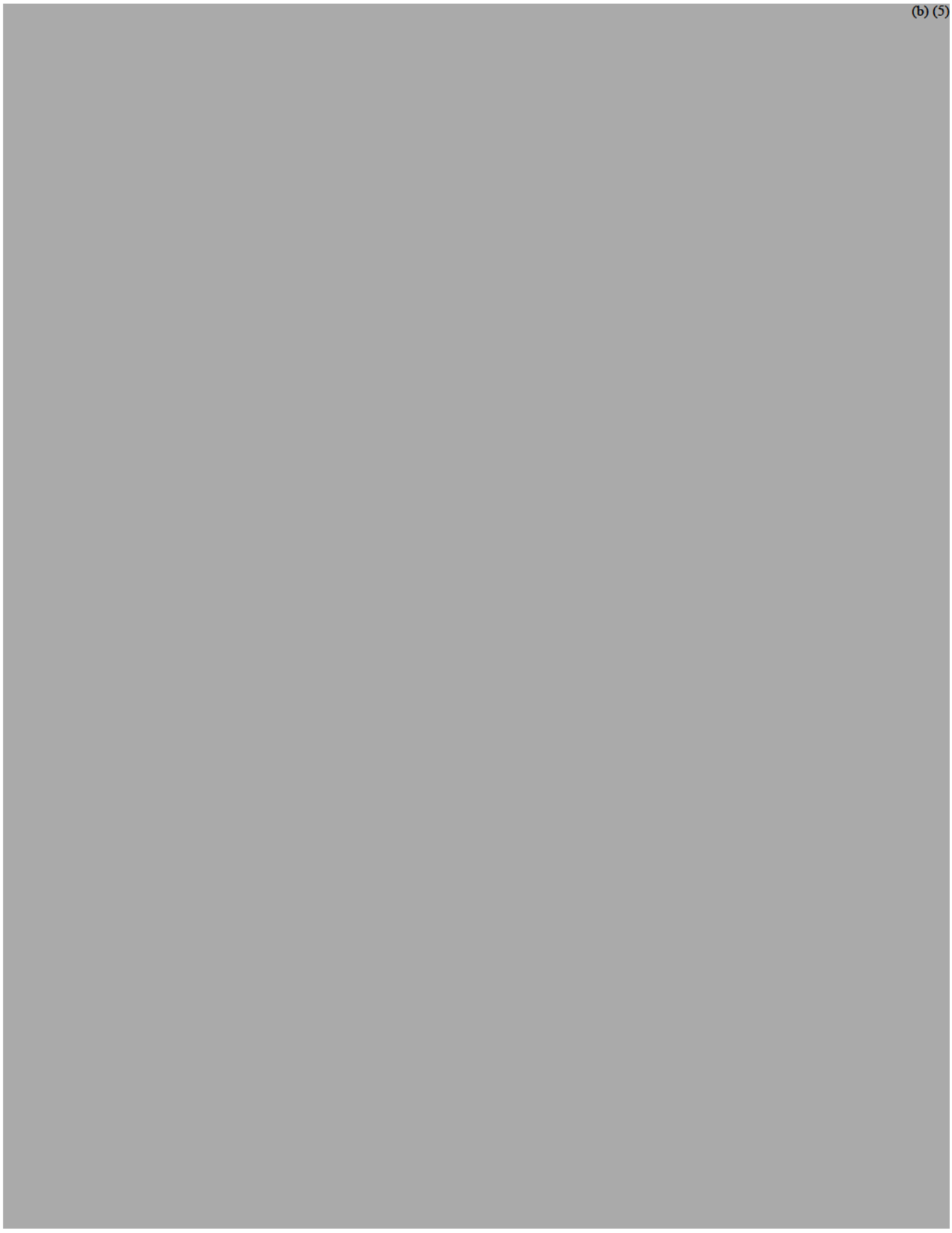
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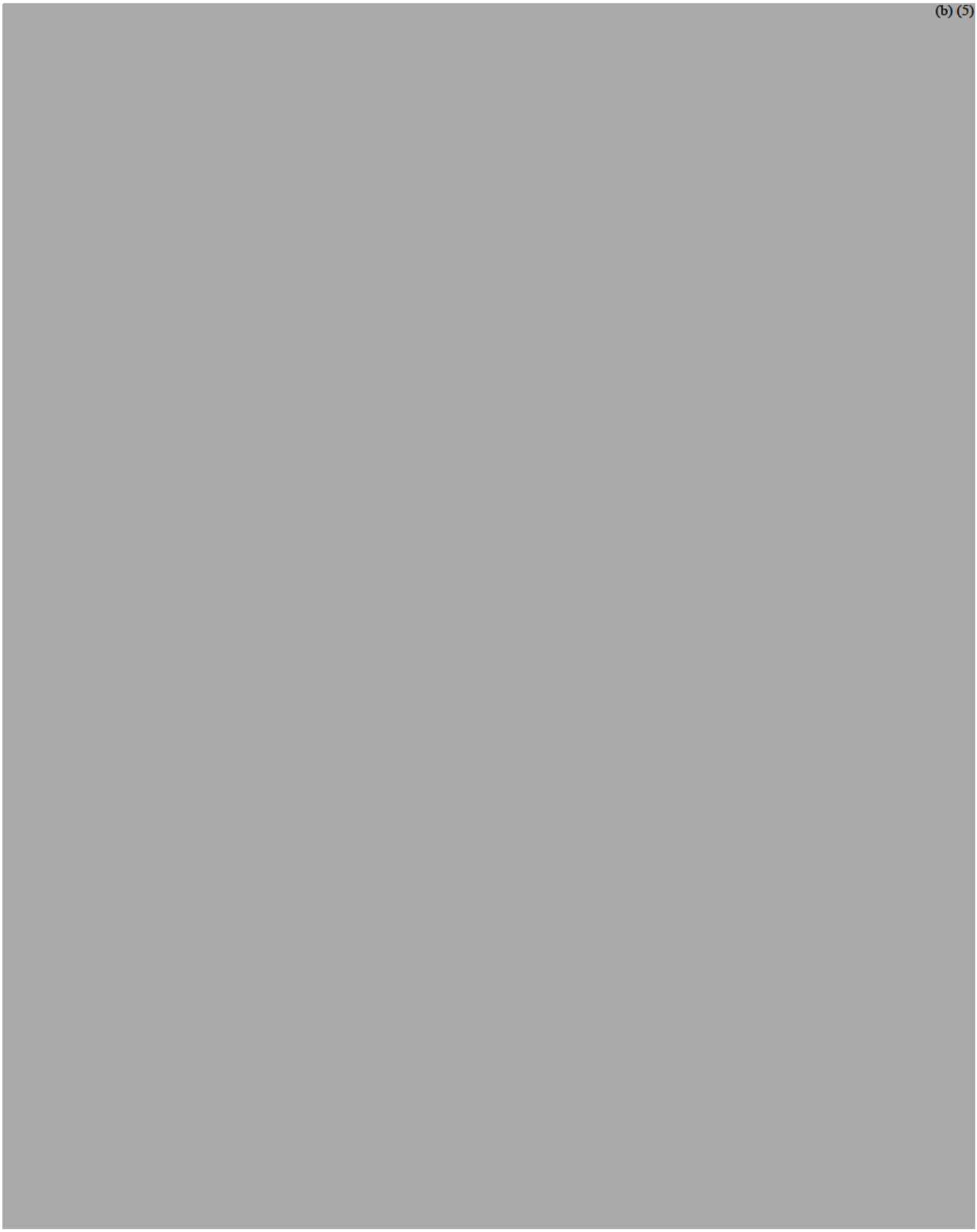
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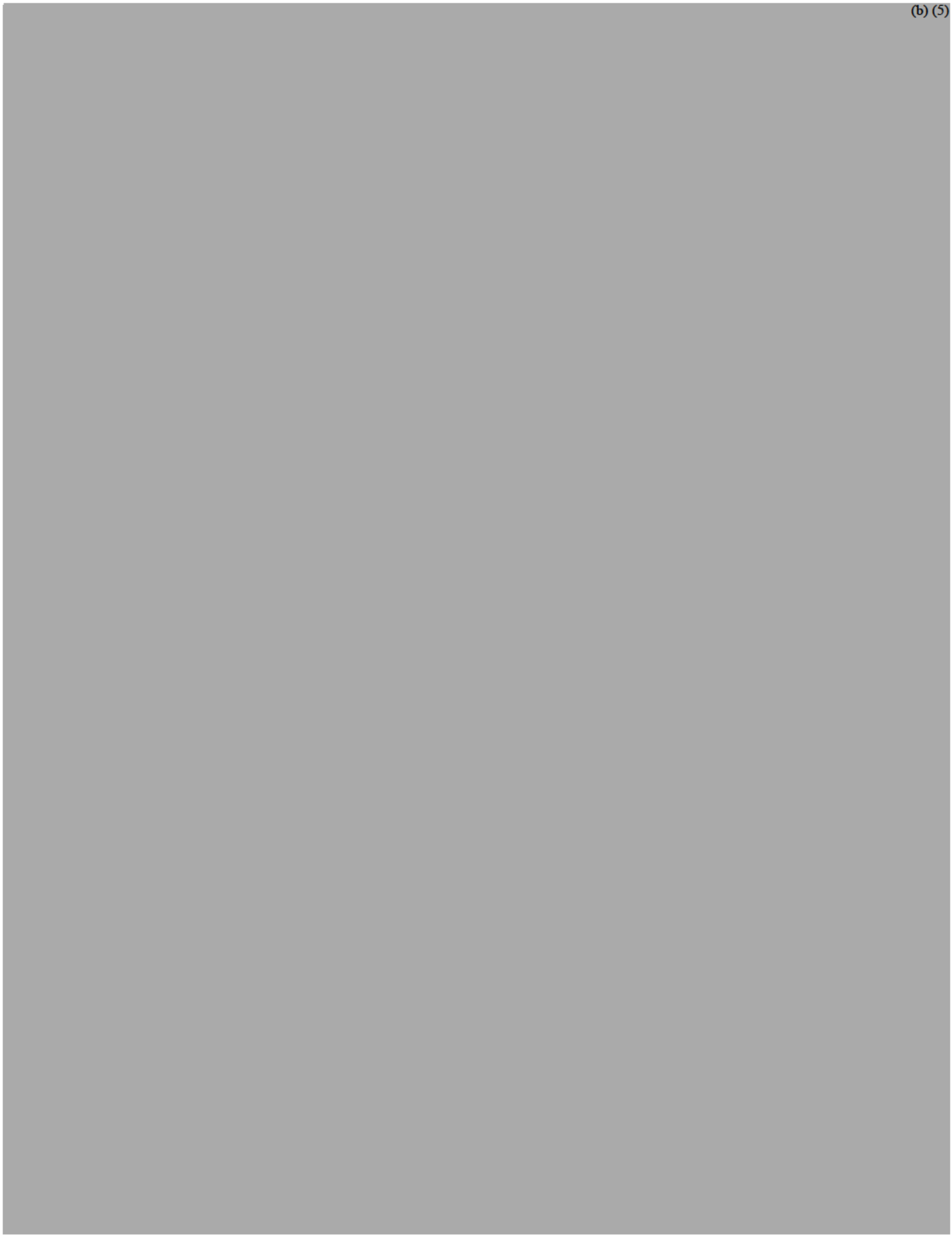
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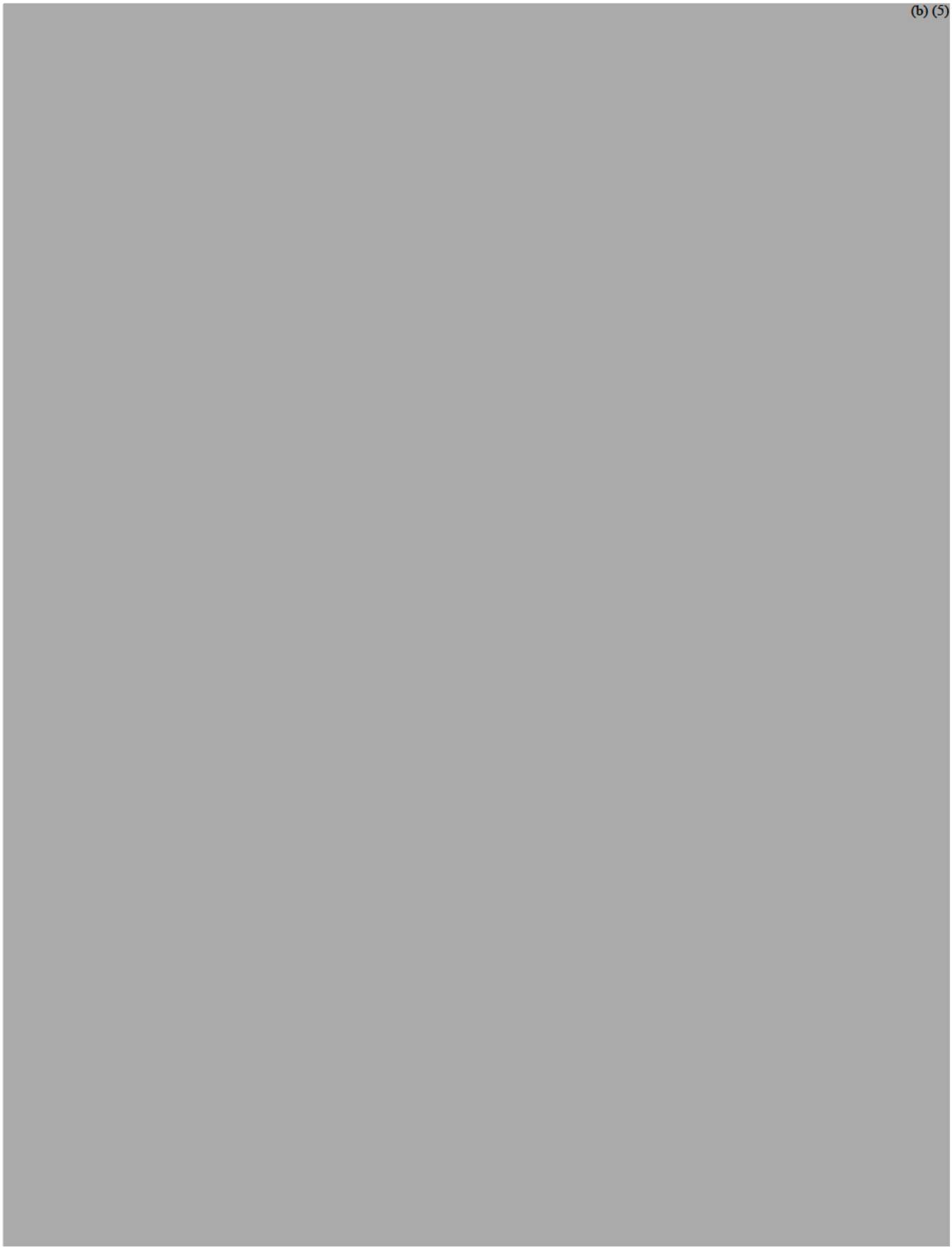
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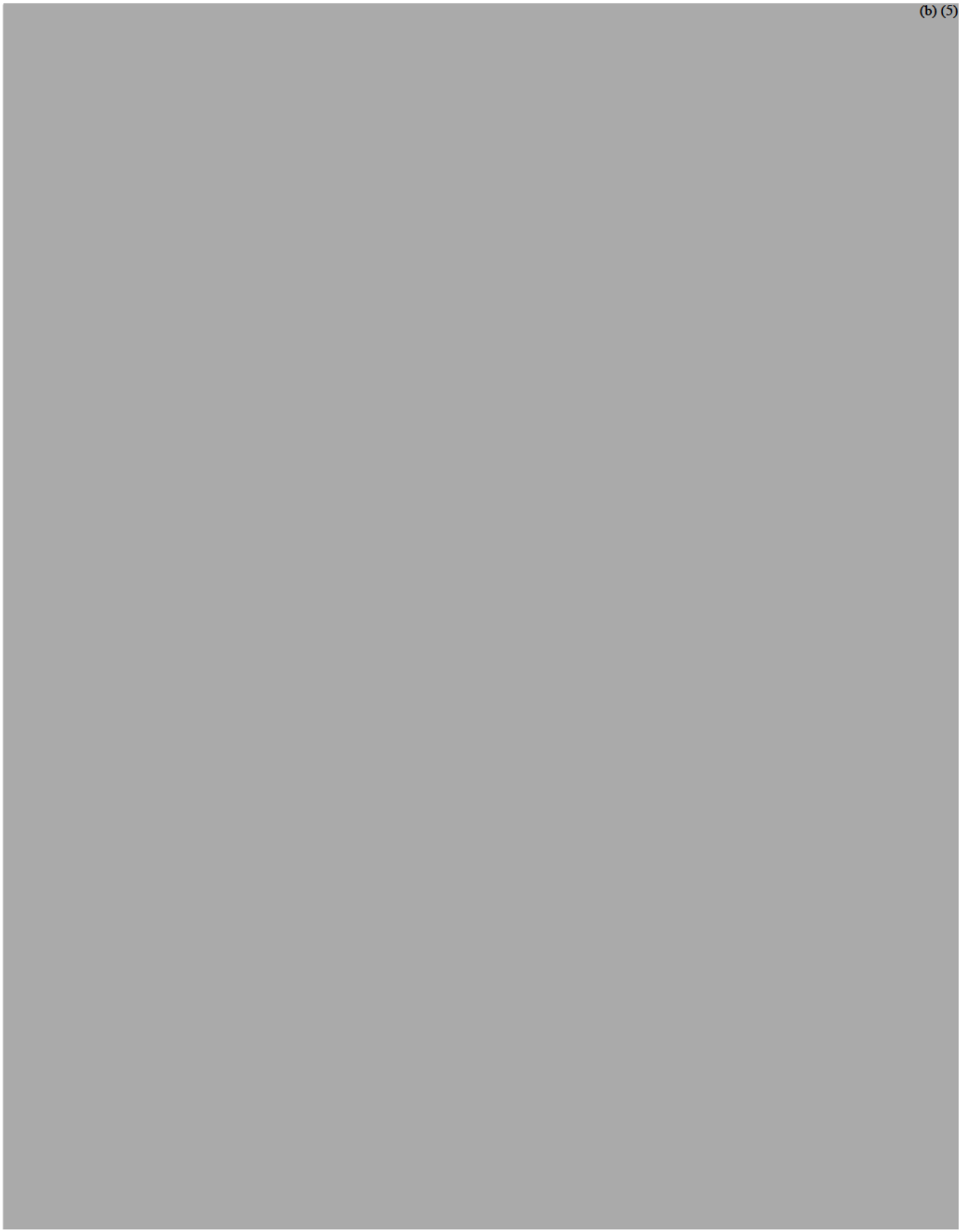
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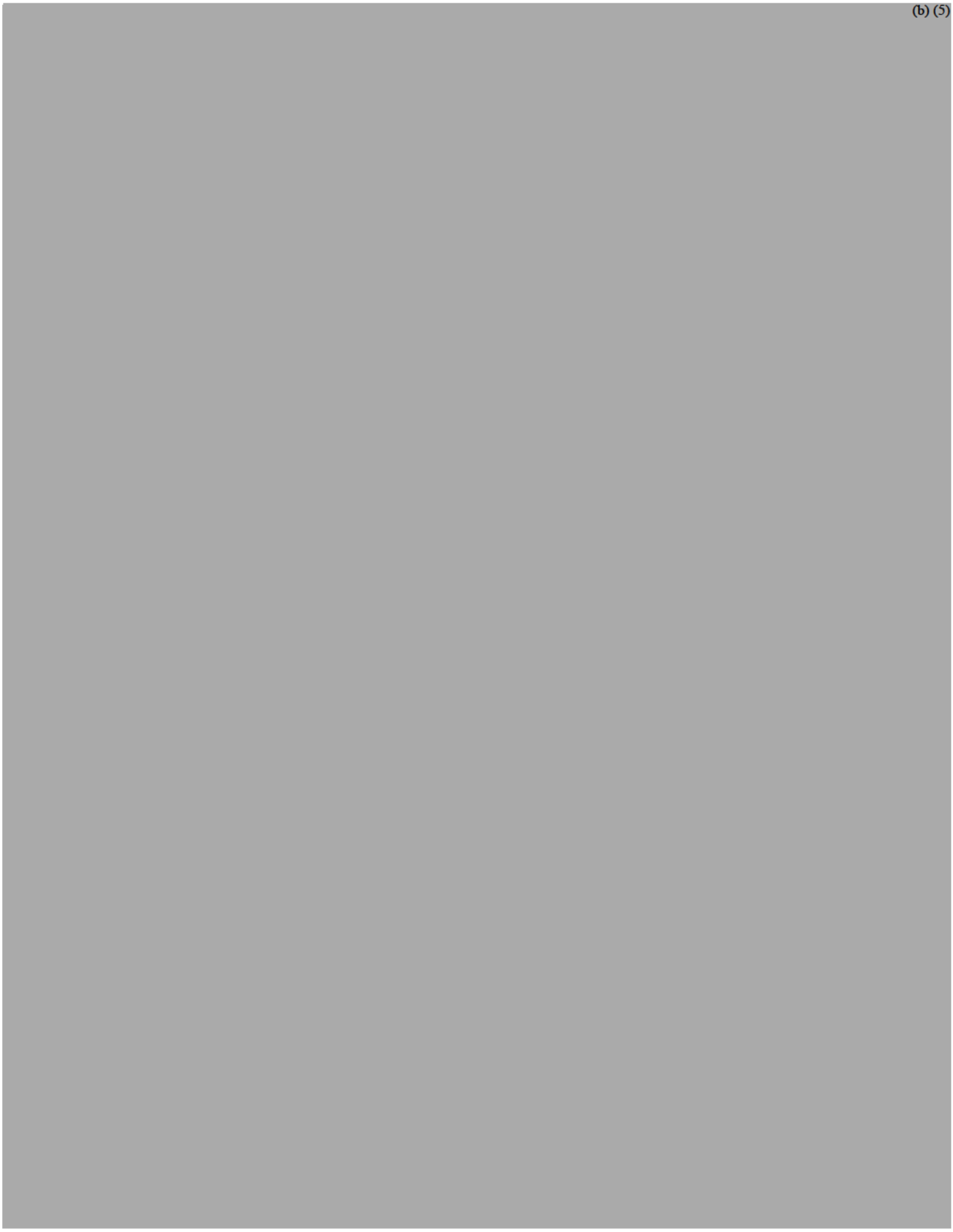
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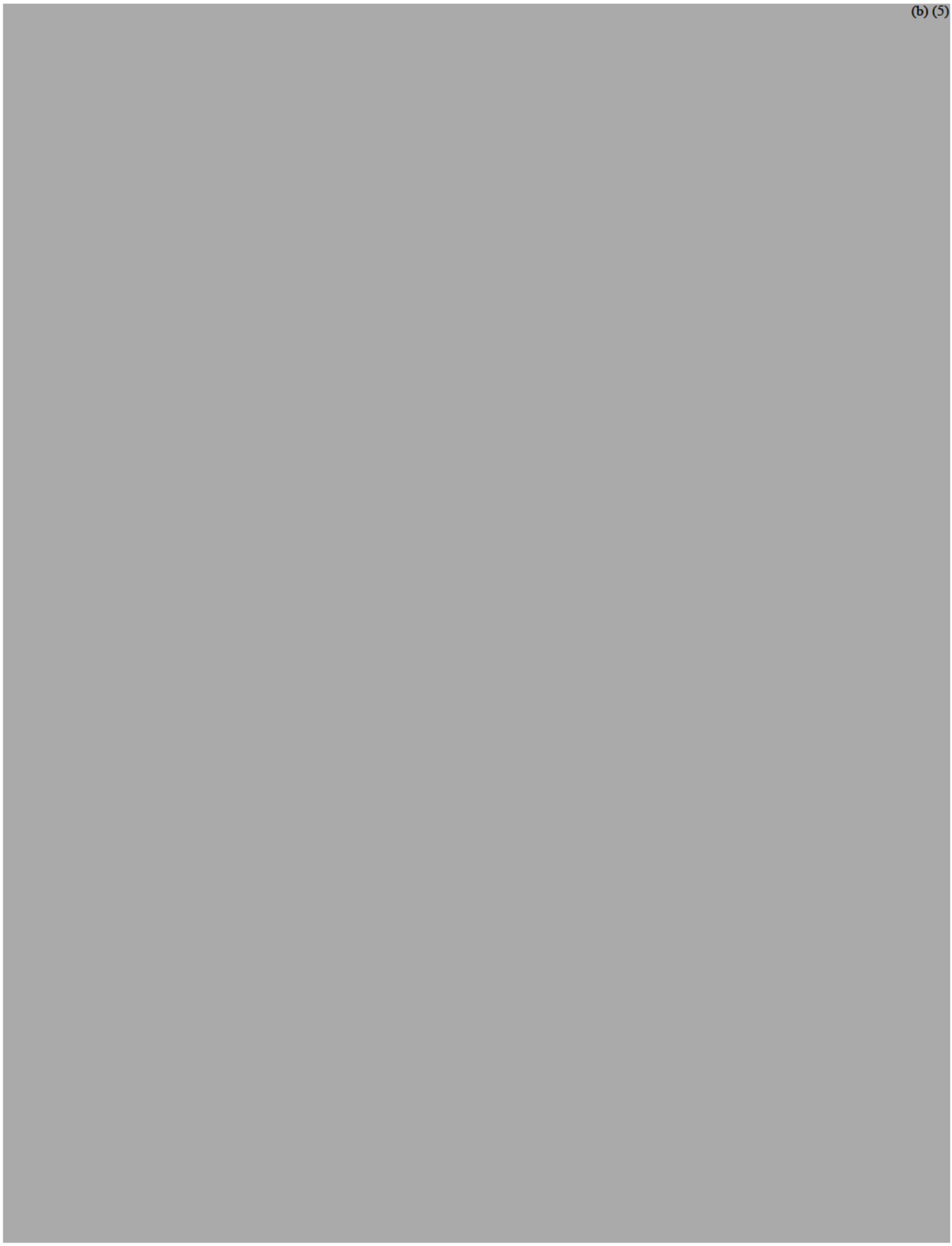

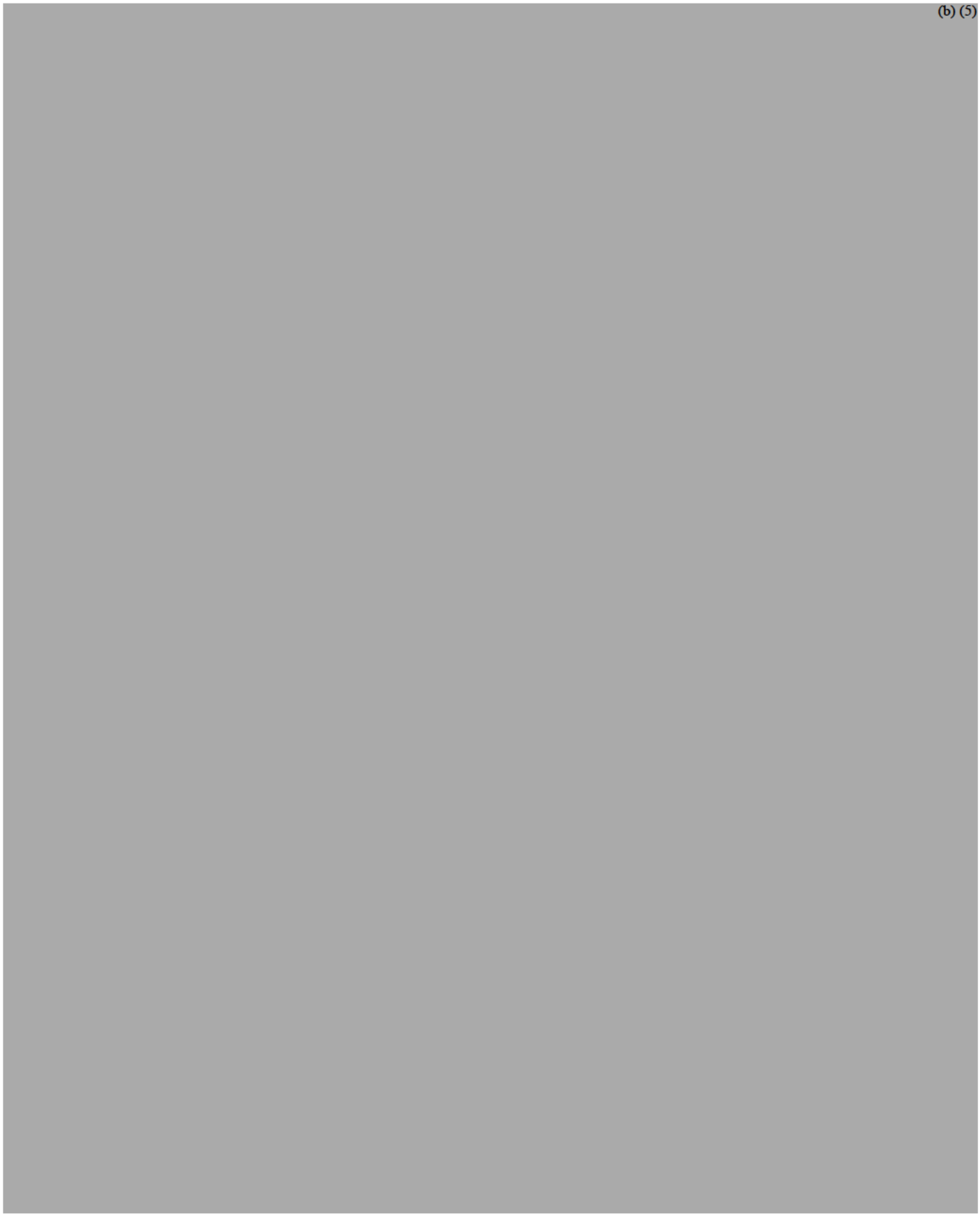
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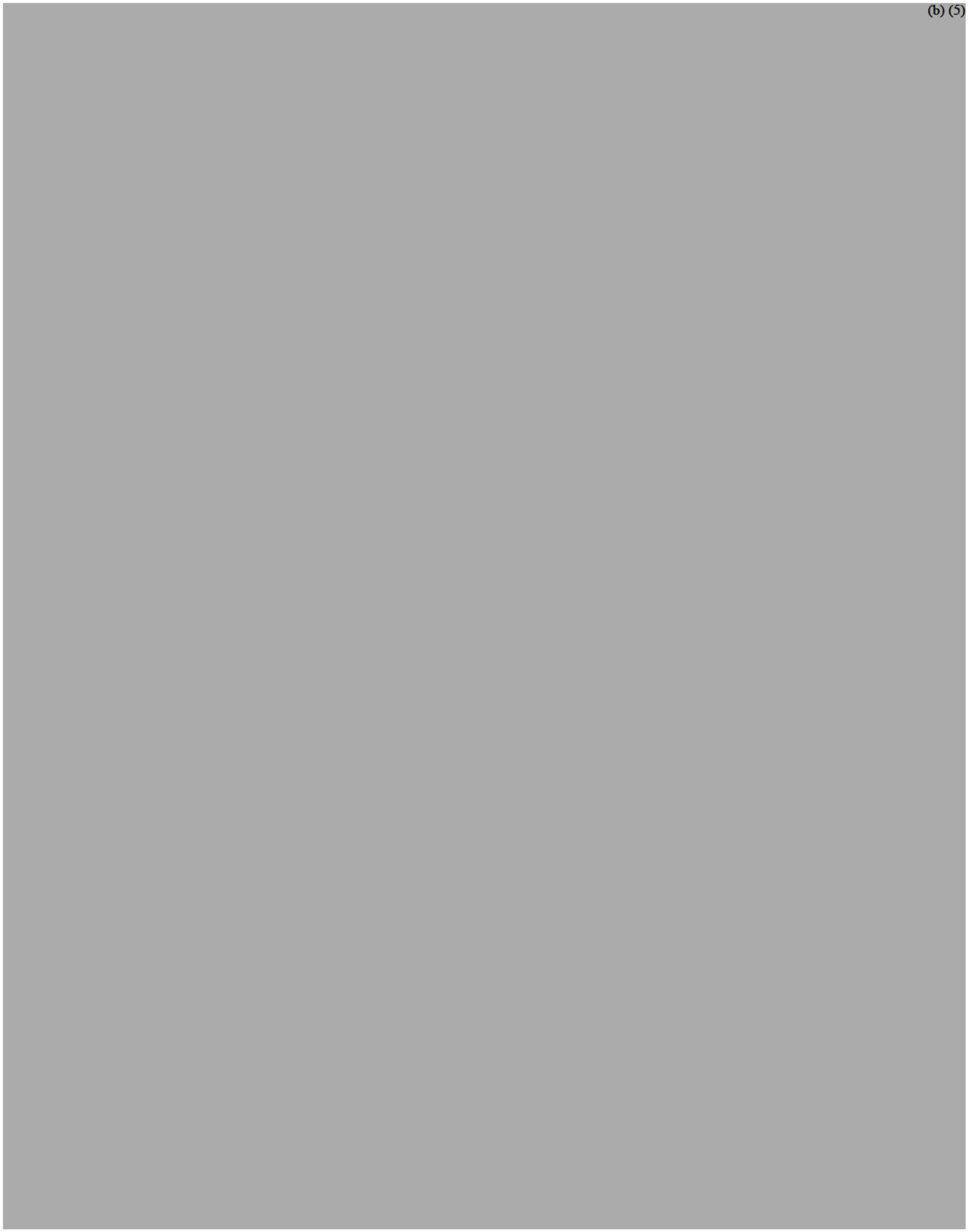
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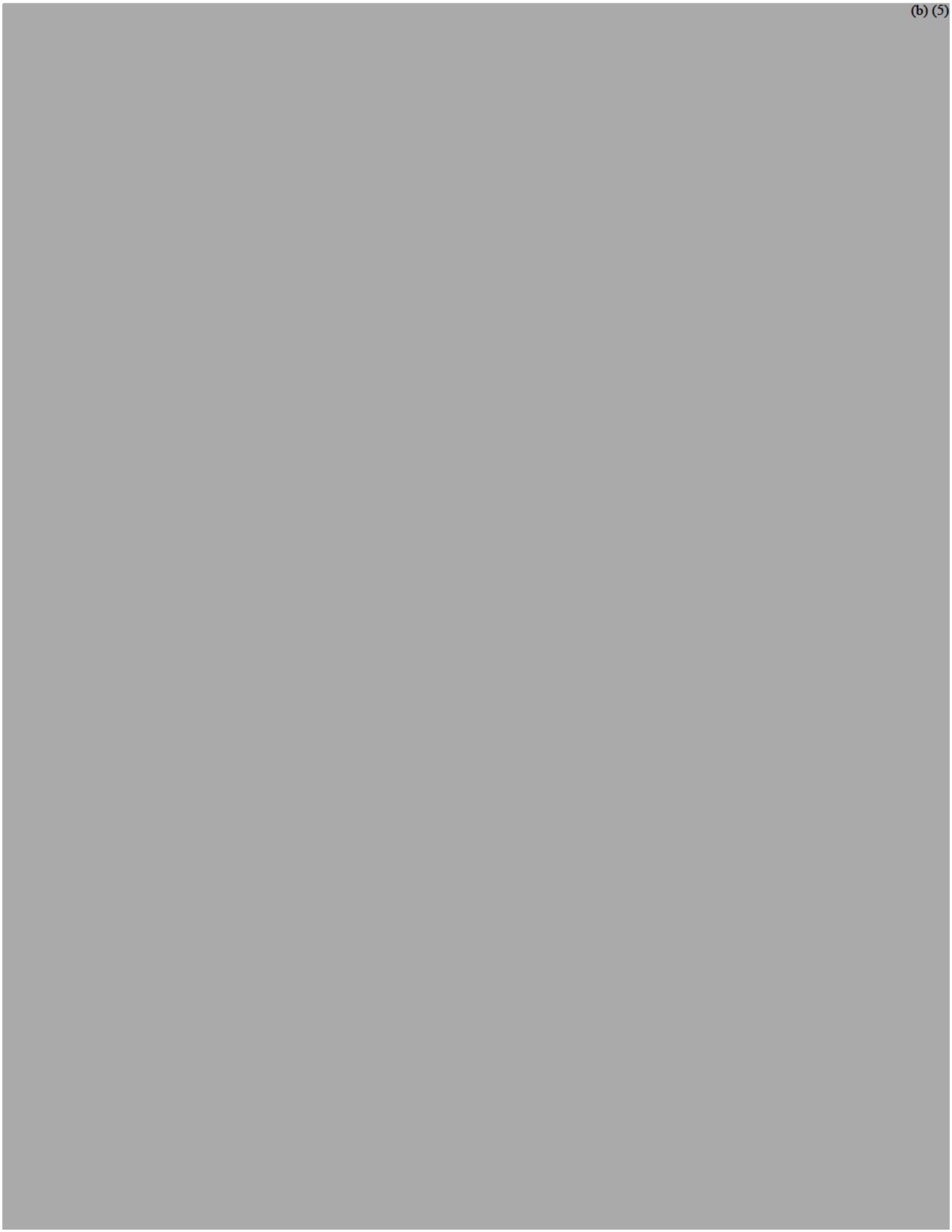
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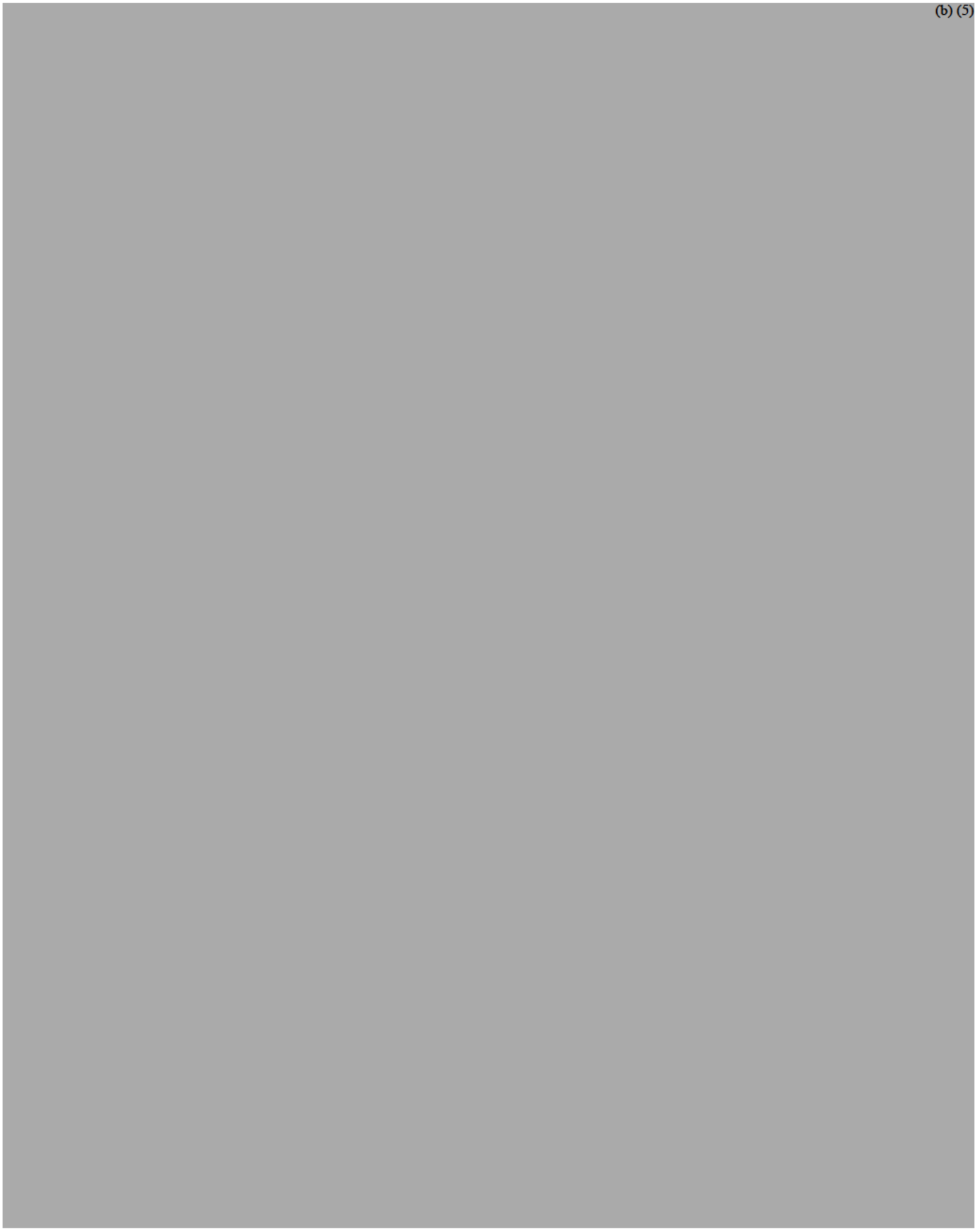
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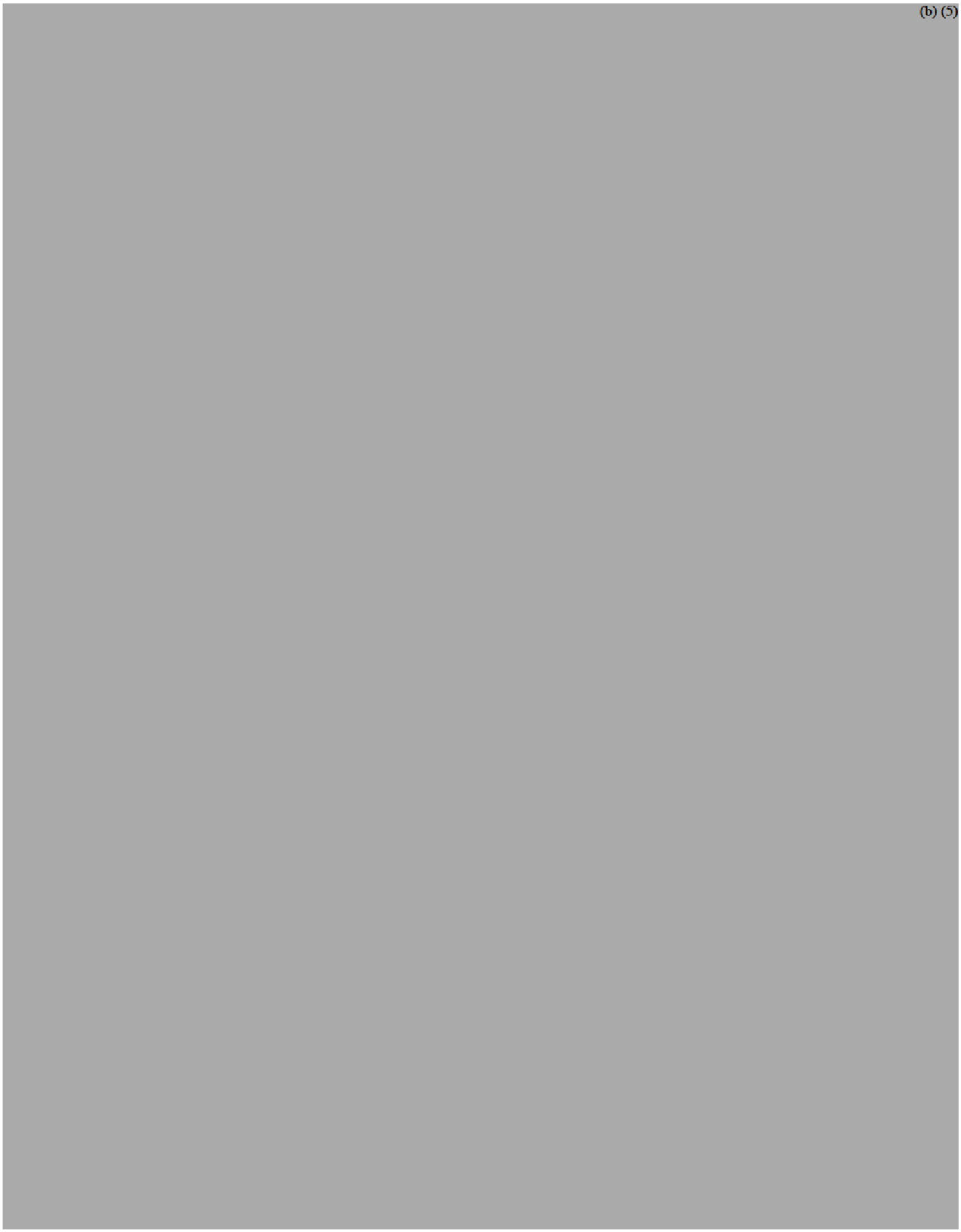
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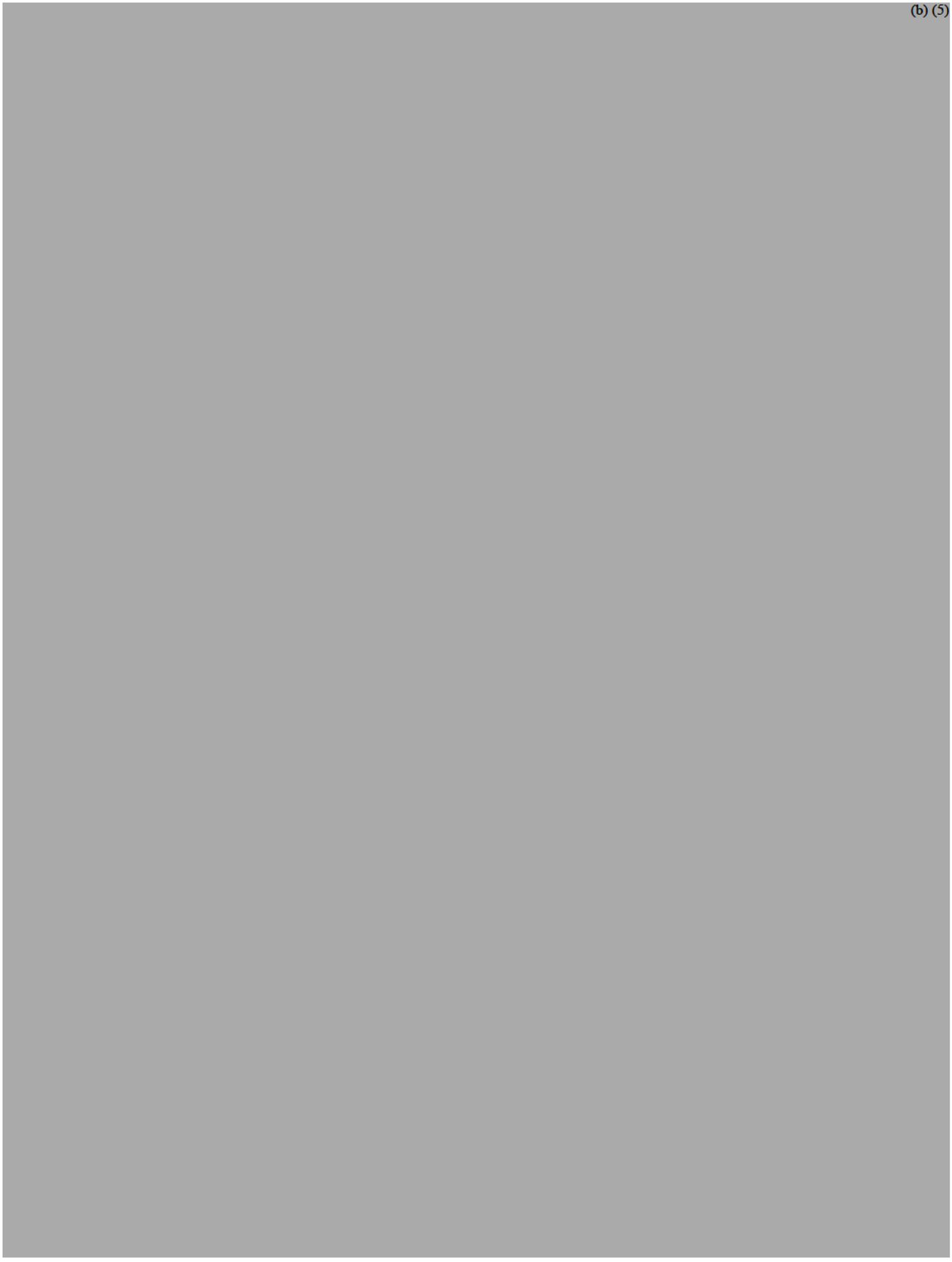
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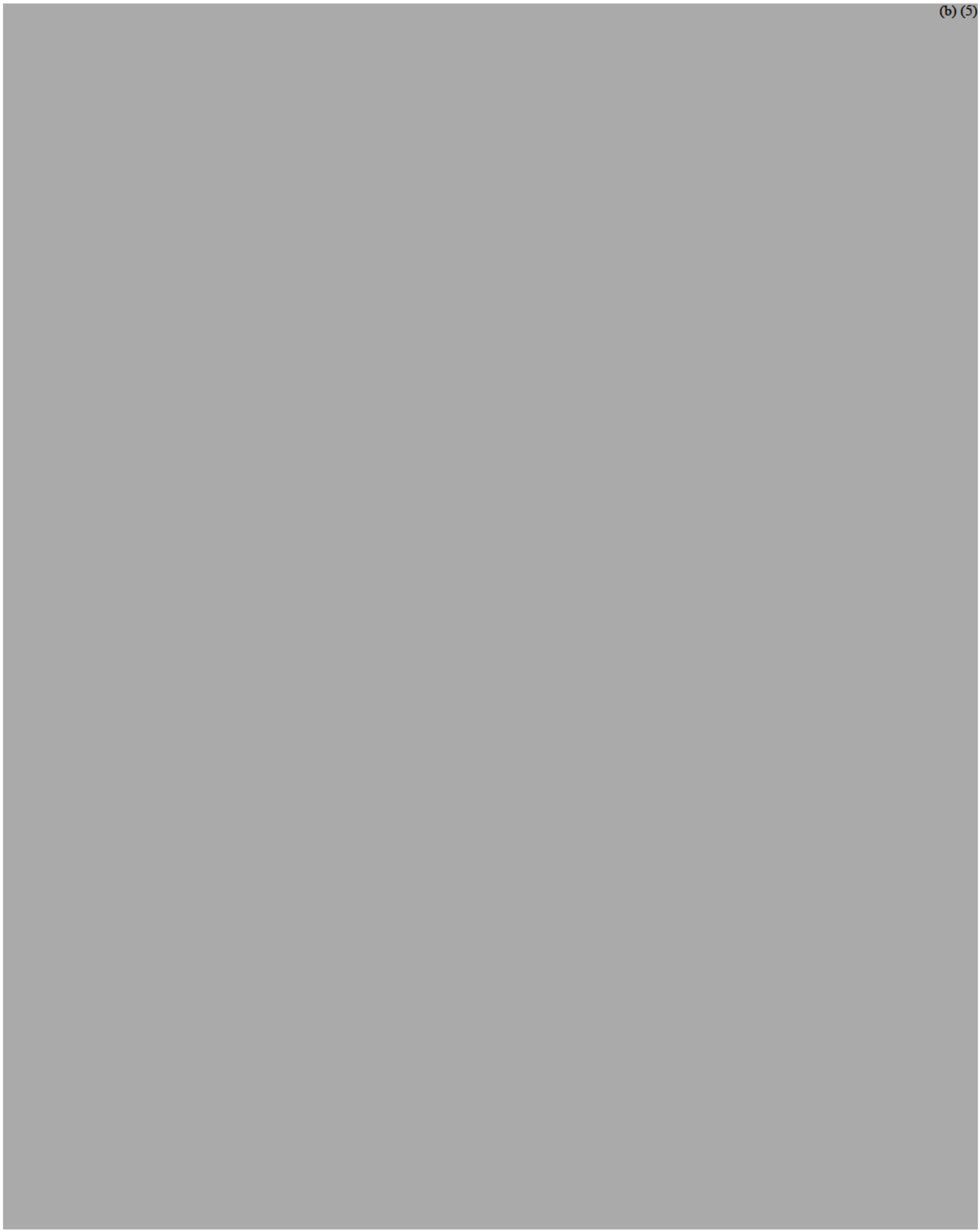
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Appendix H:

Actions Undertaken to Carry Out Scientific Frameworks on Recalcitrant Cancer

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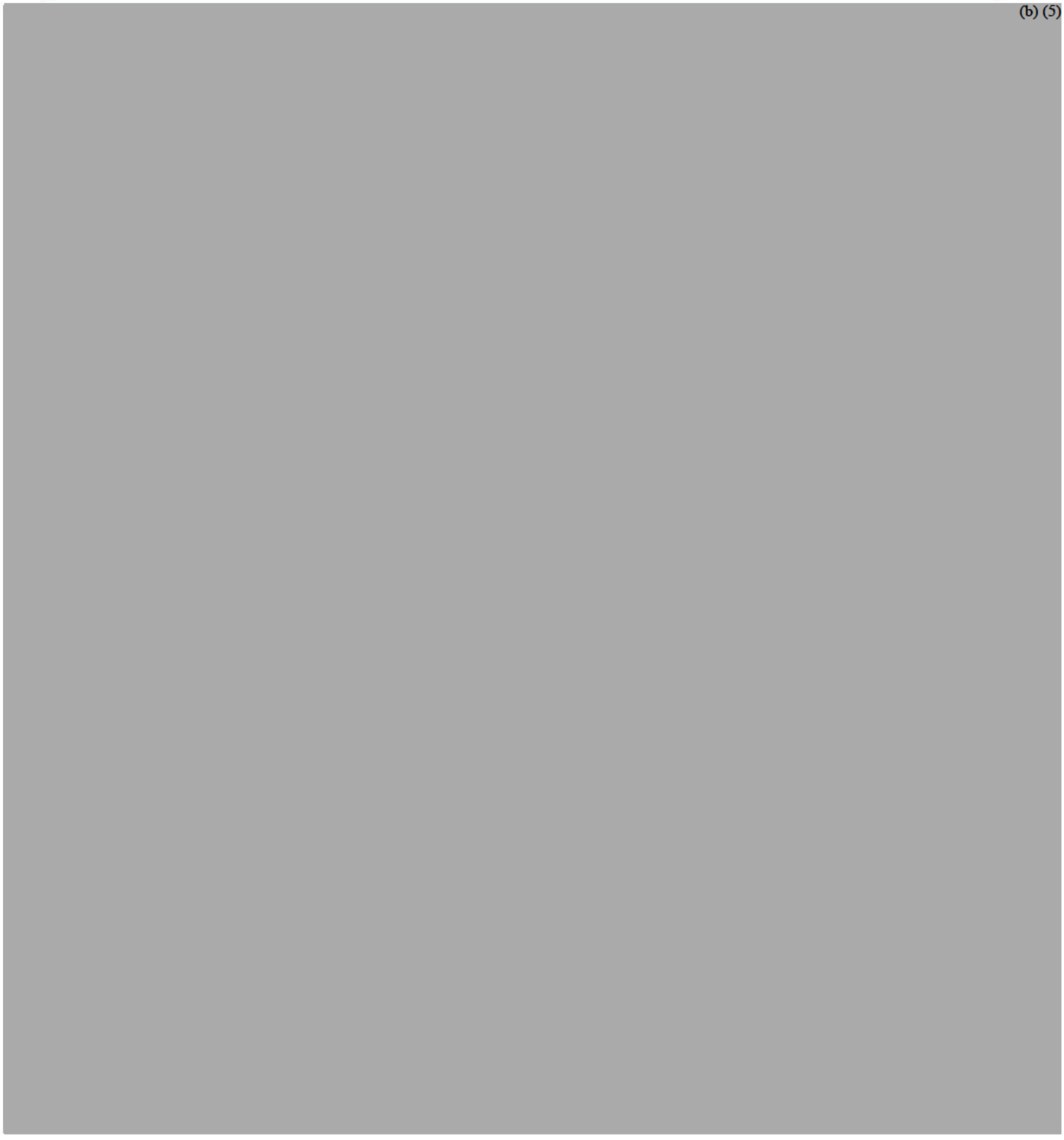

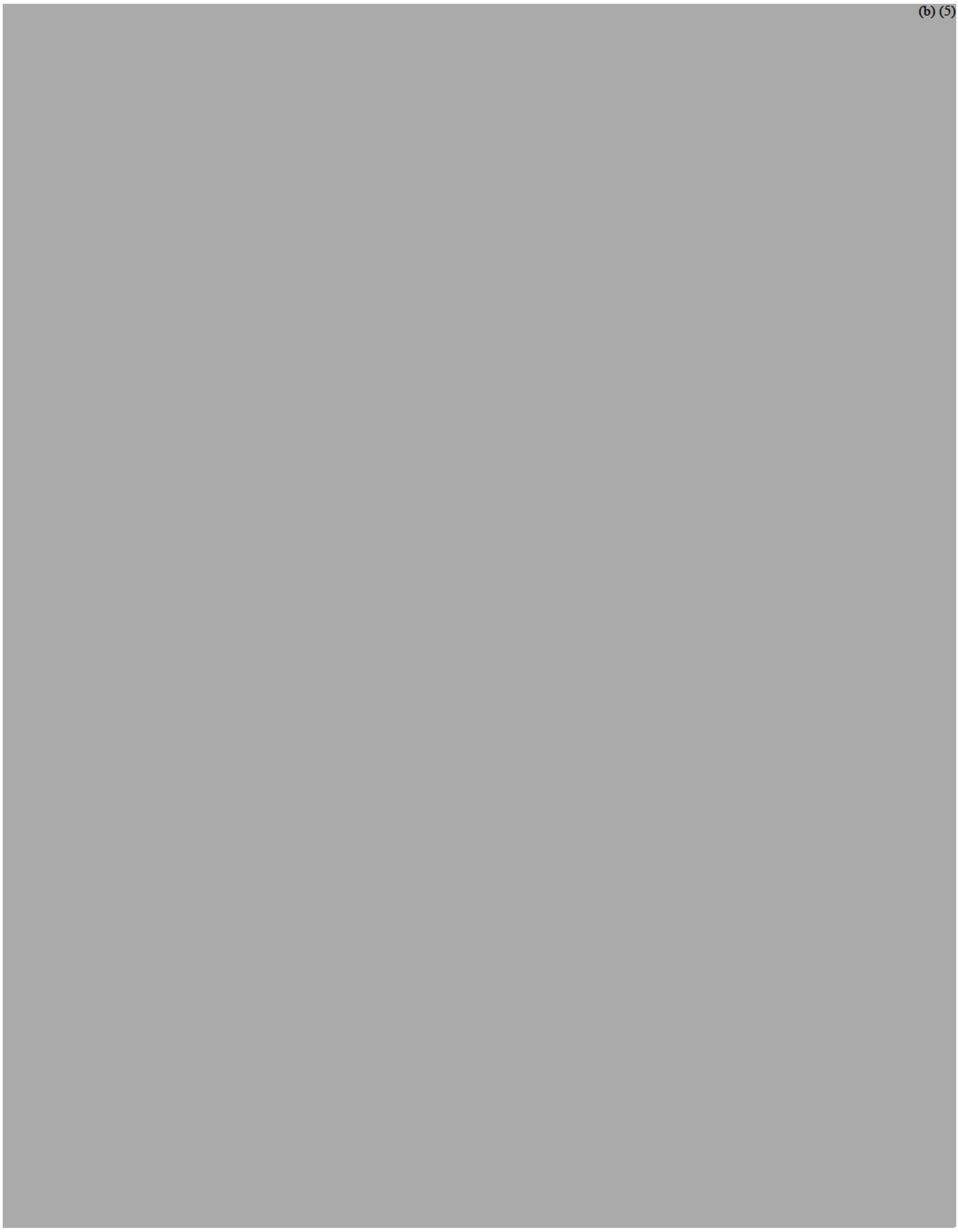

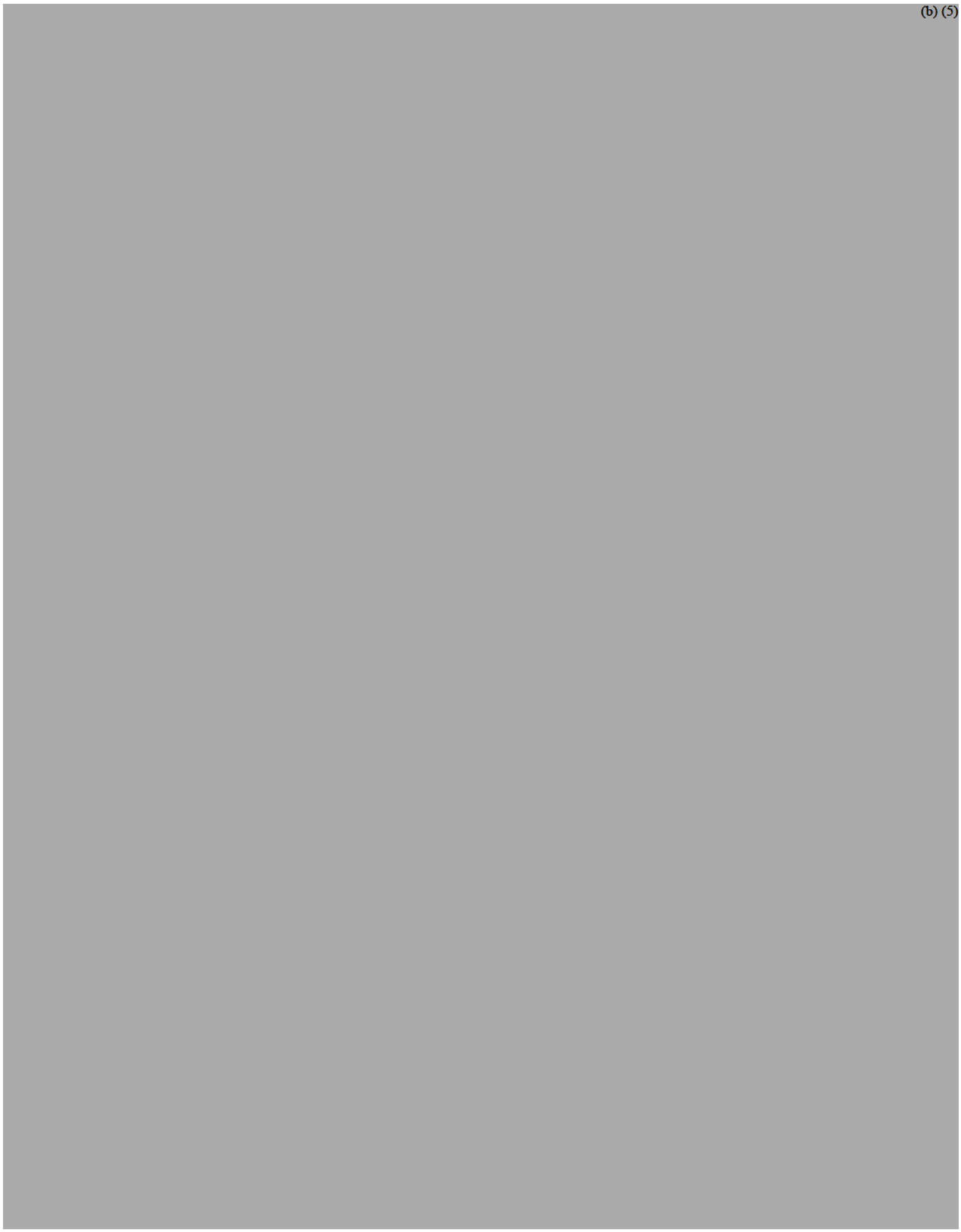
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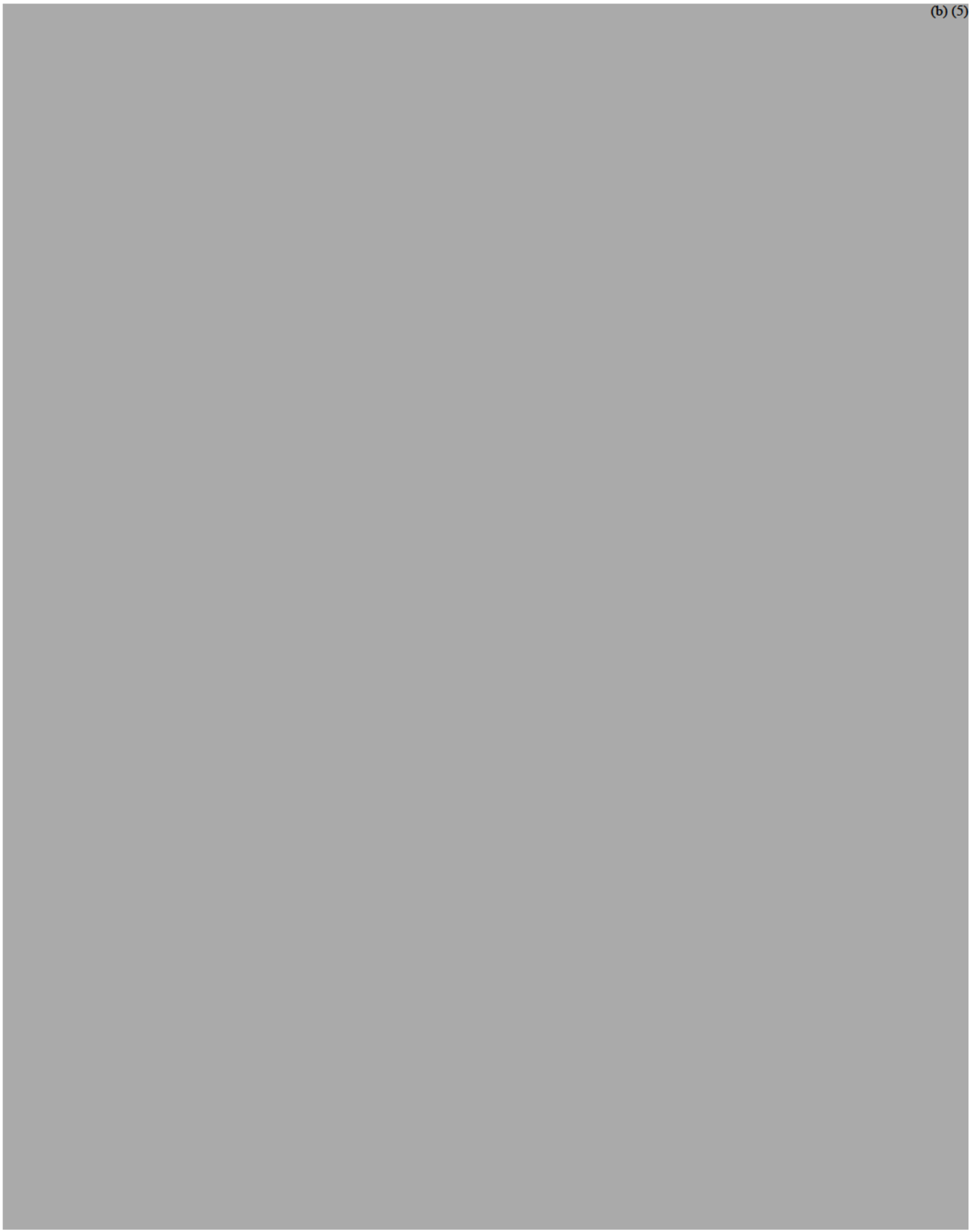
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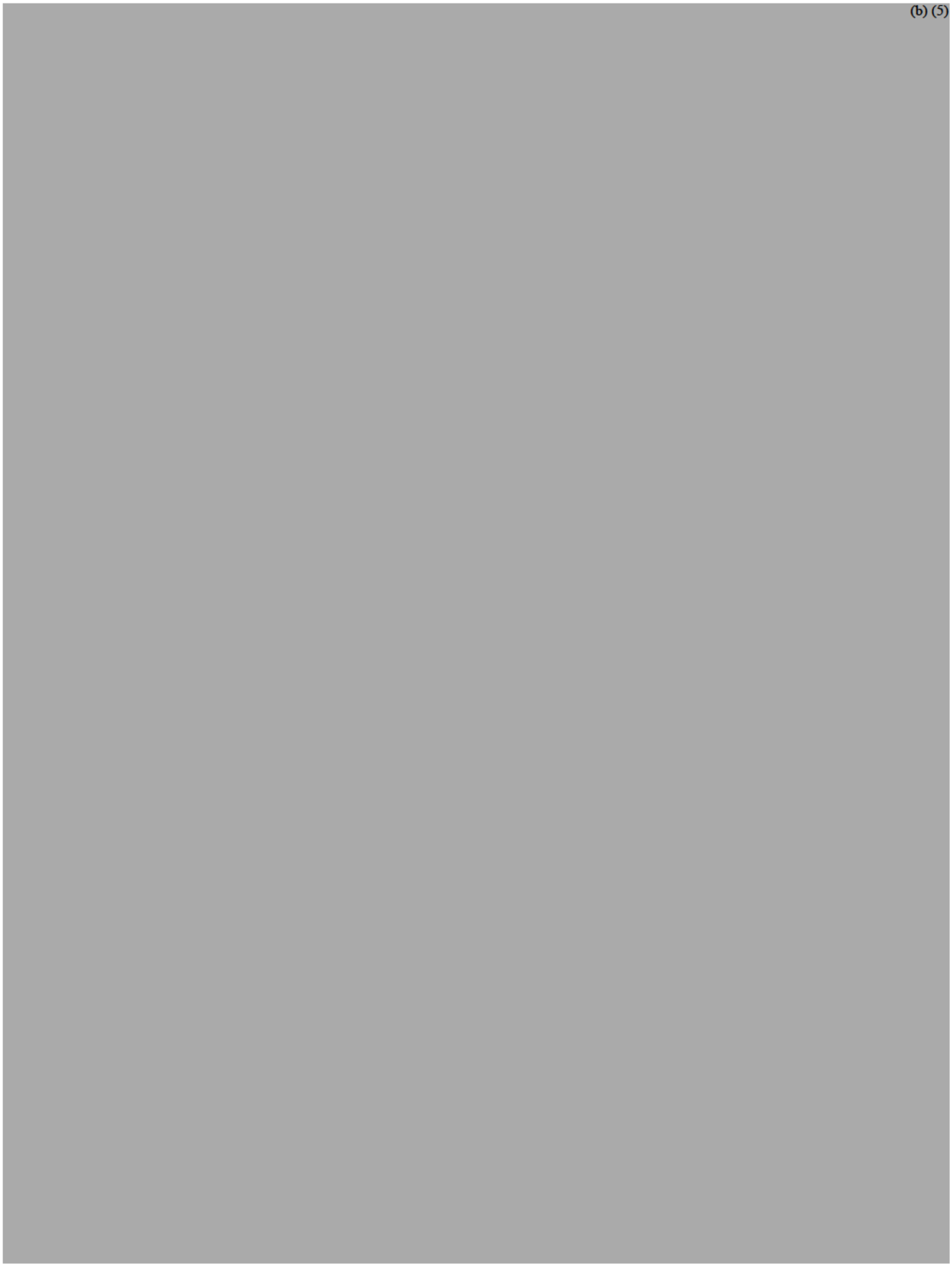
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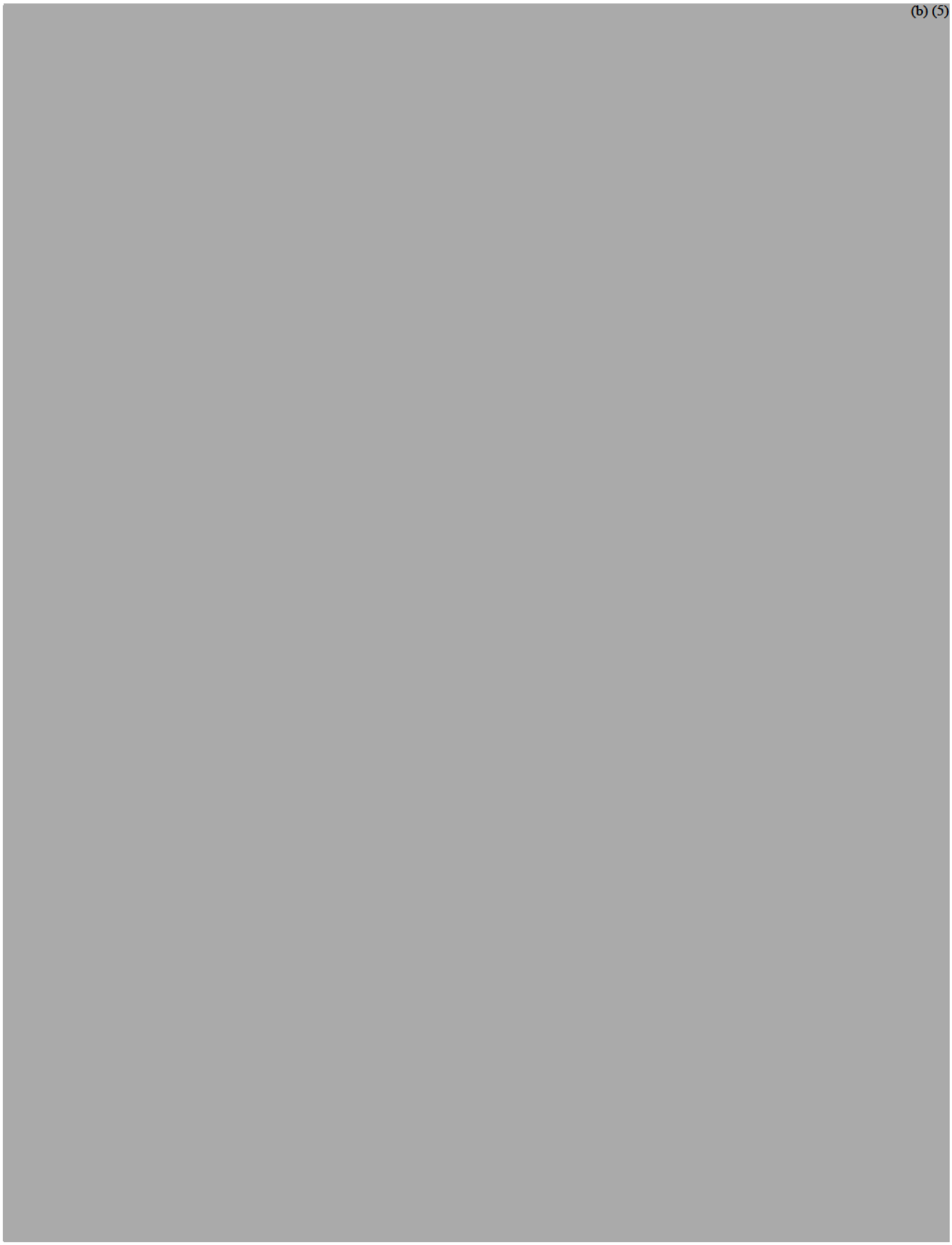
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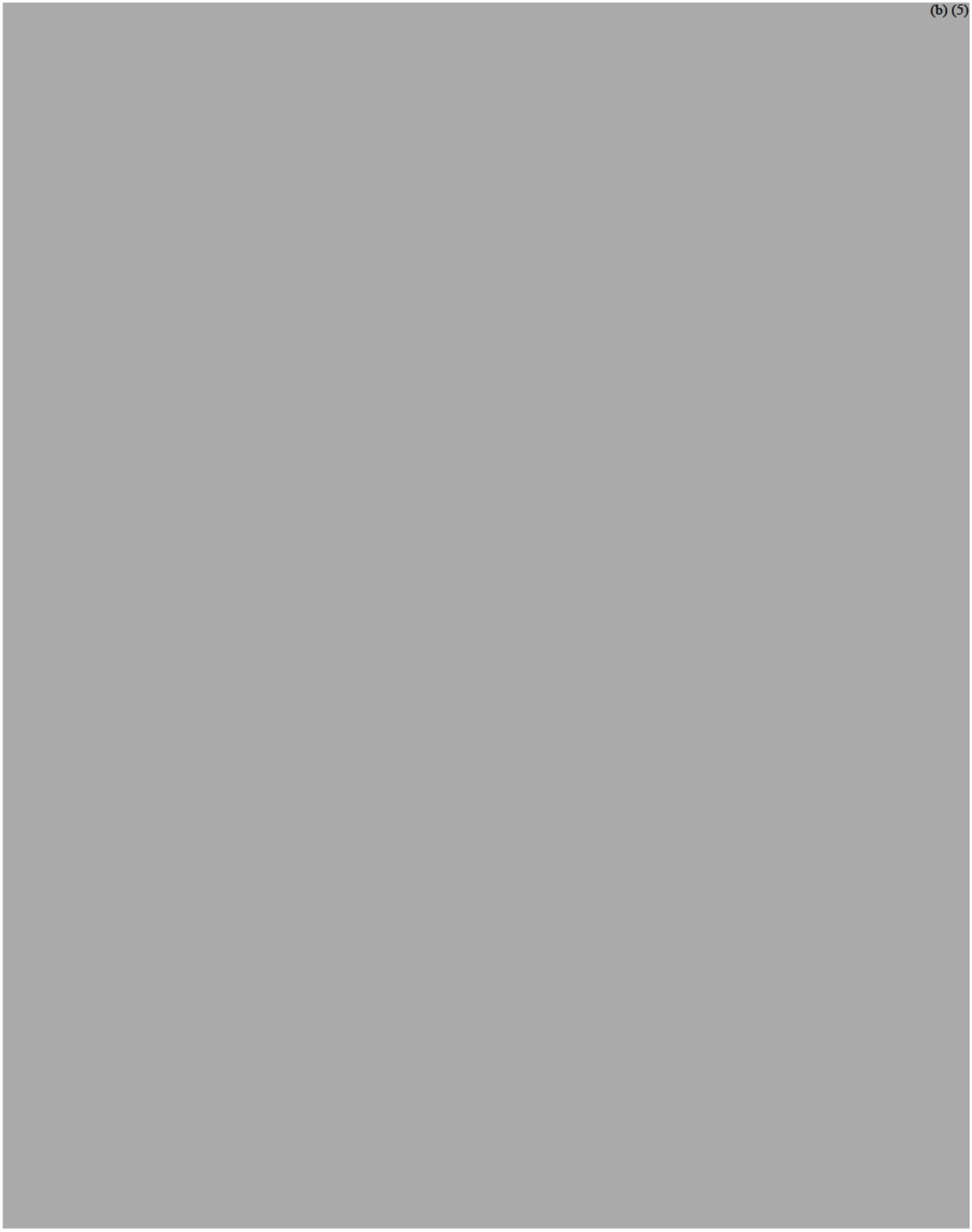
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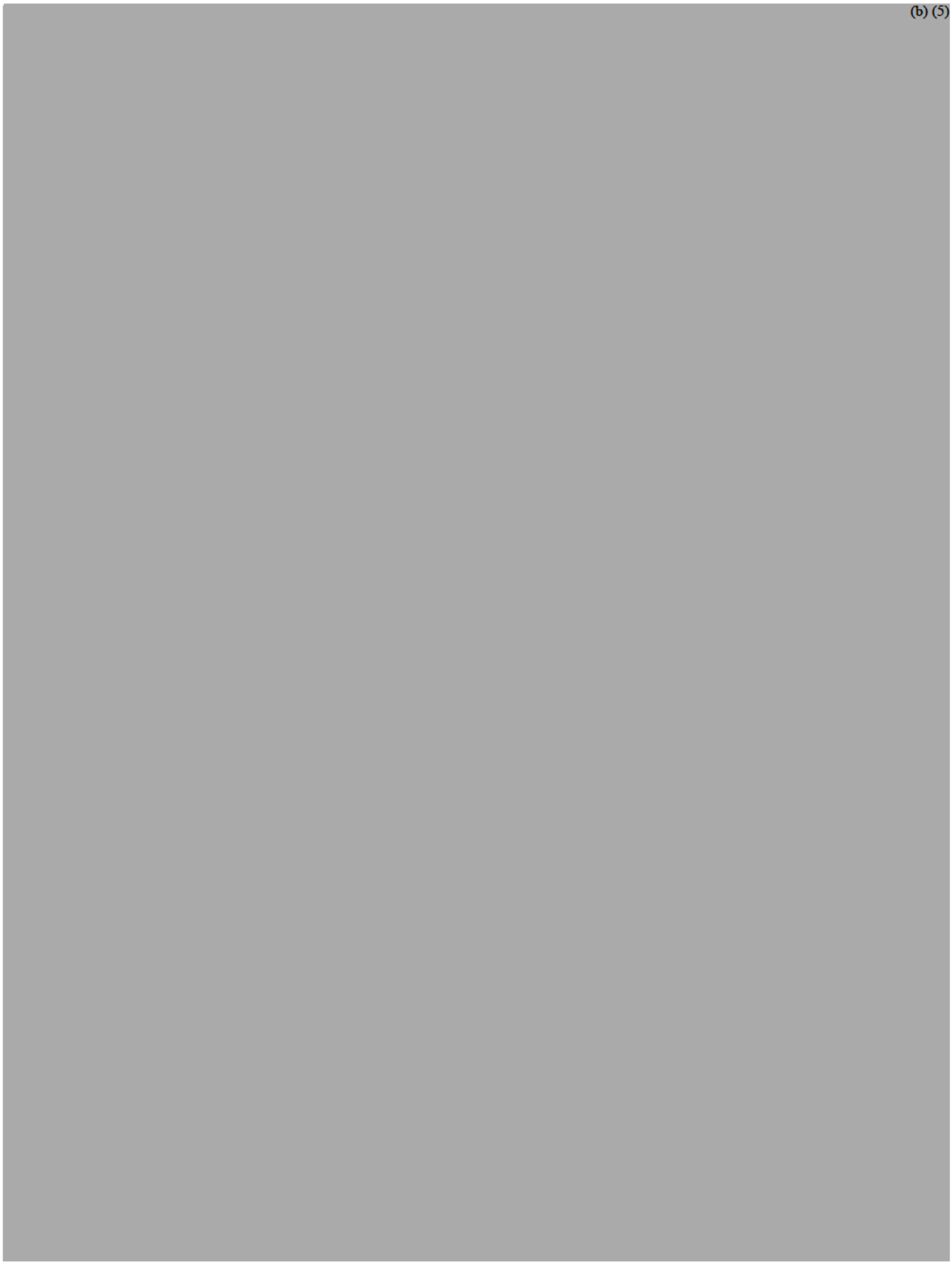
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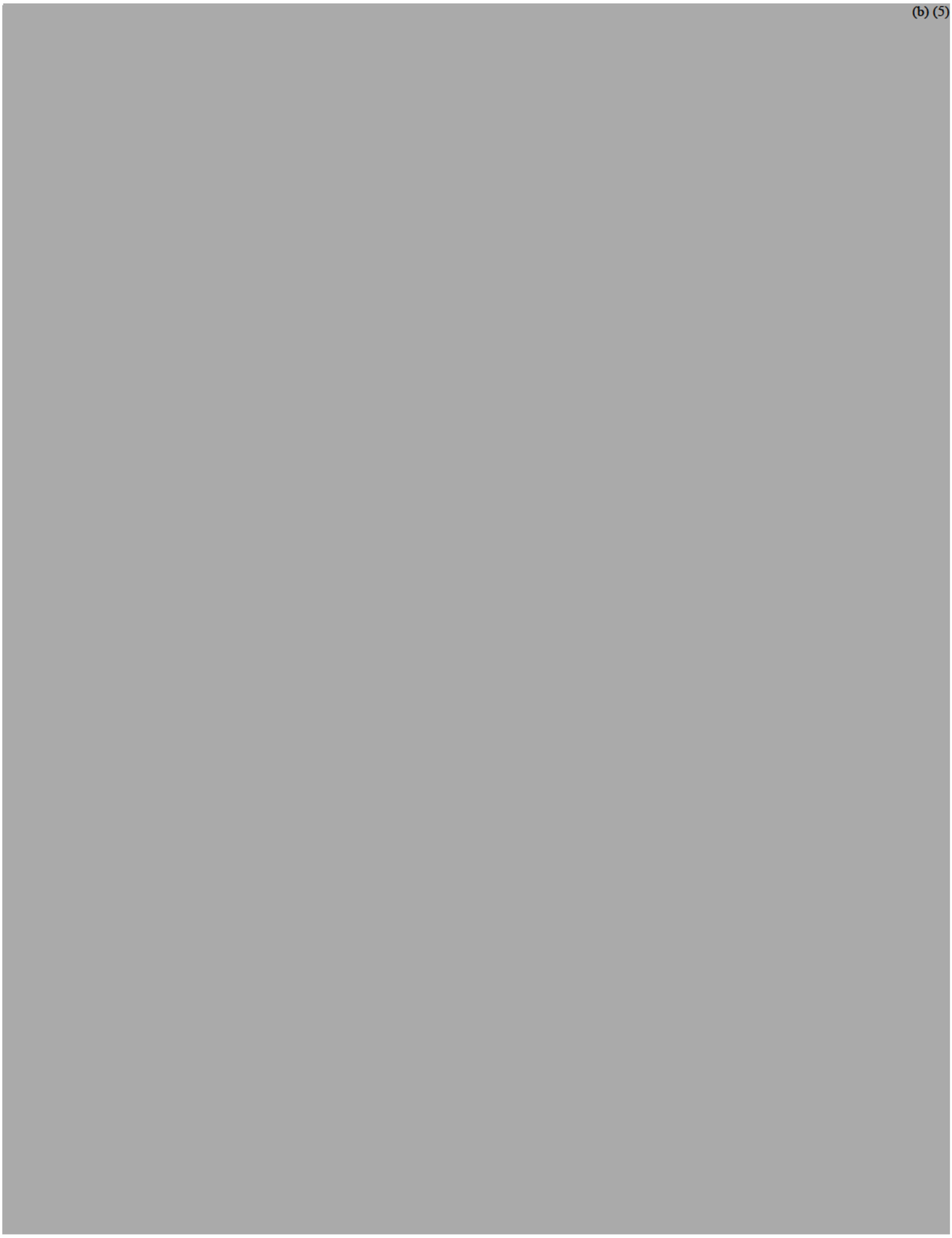
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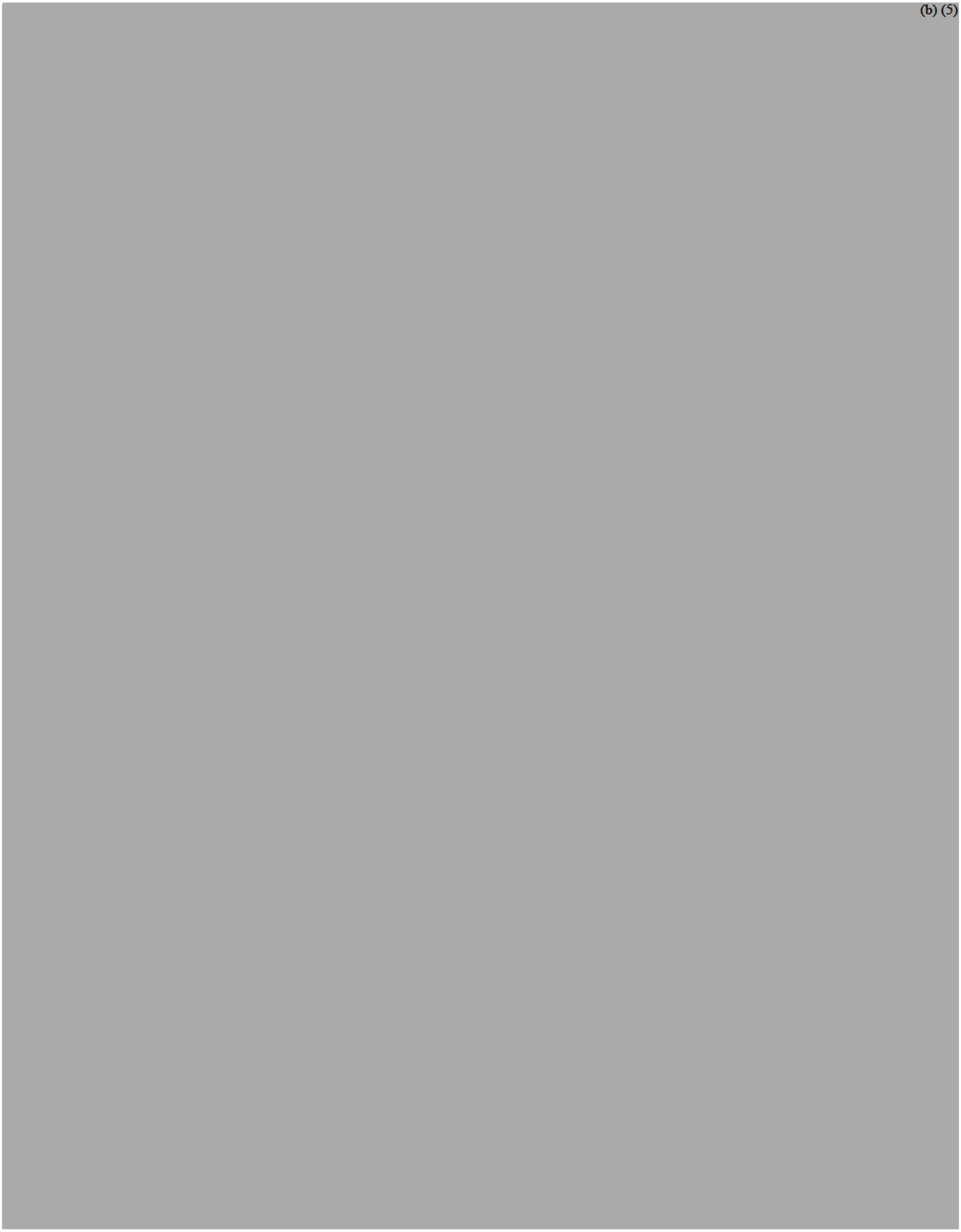
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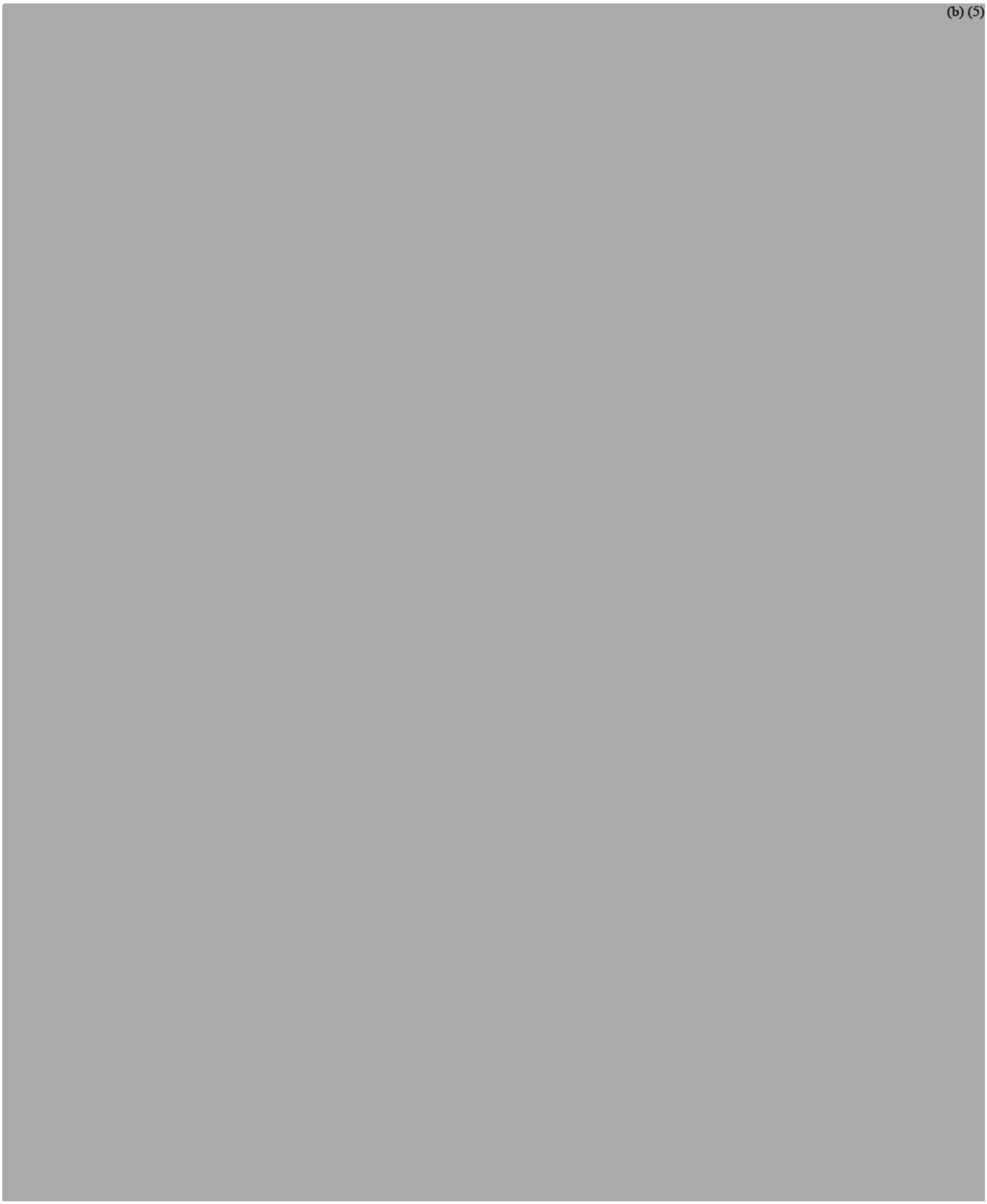
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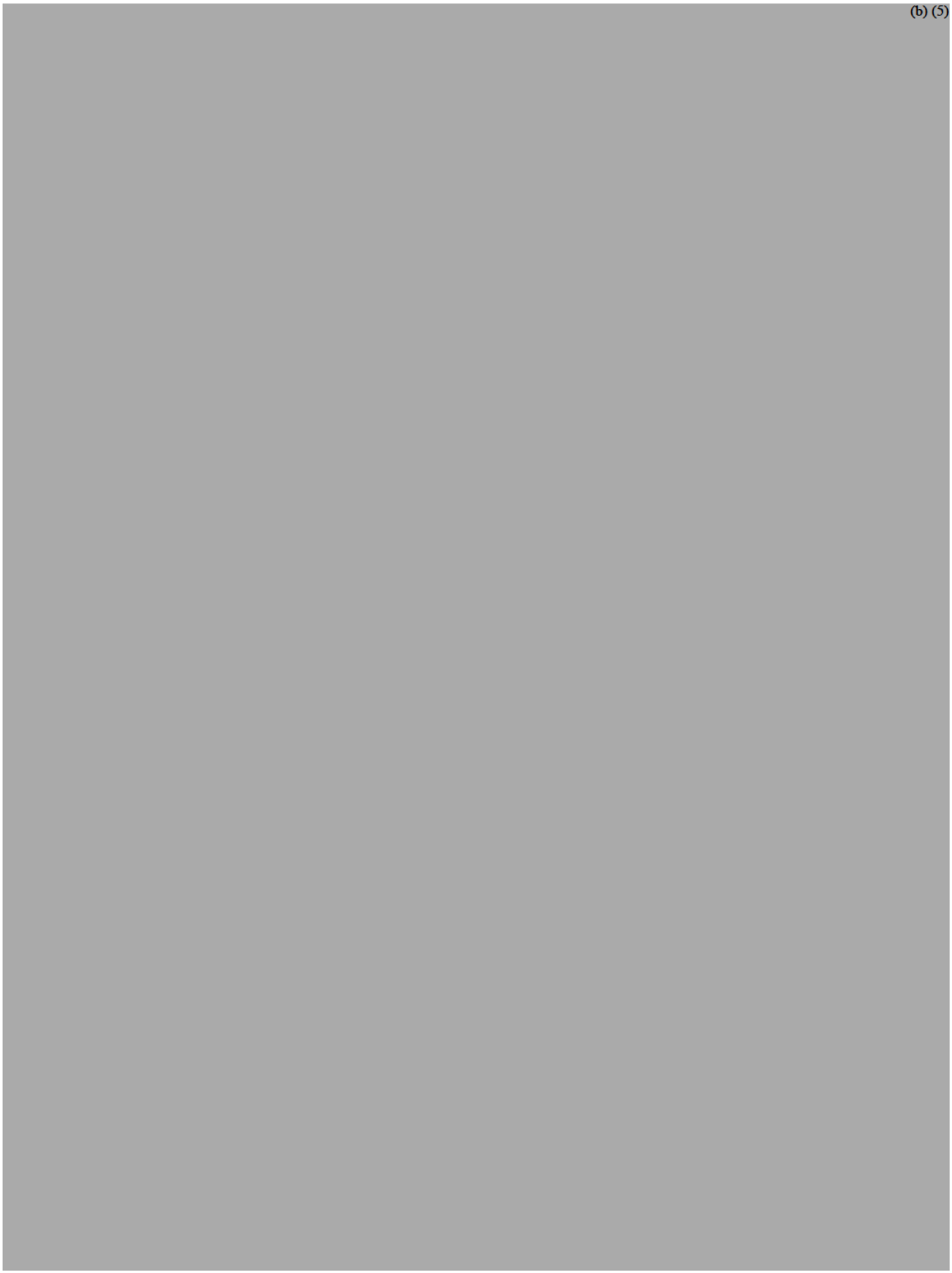
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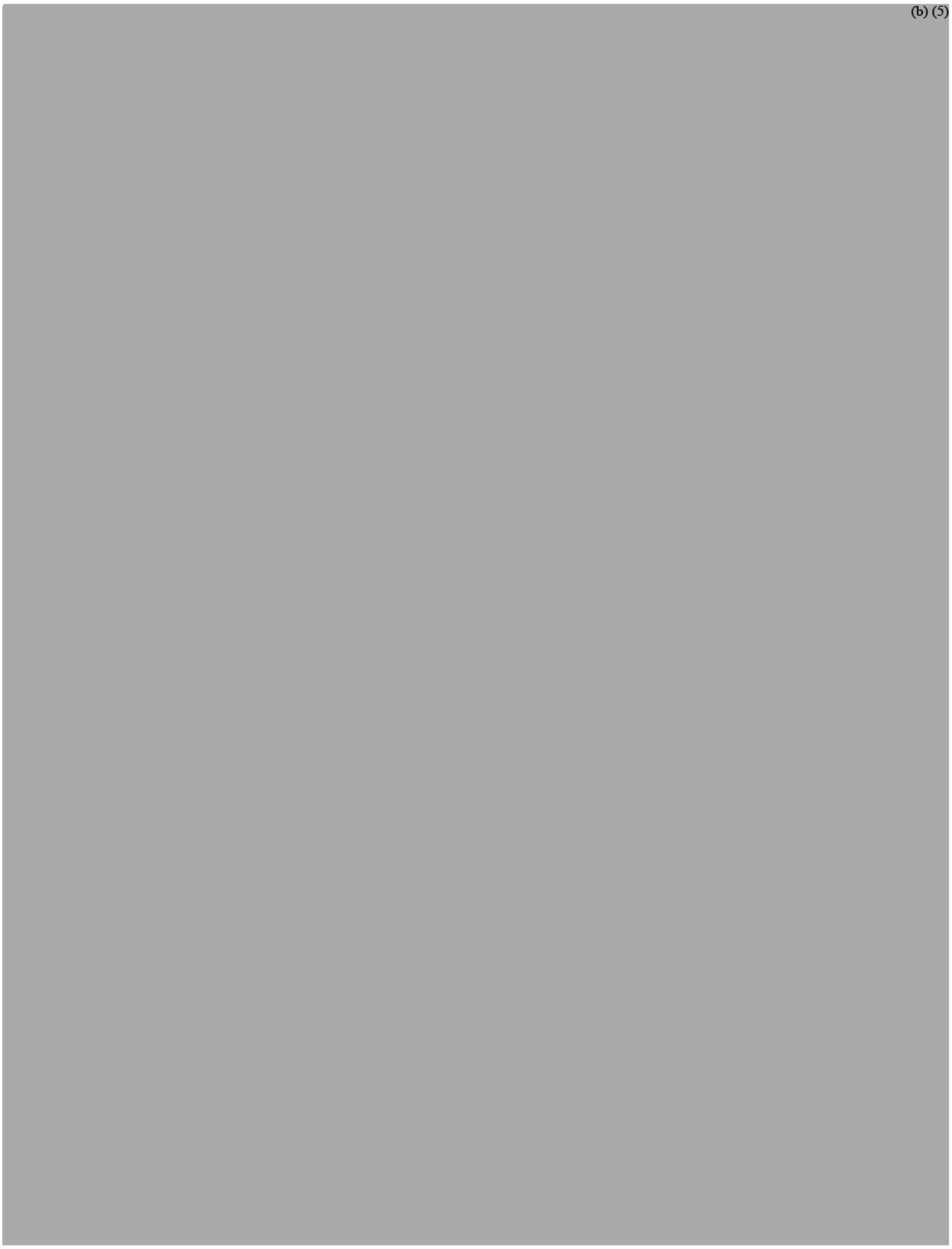
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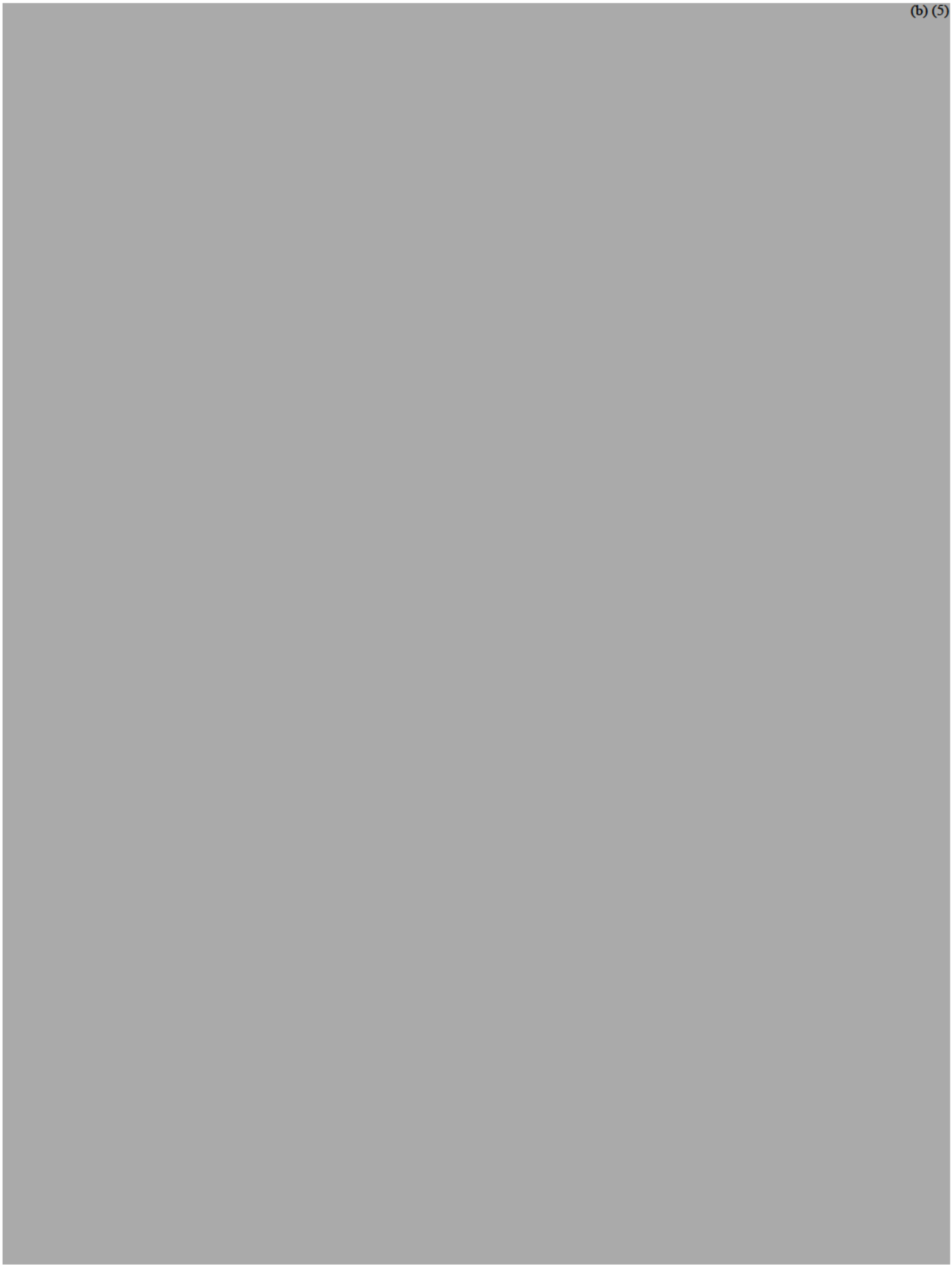
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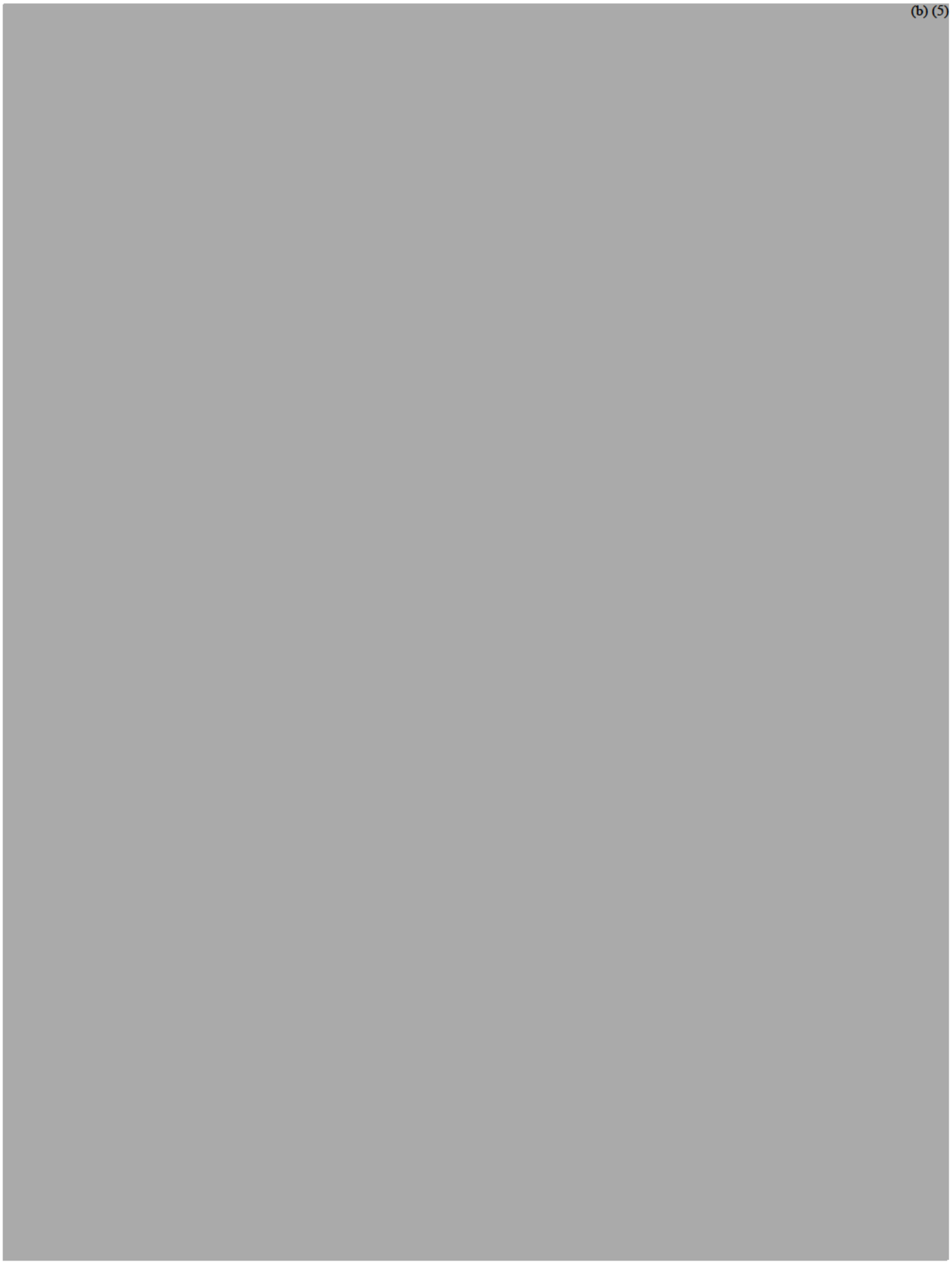
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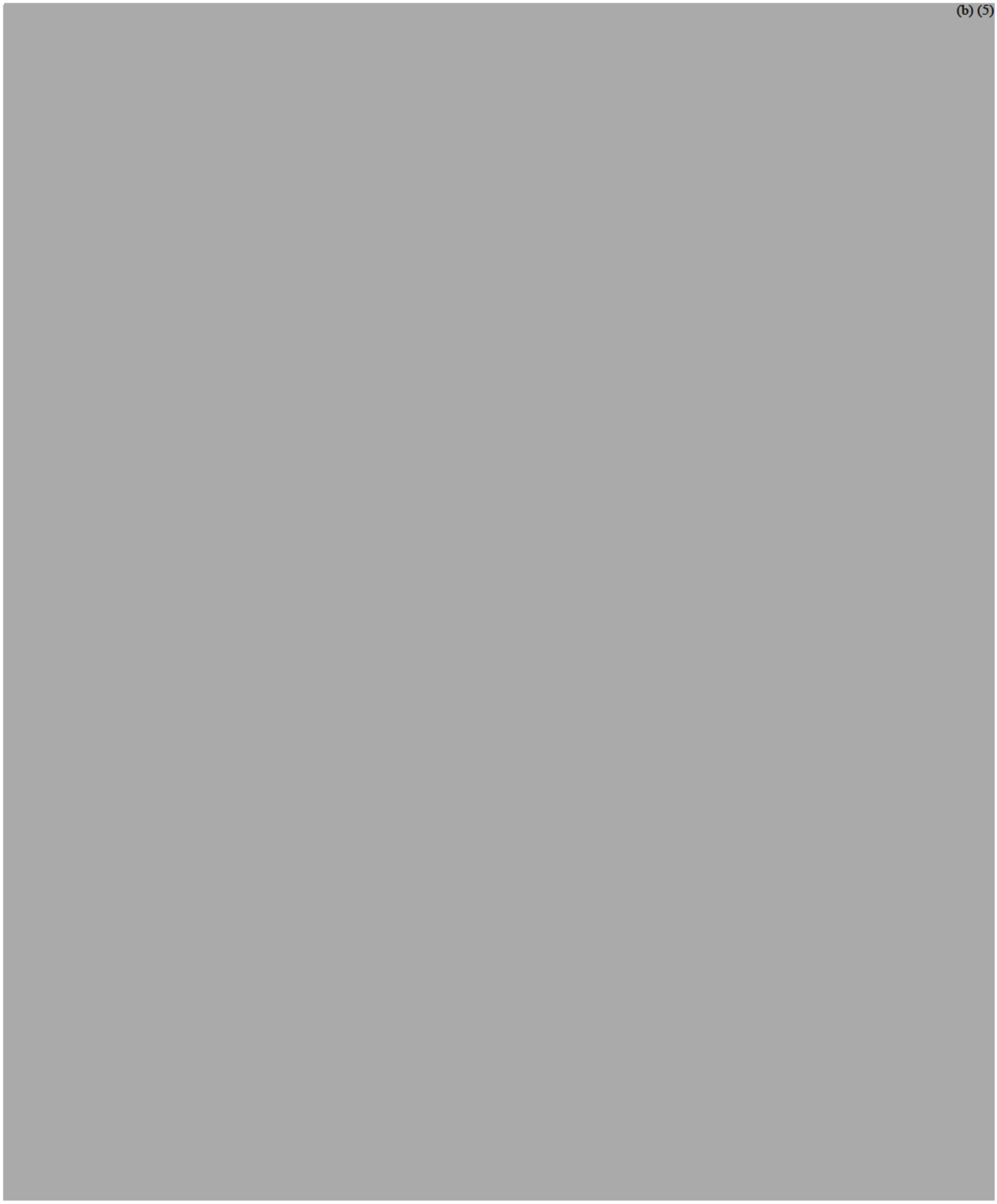
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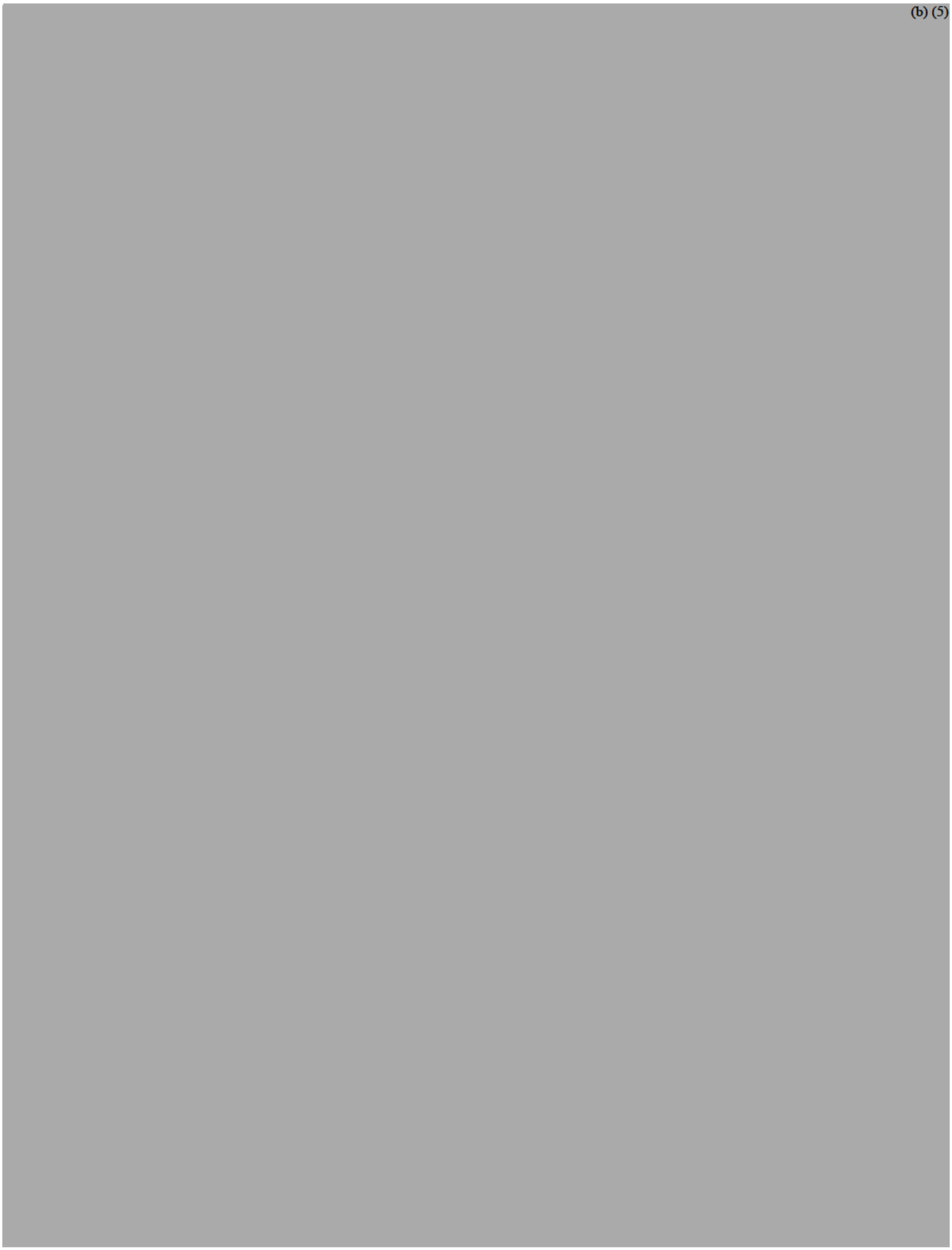
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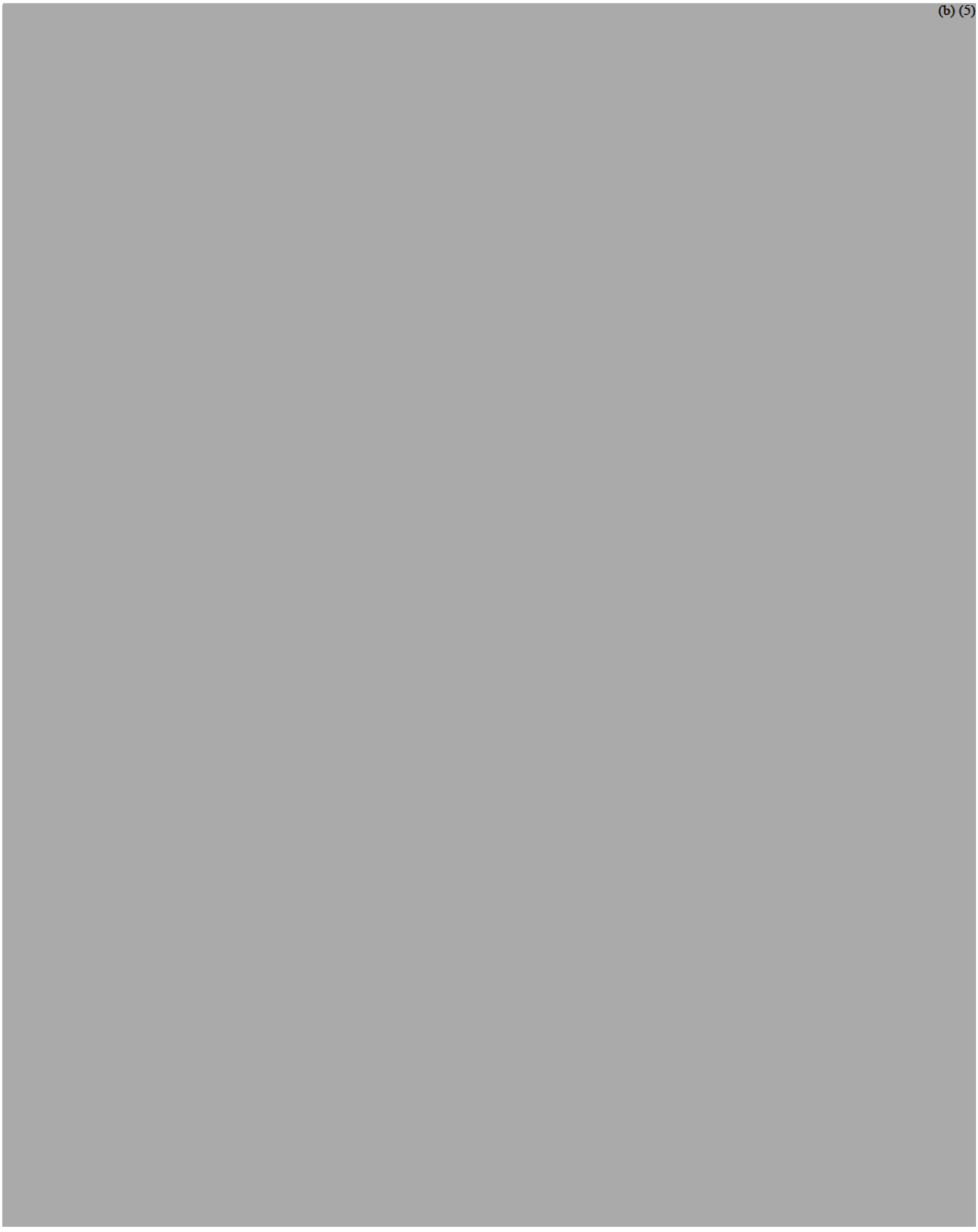
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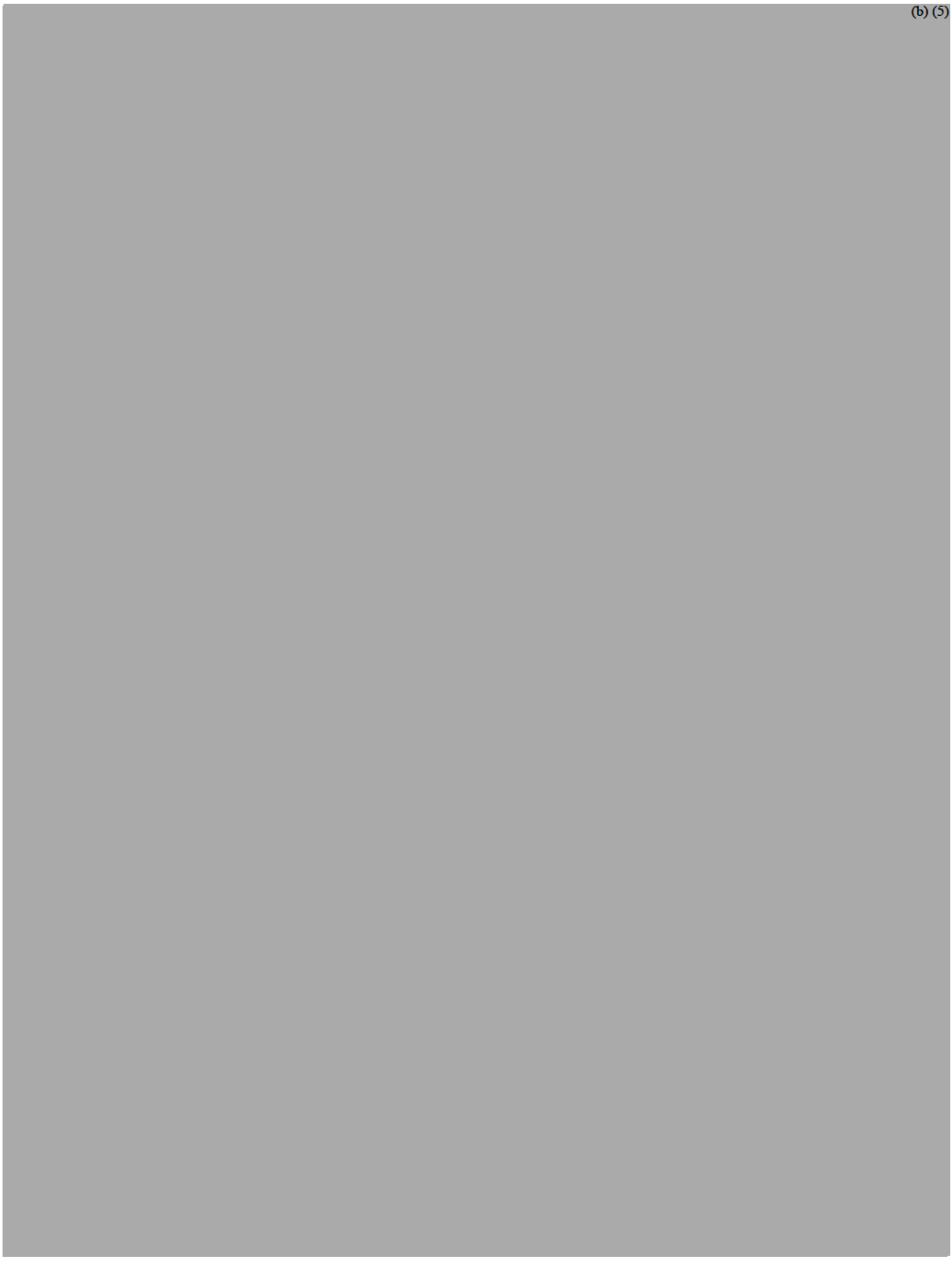
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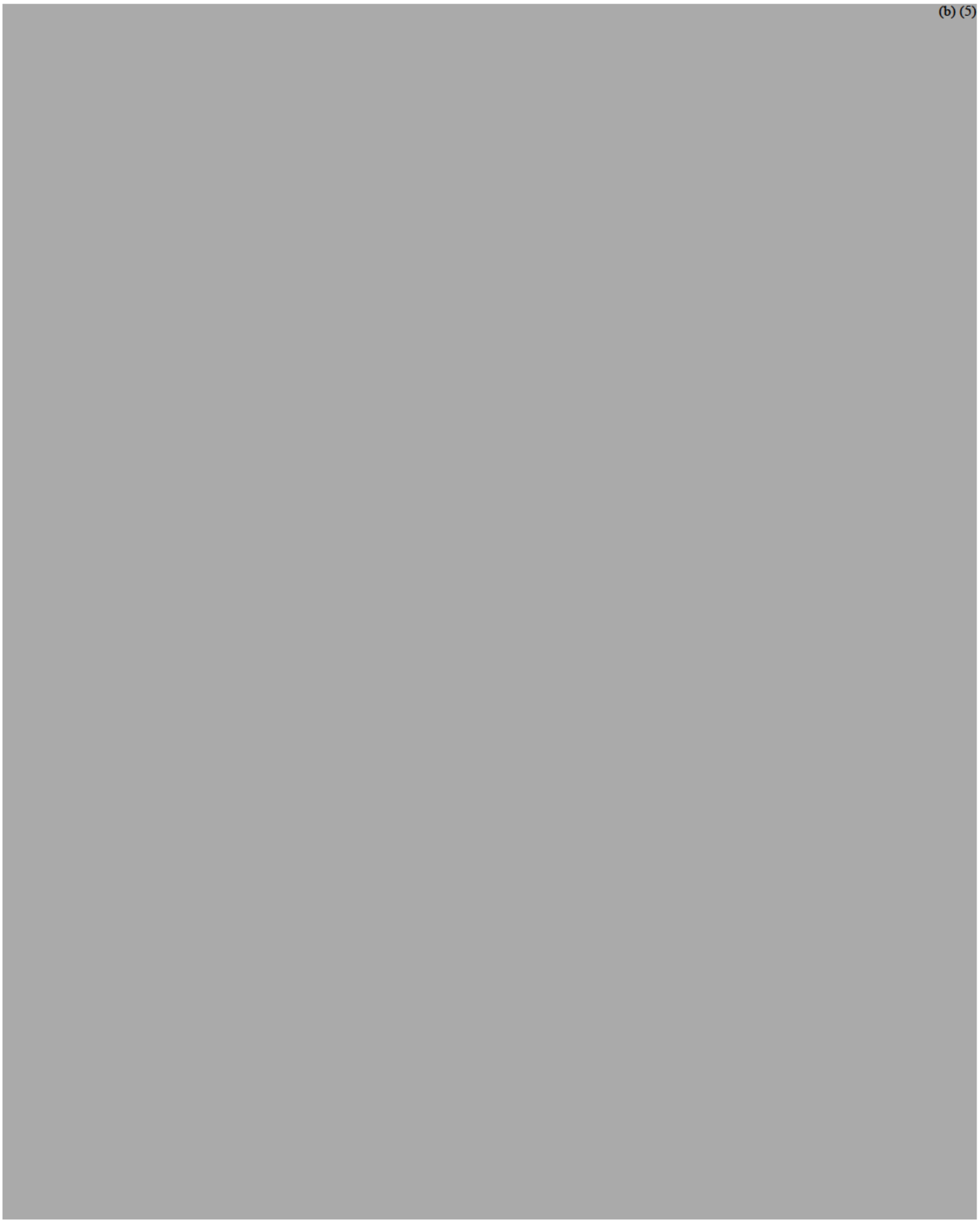
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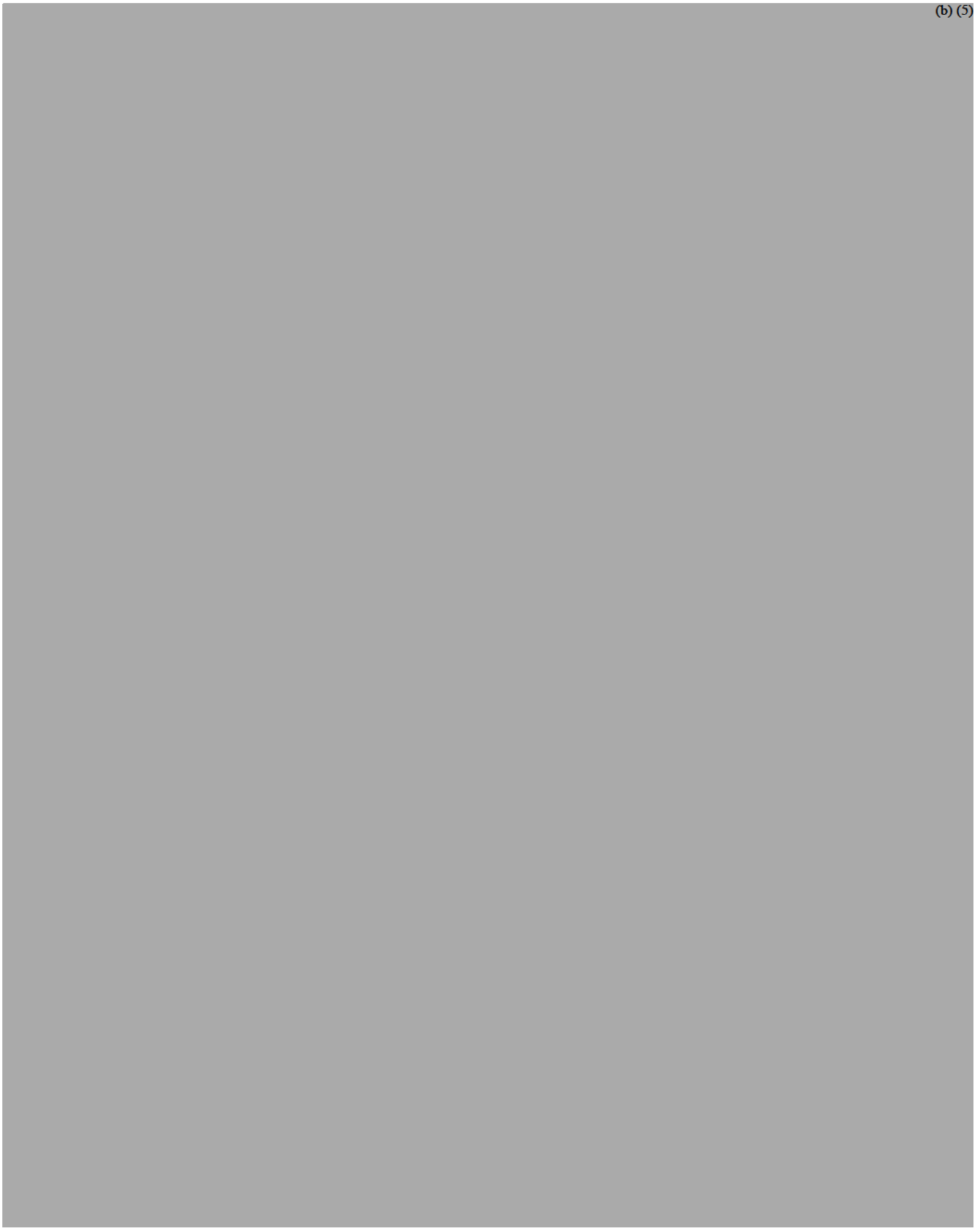
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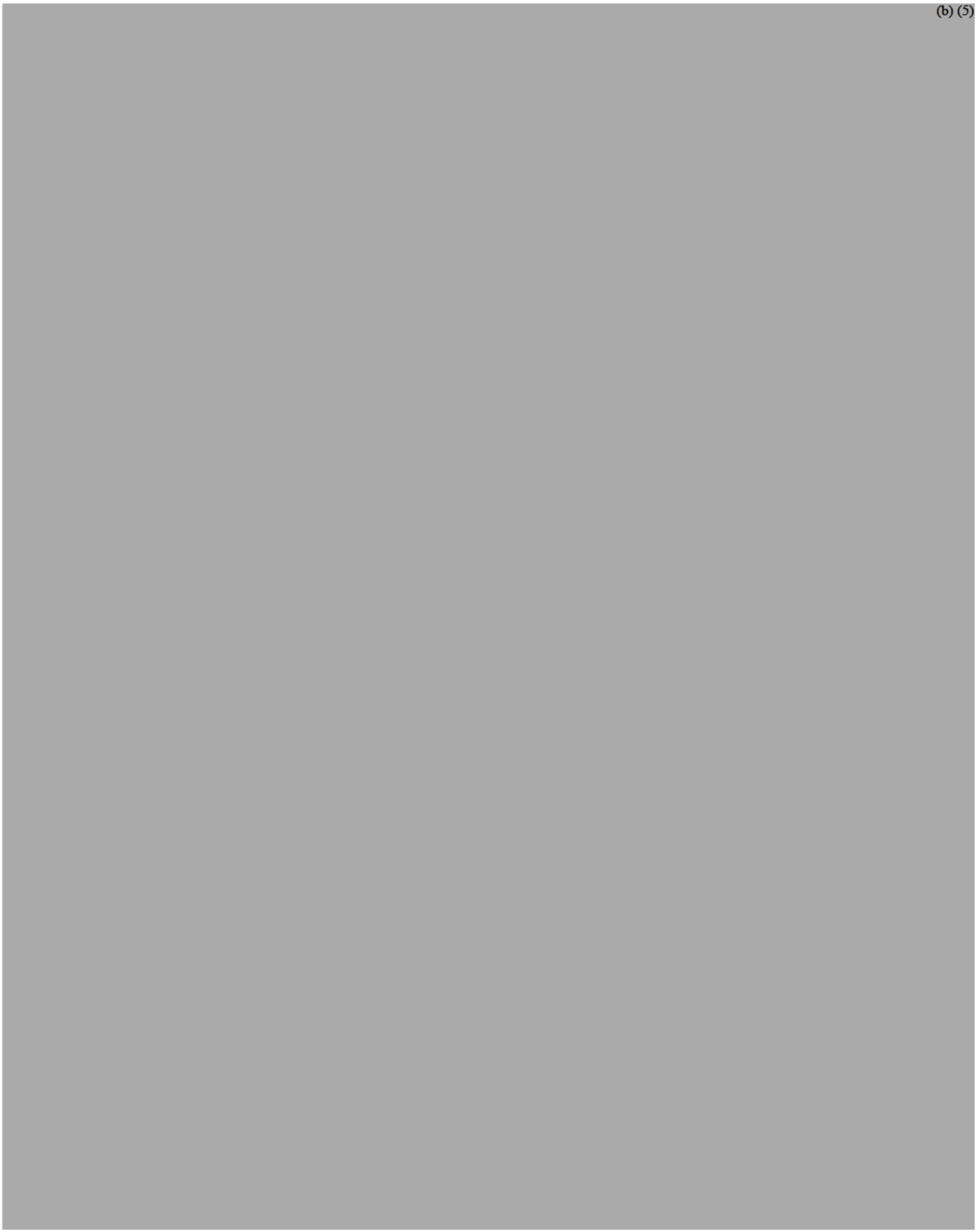
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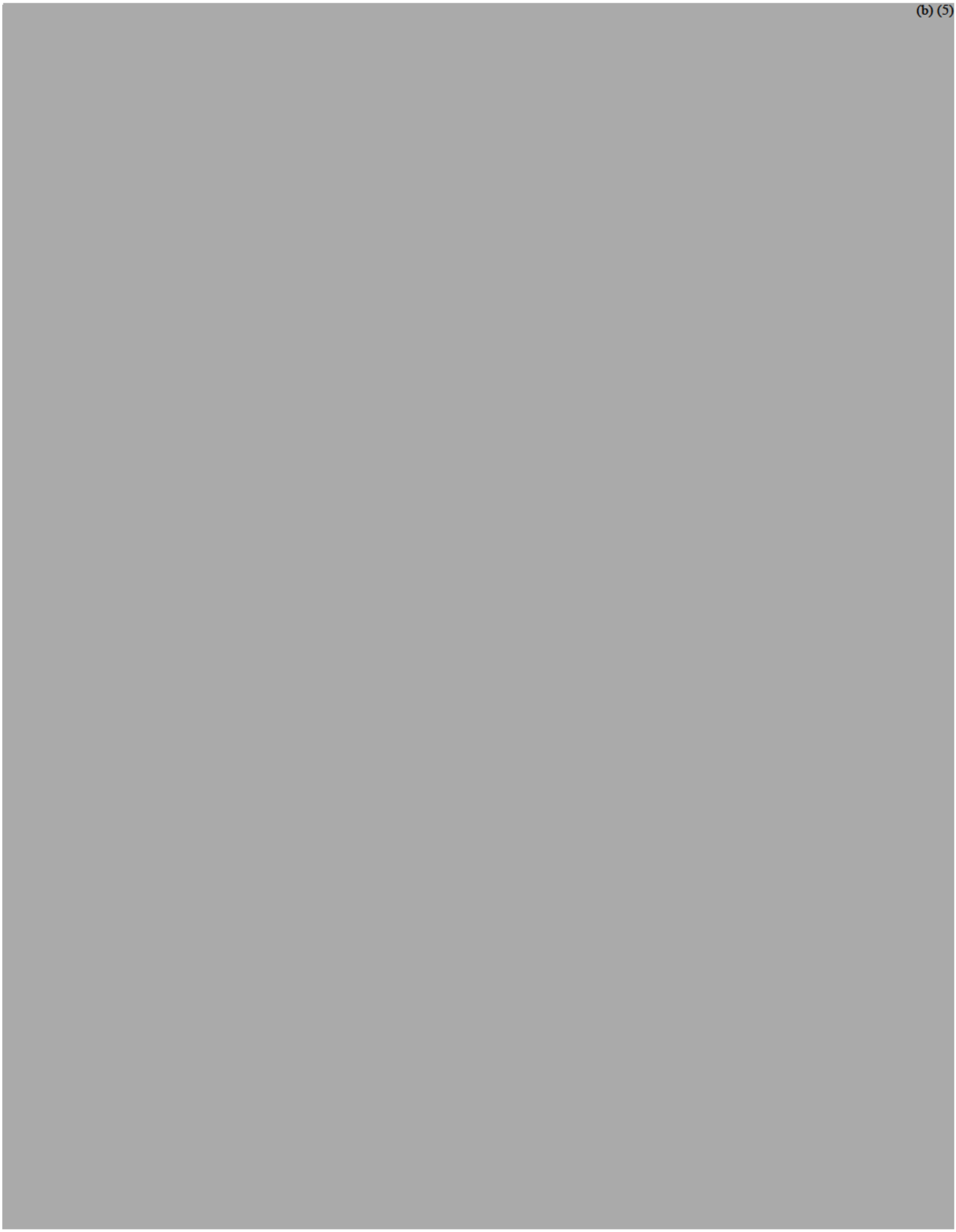
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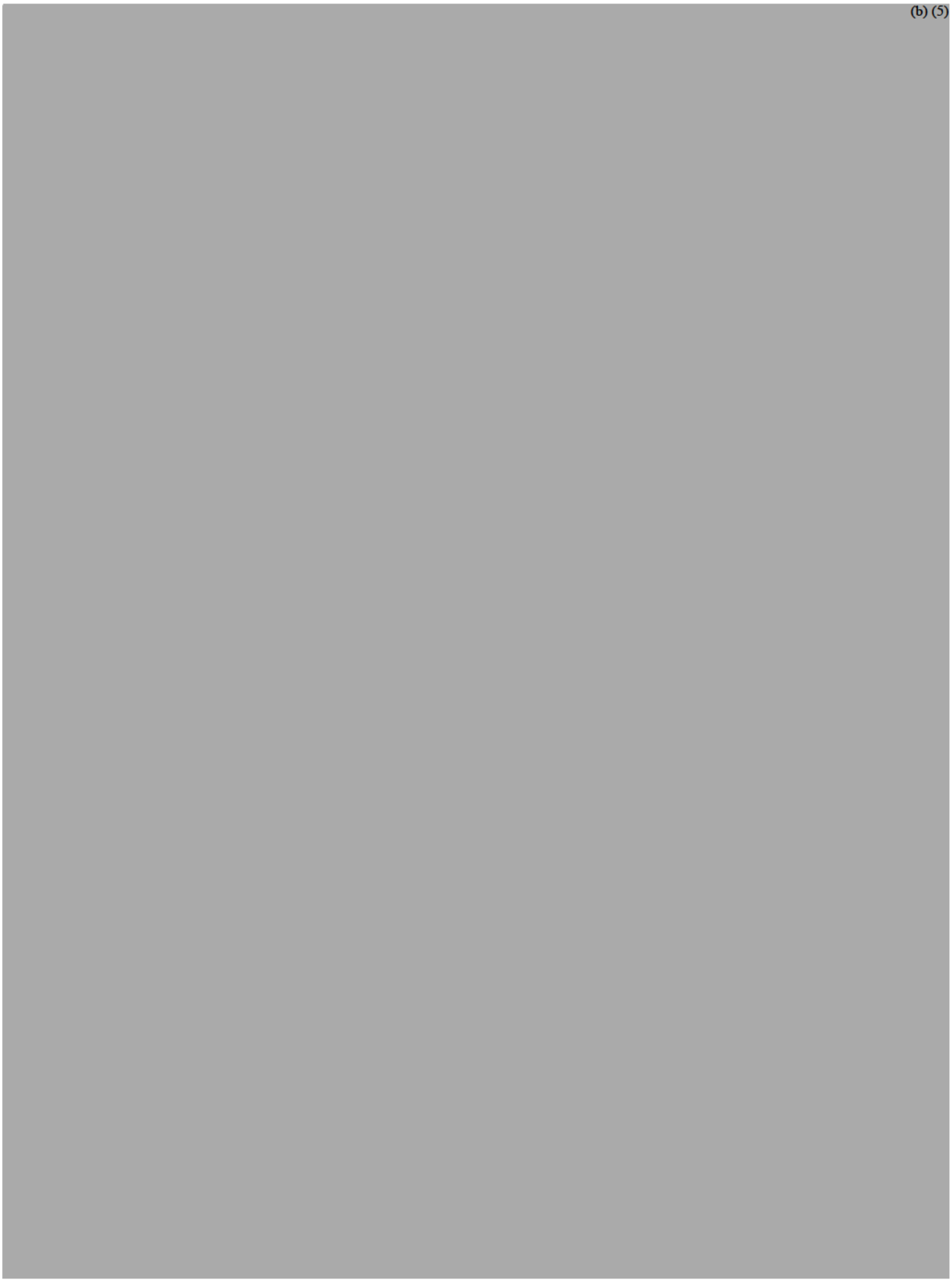
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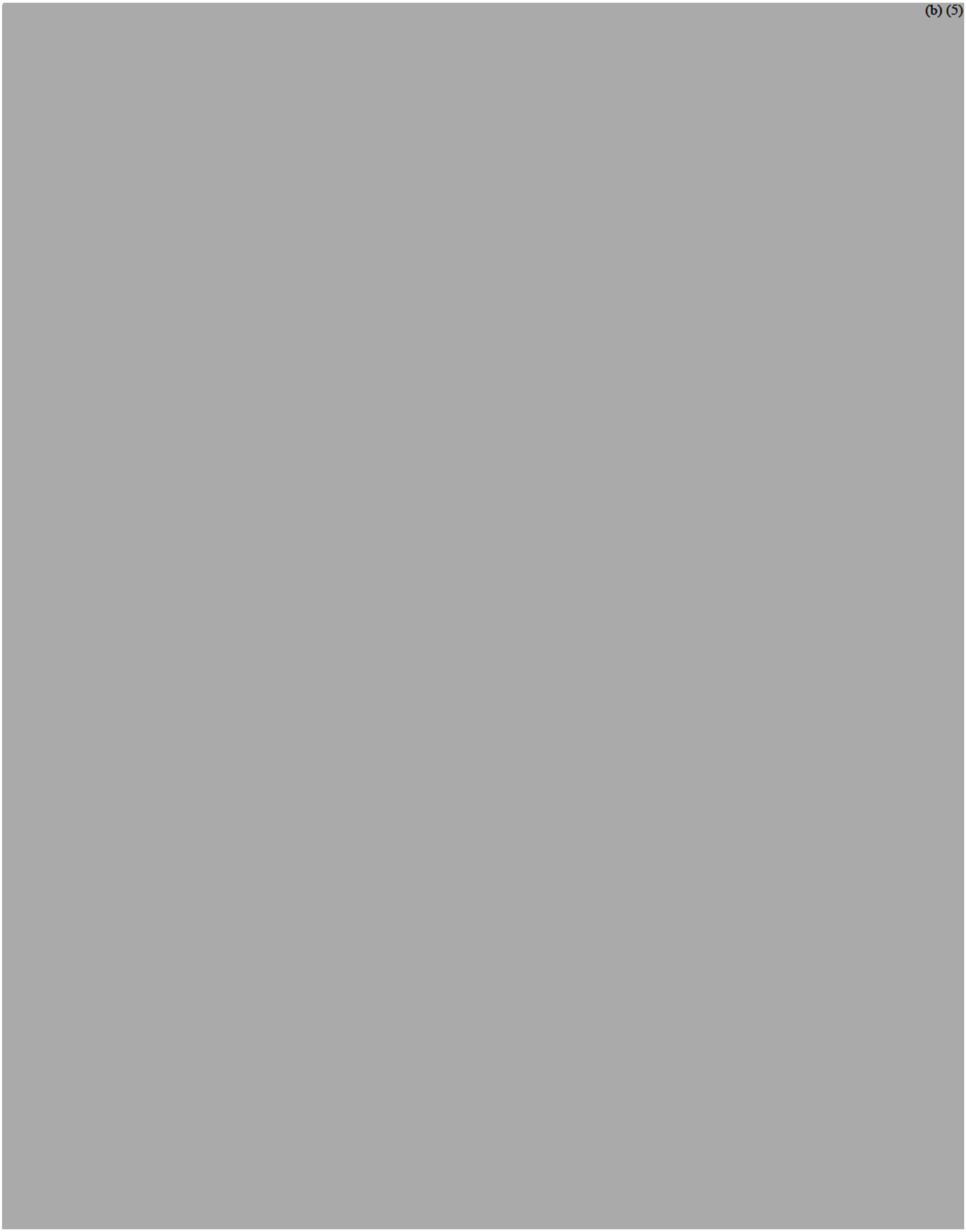
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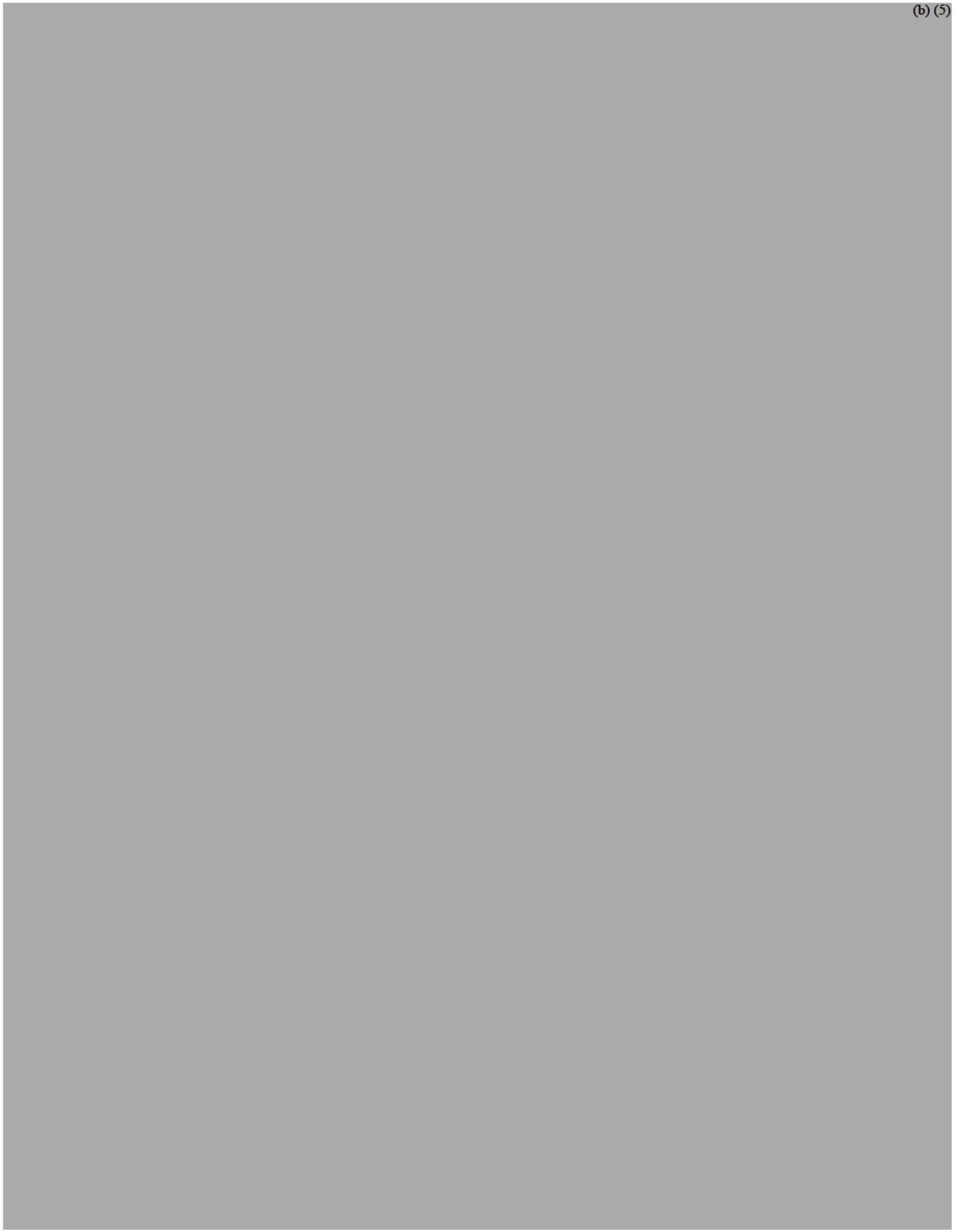
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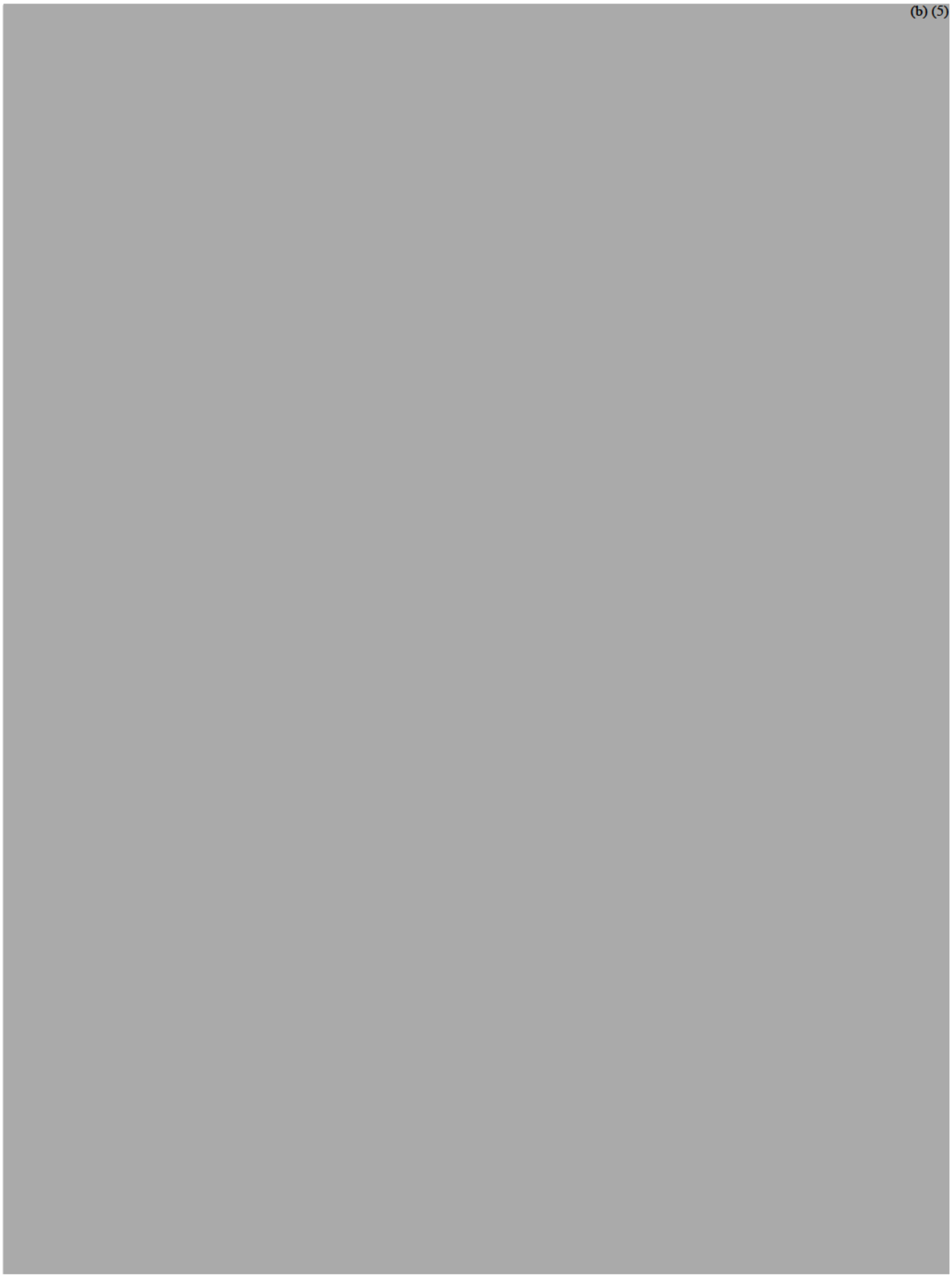
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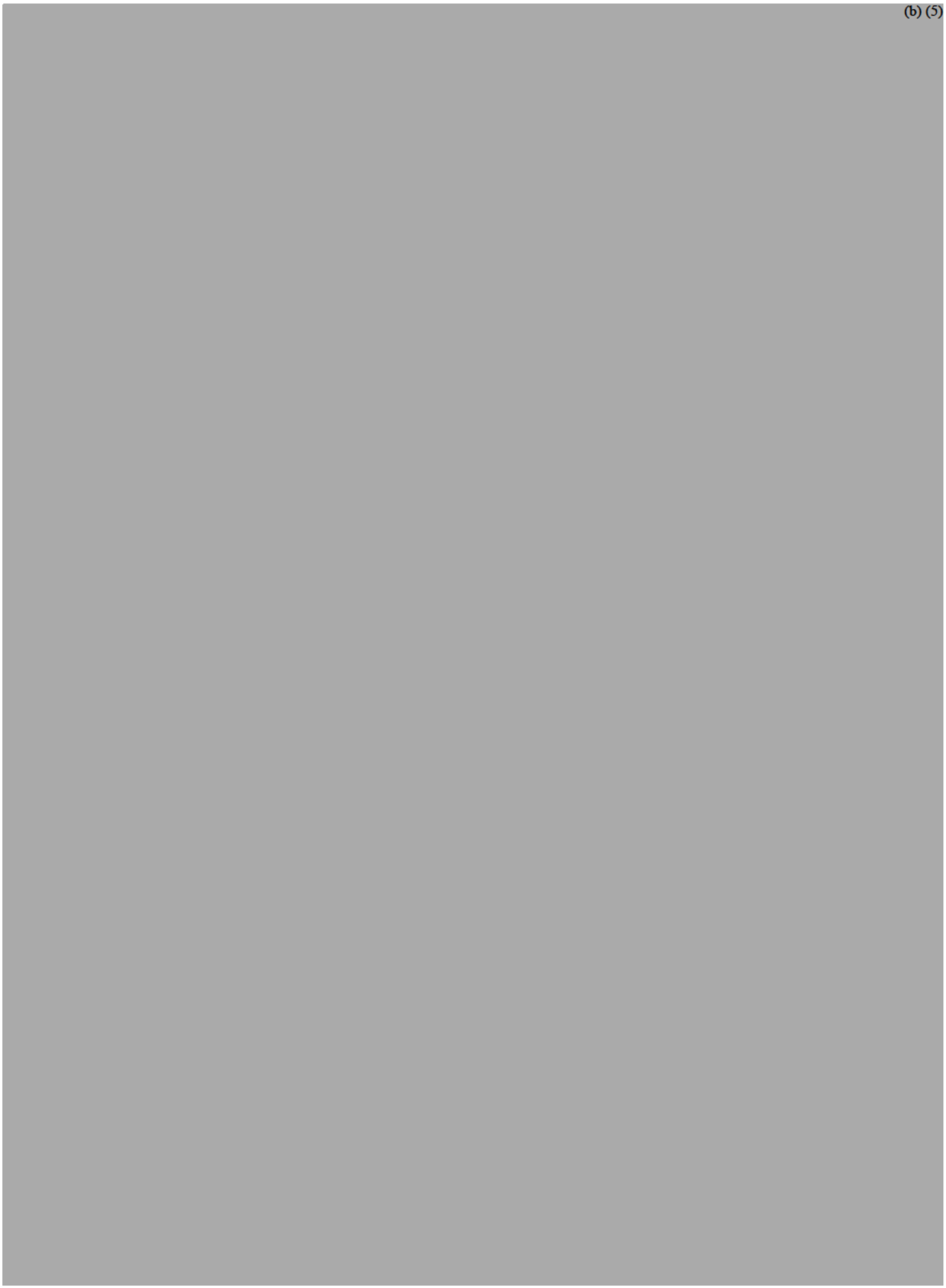
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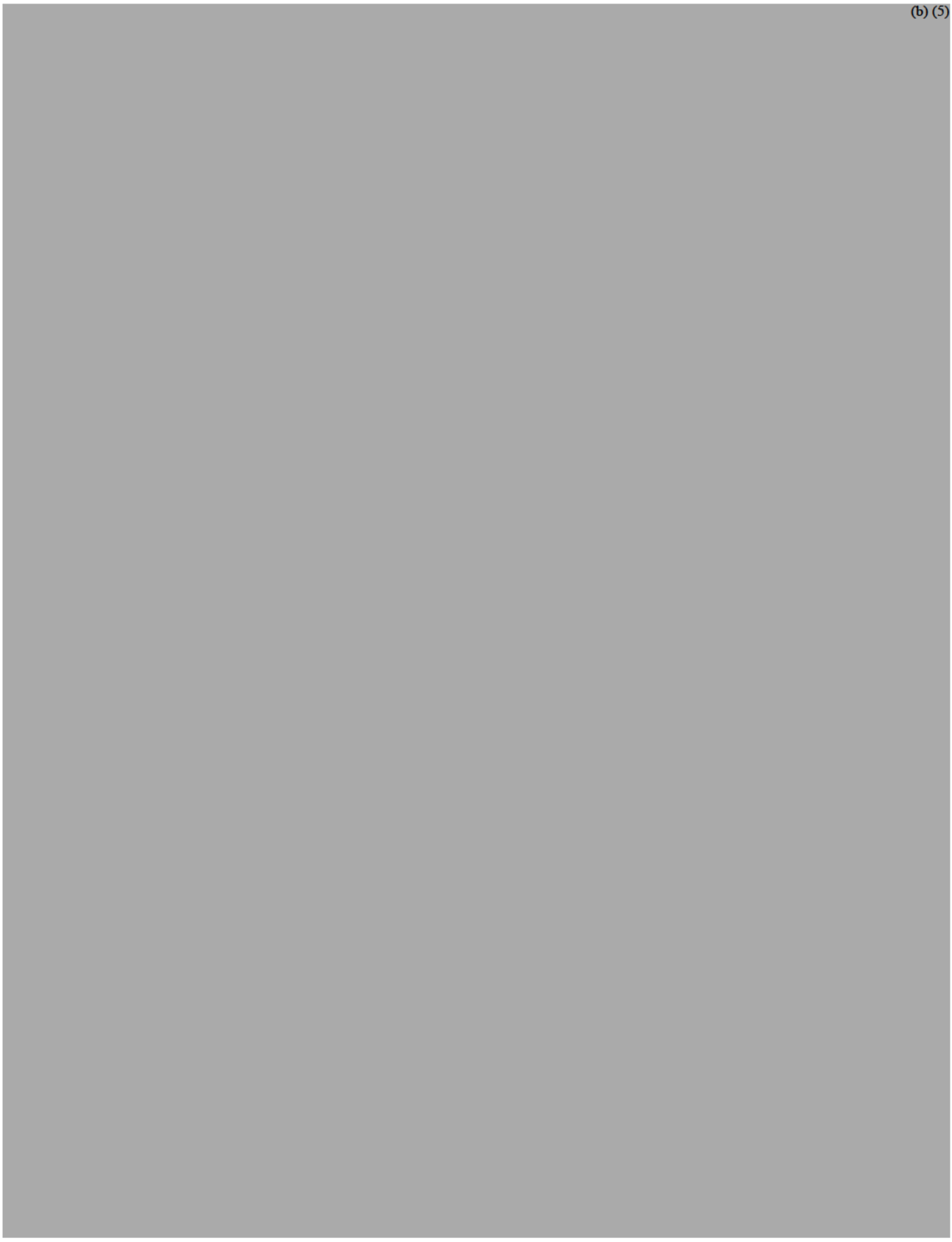
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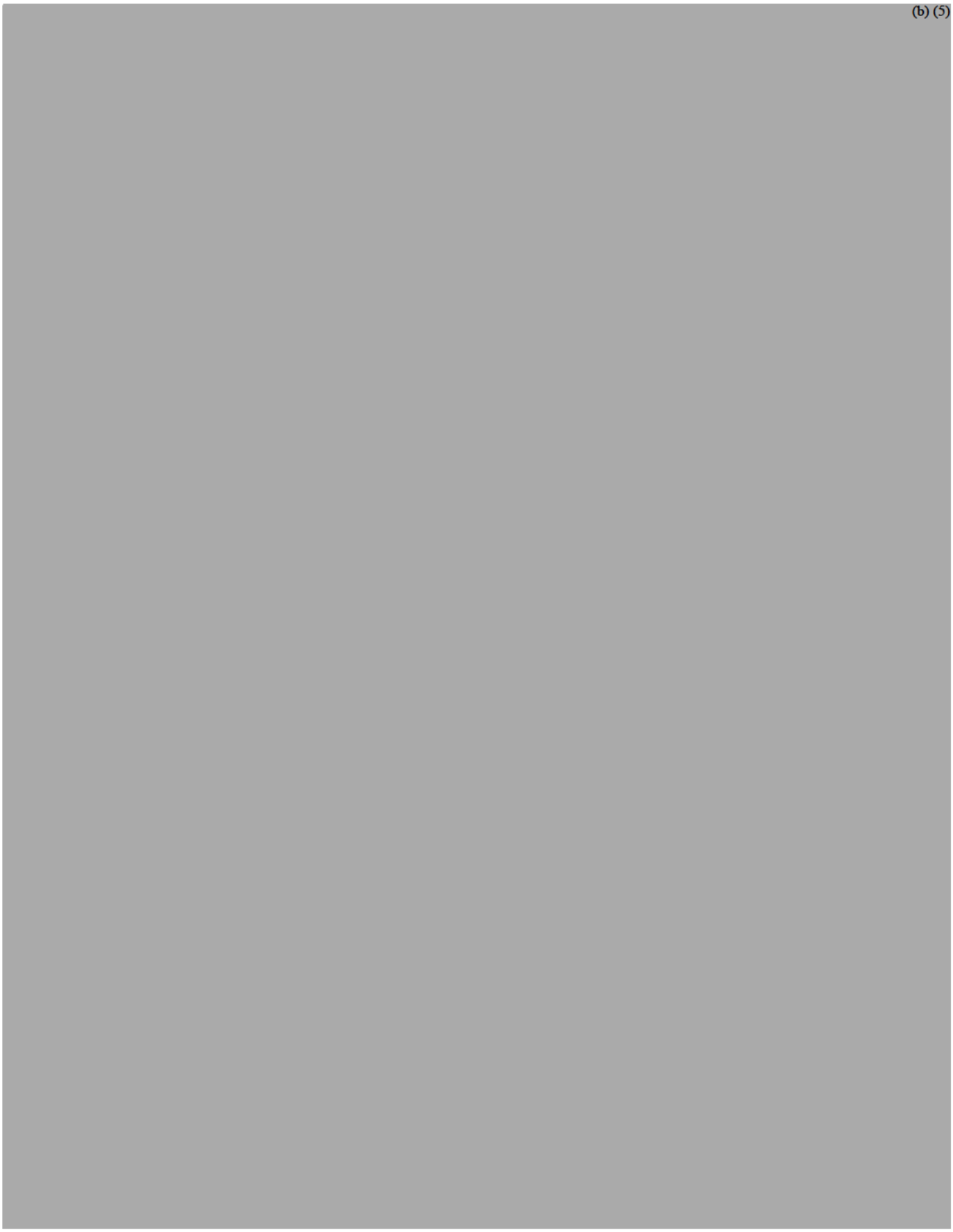
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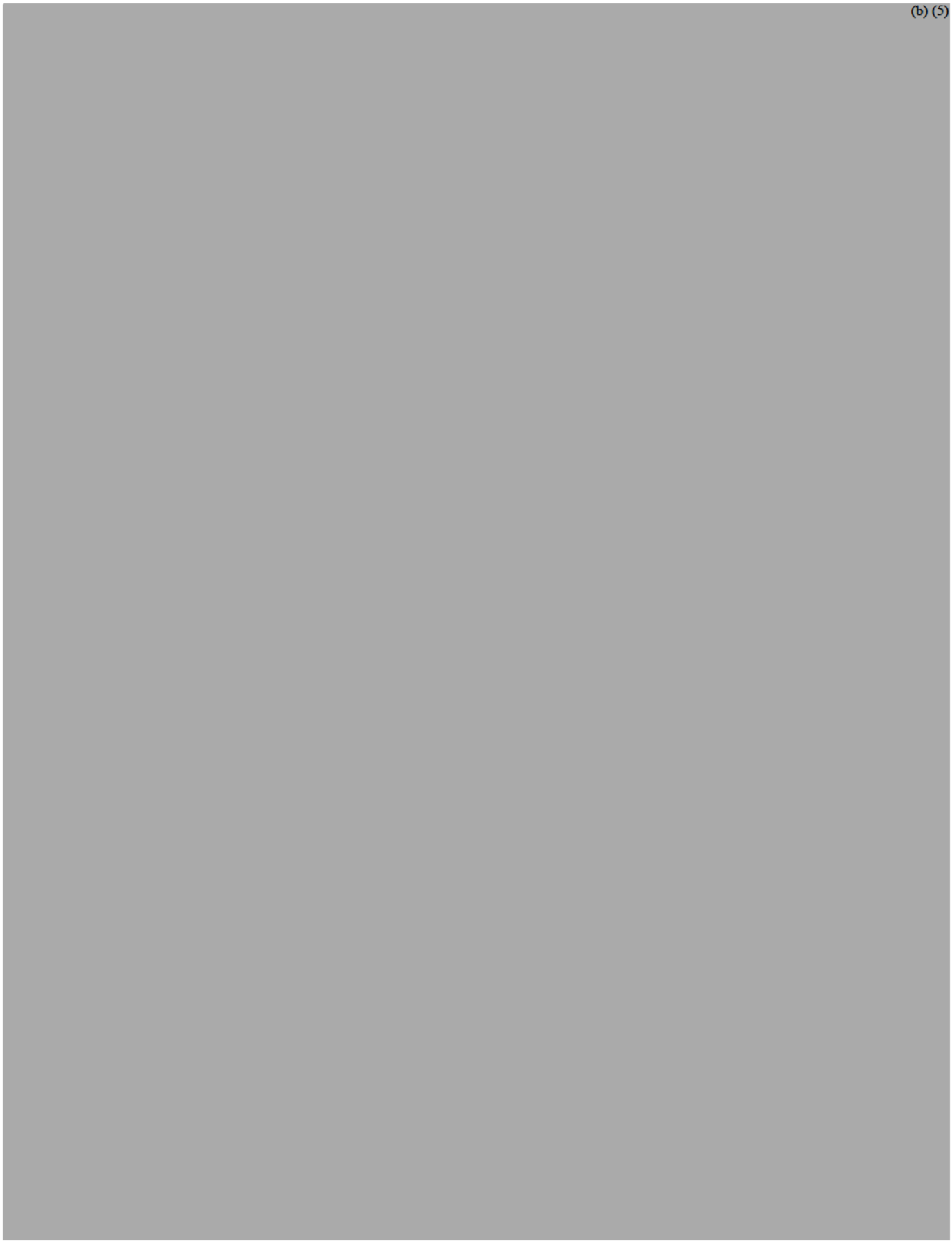
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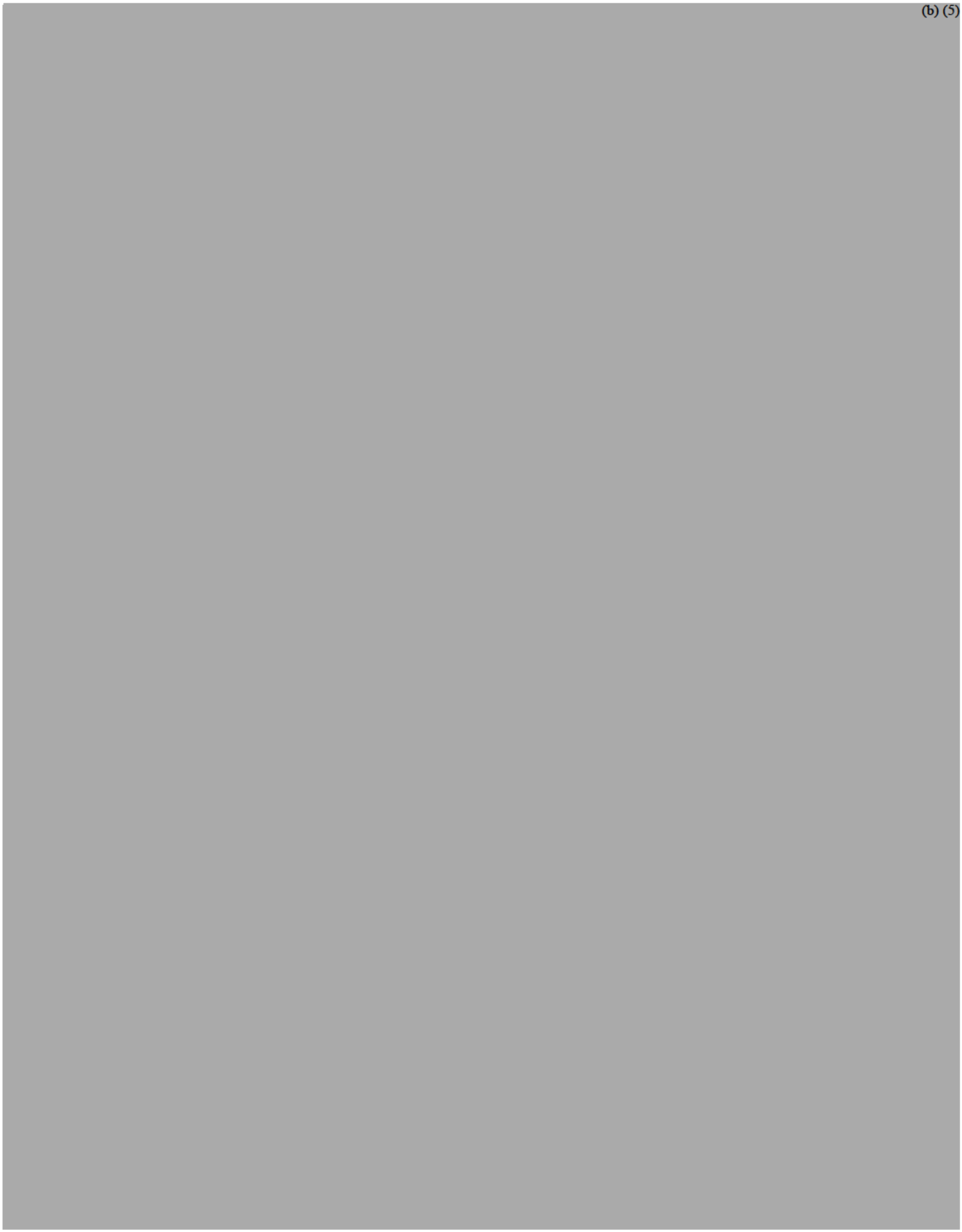
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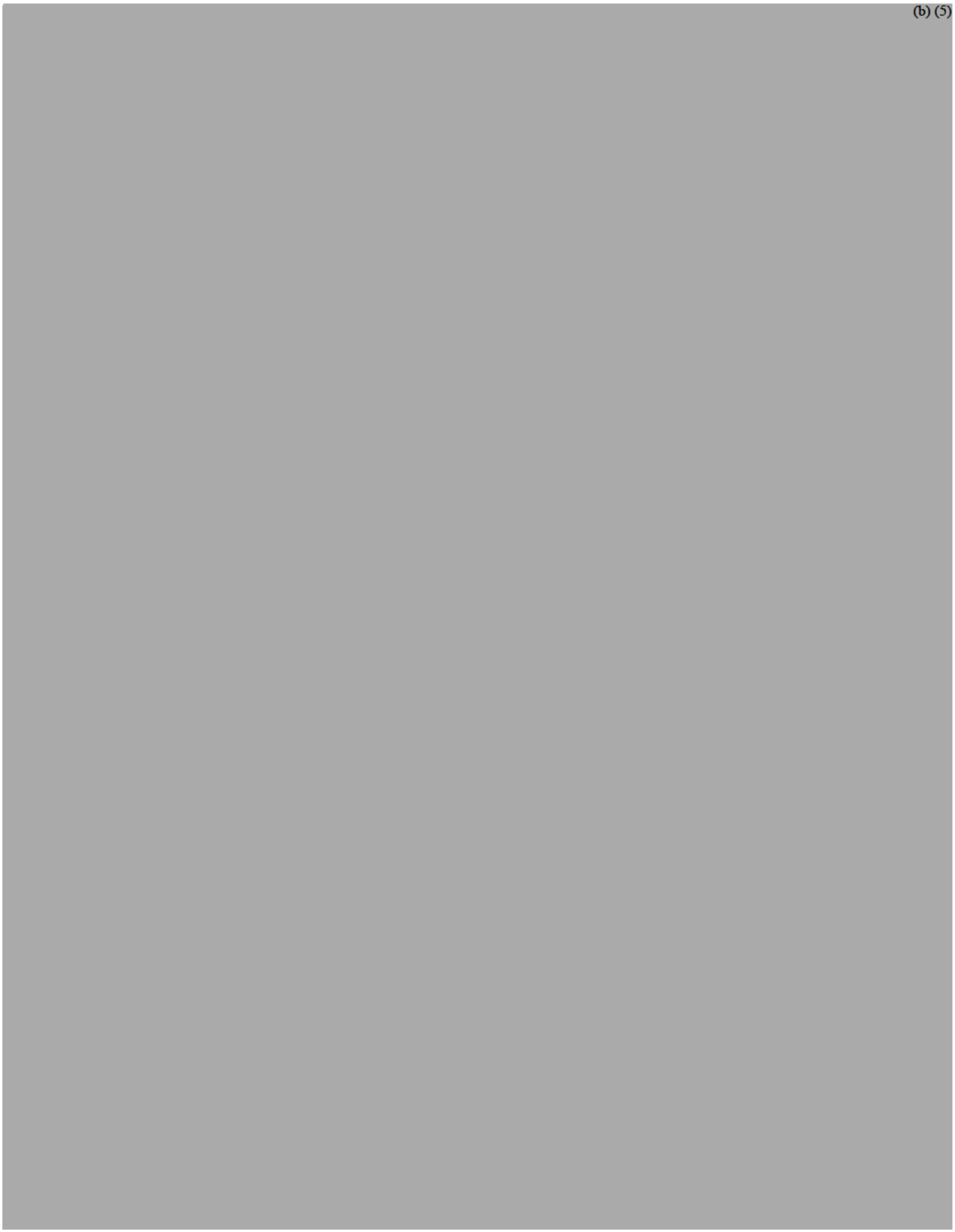
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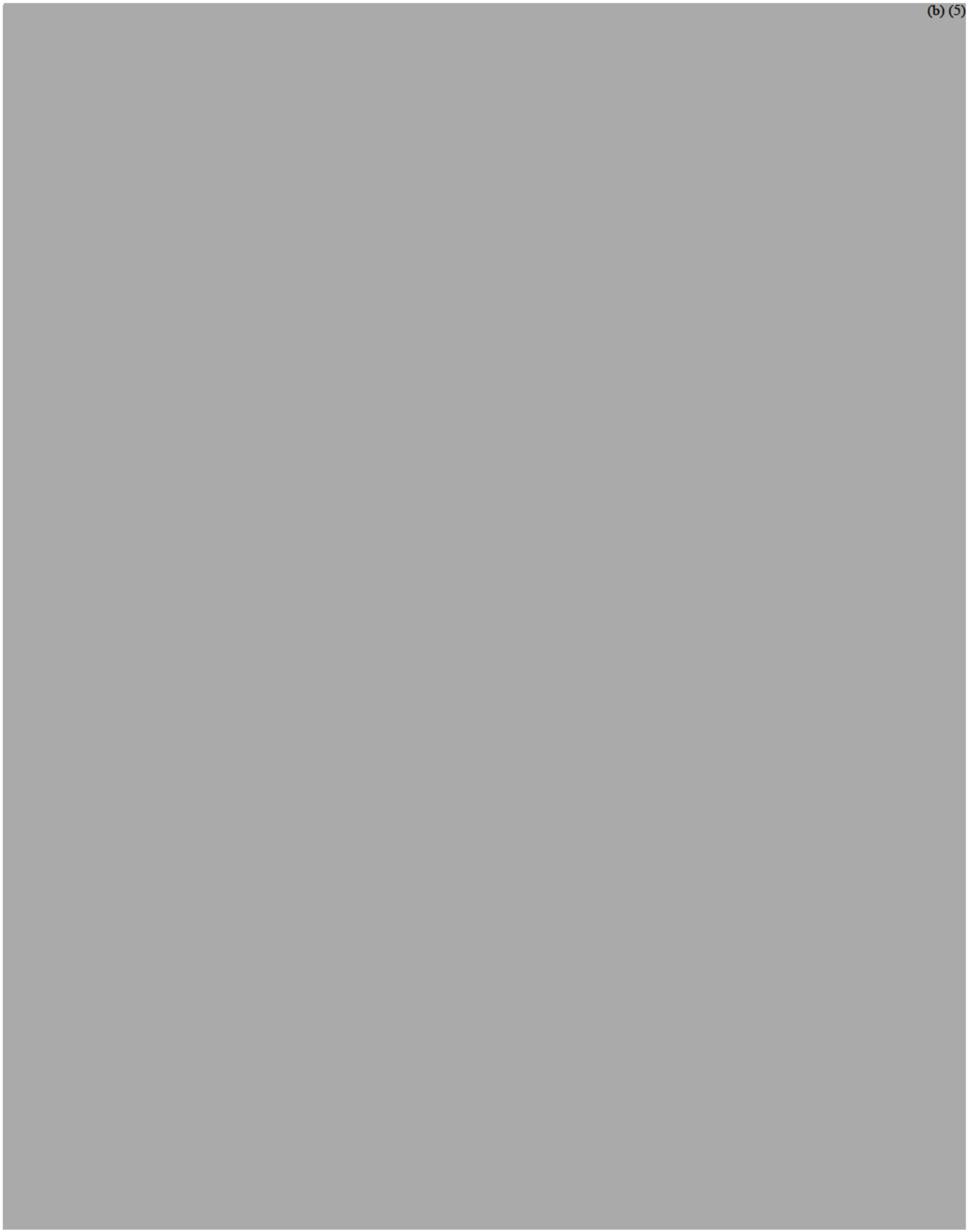
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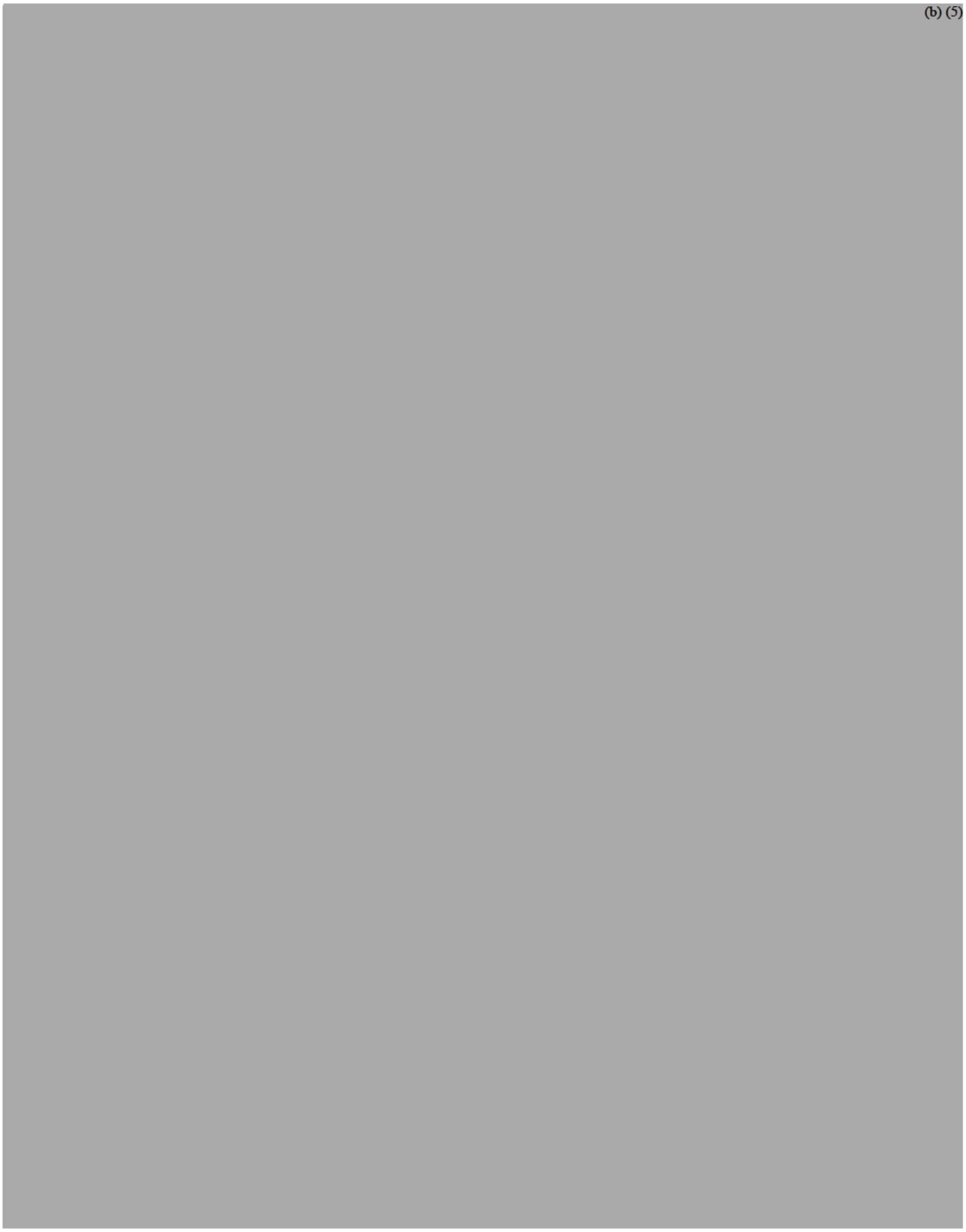
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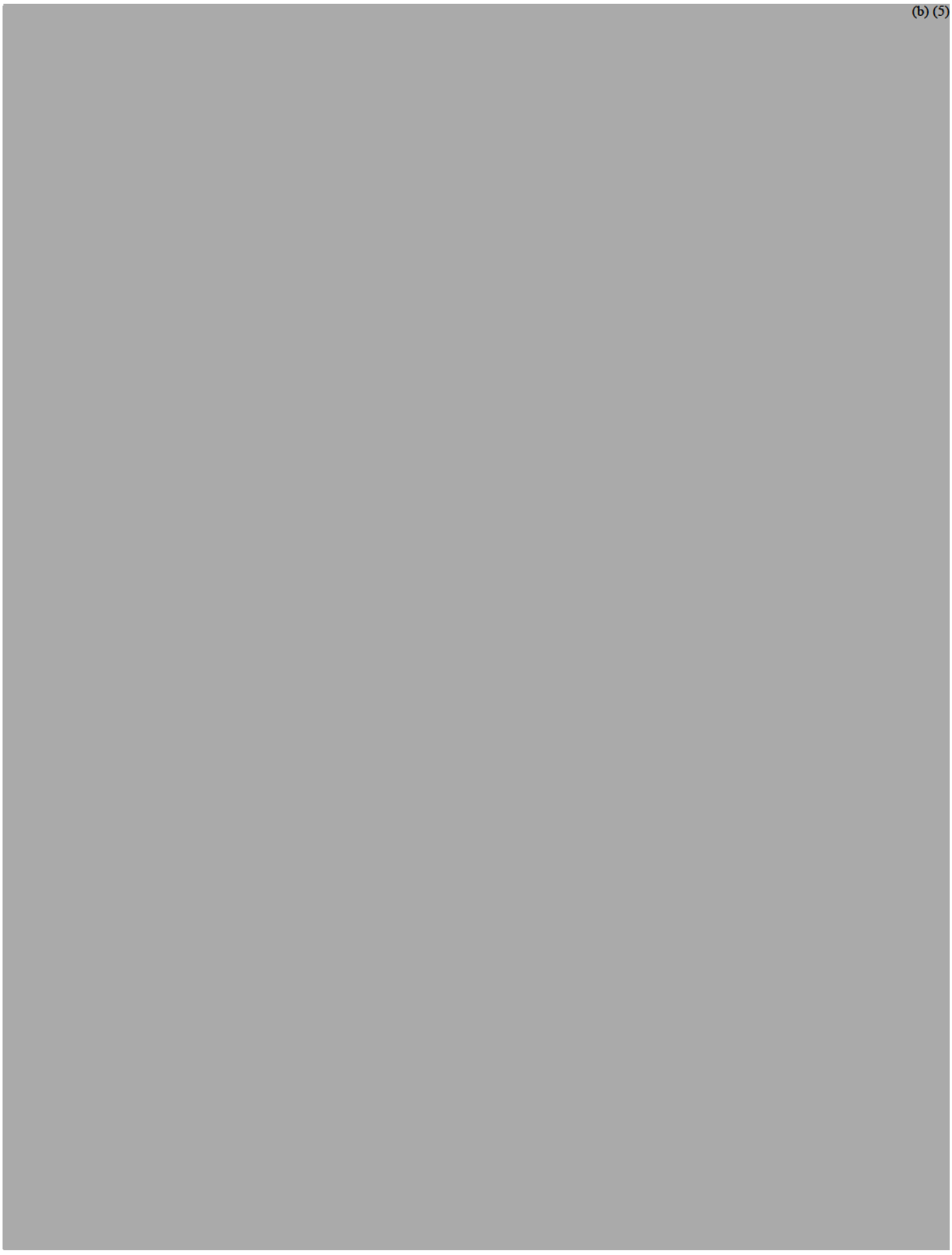

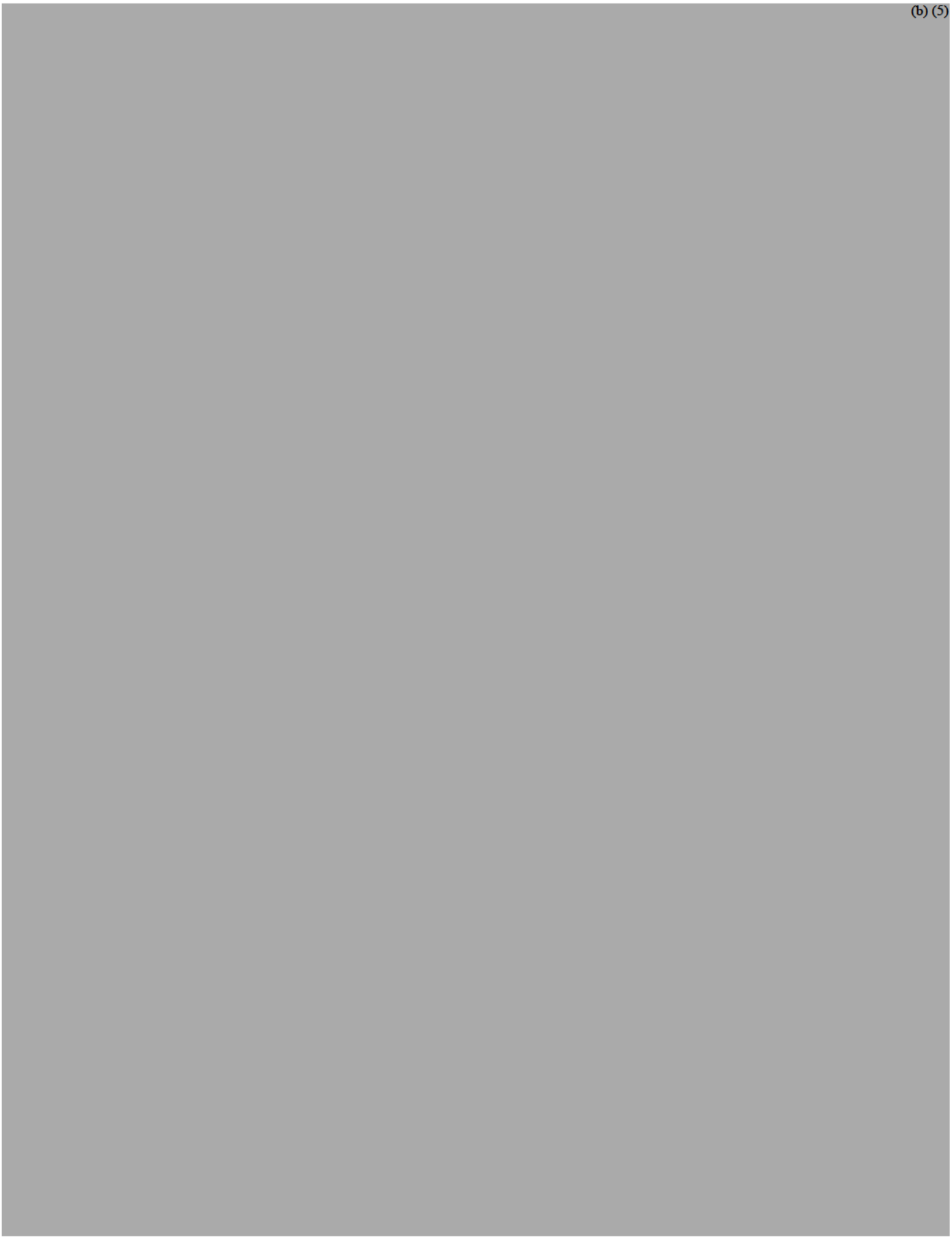
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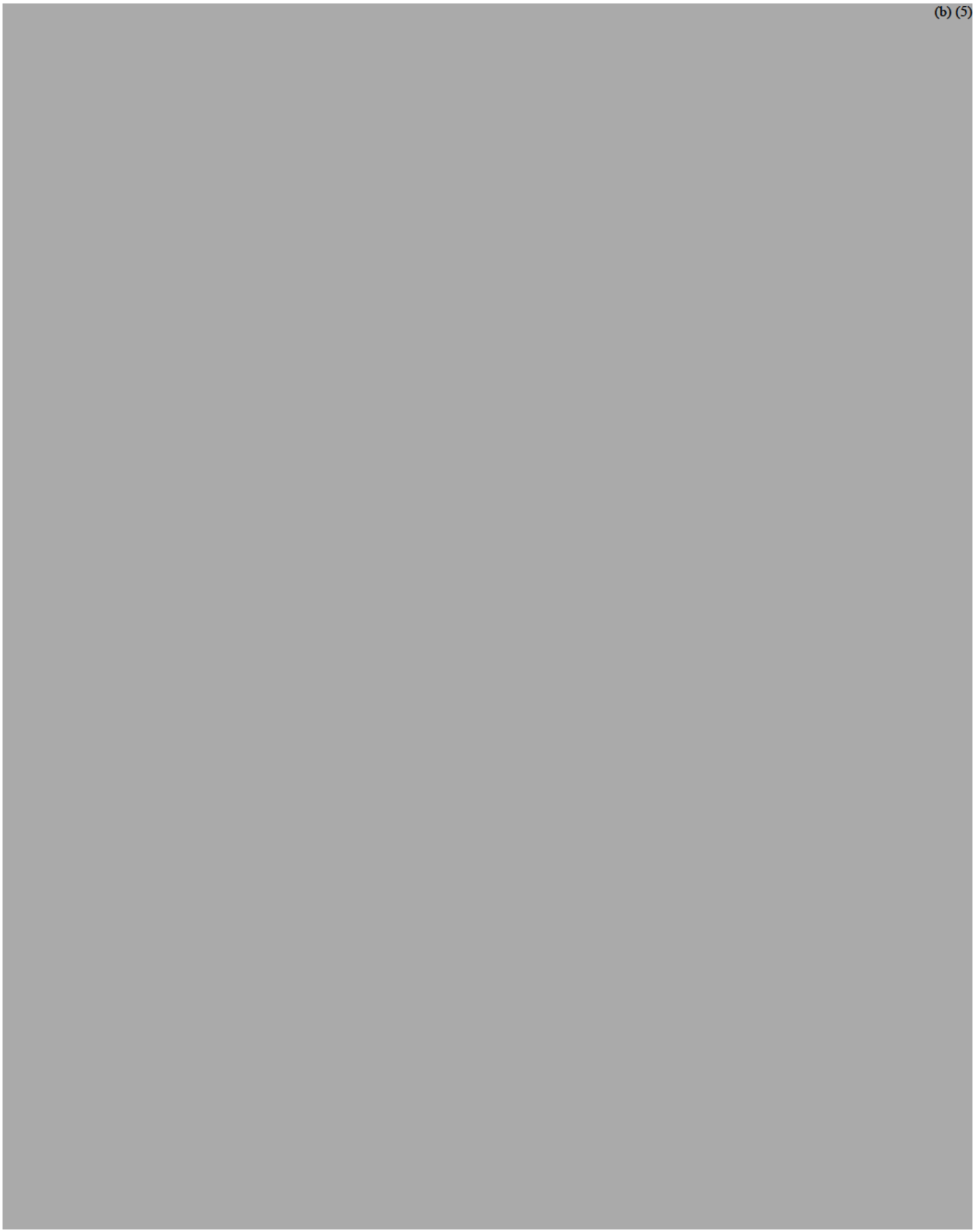
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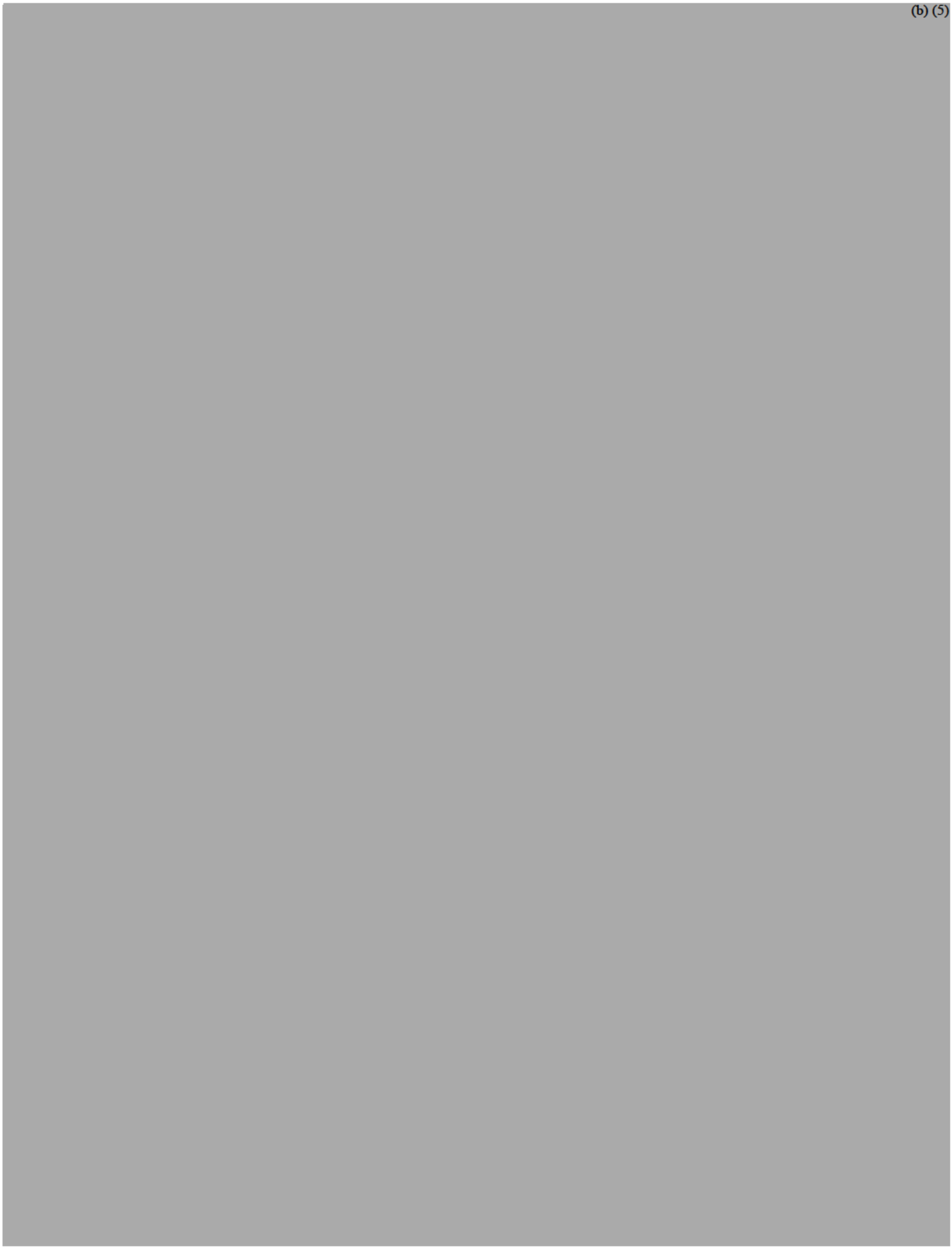
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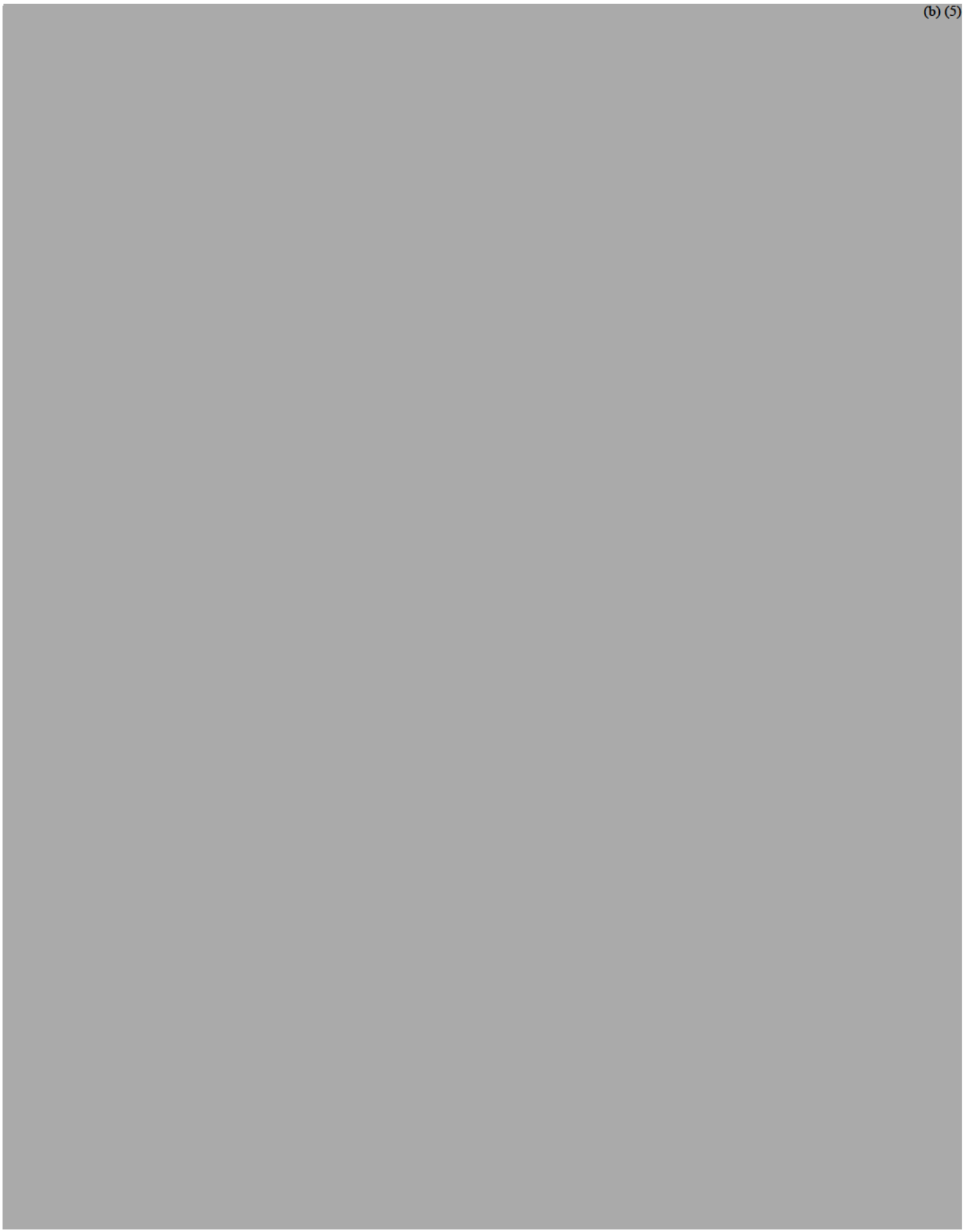
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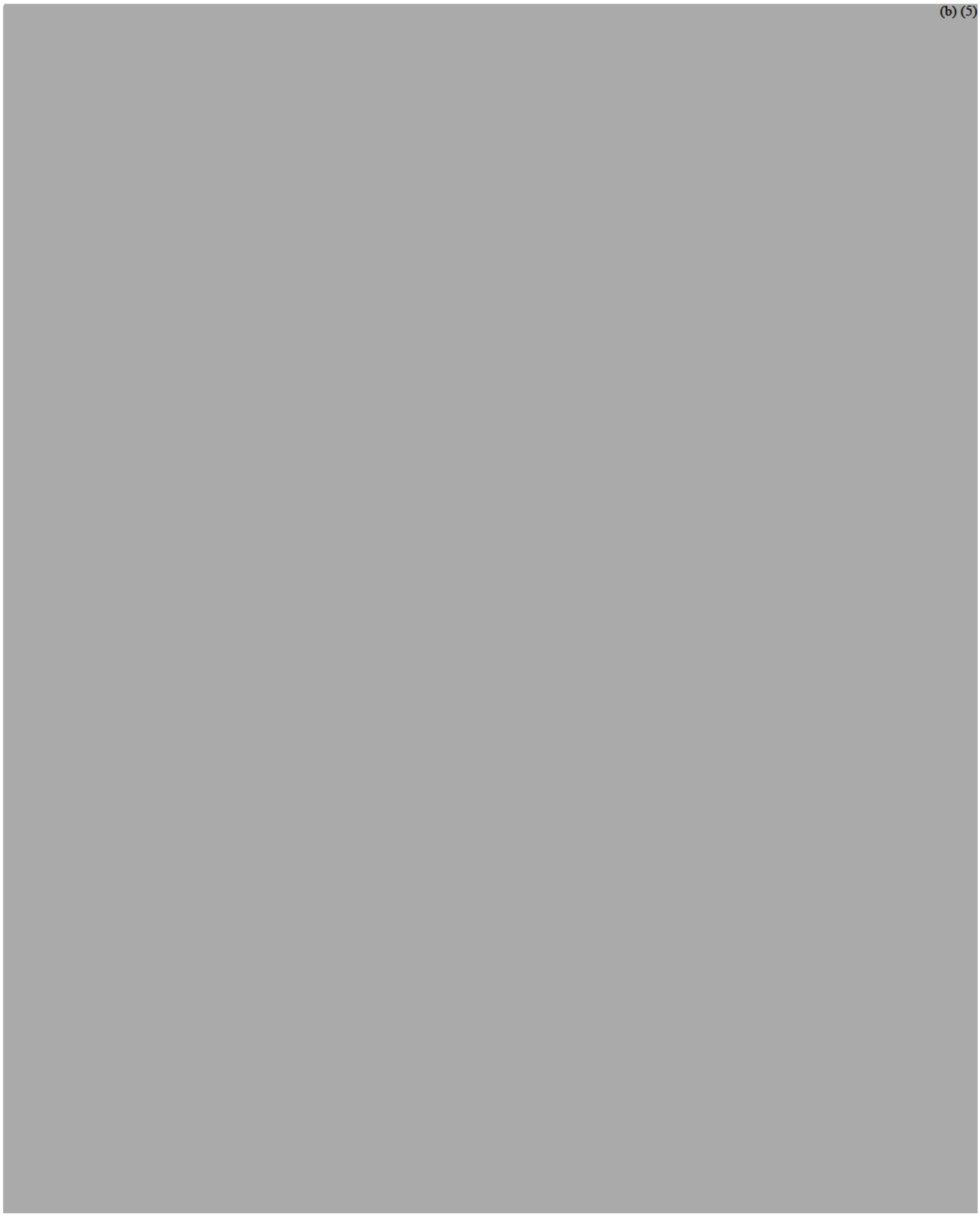
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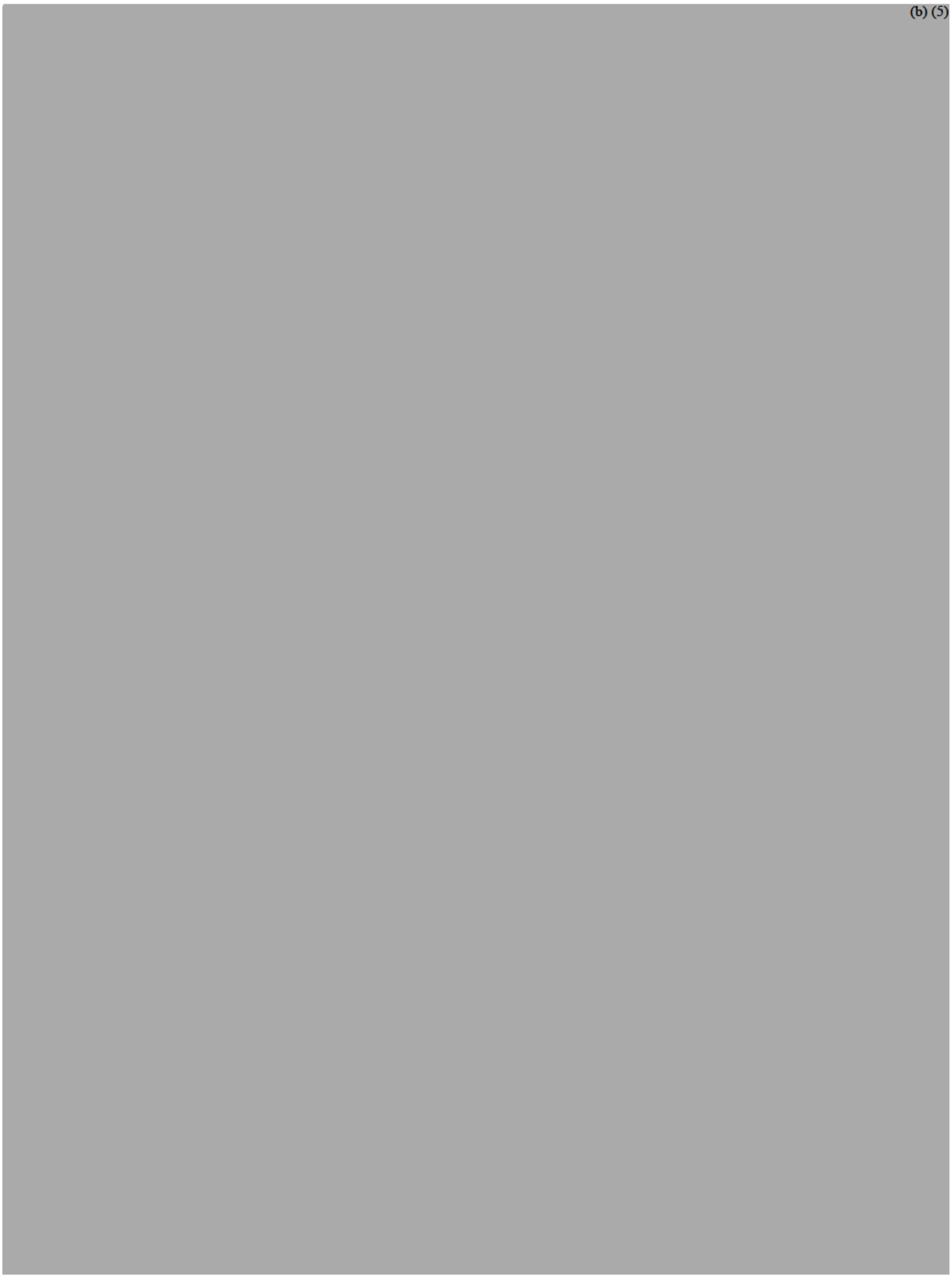
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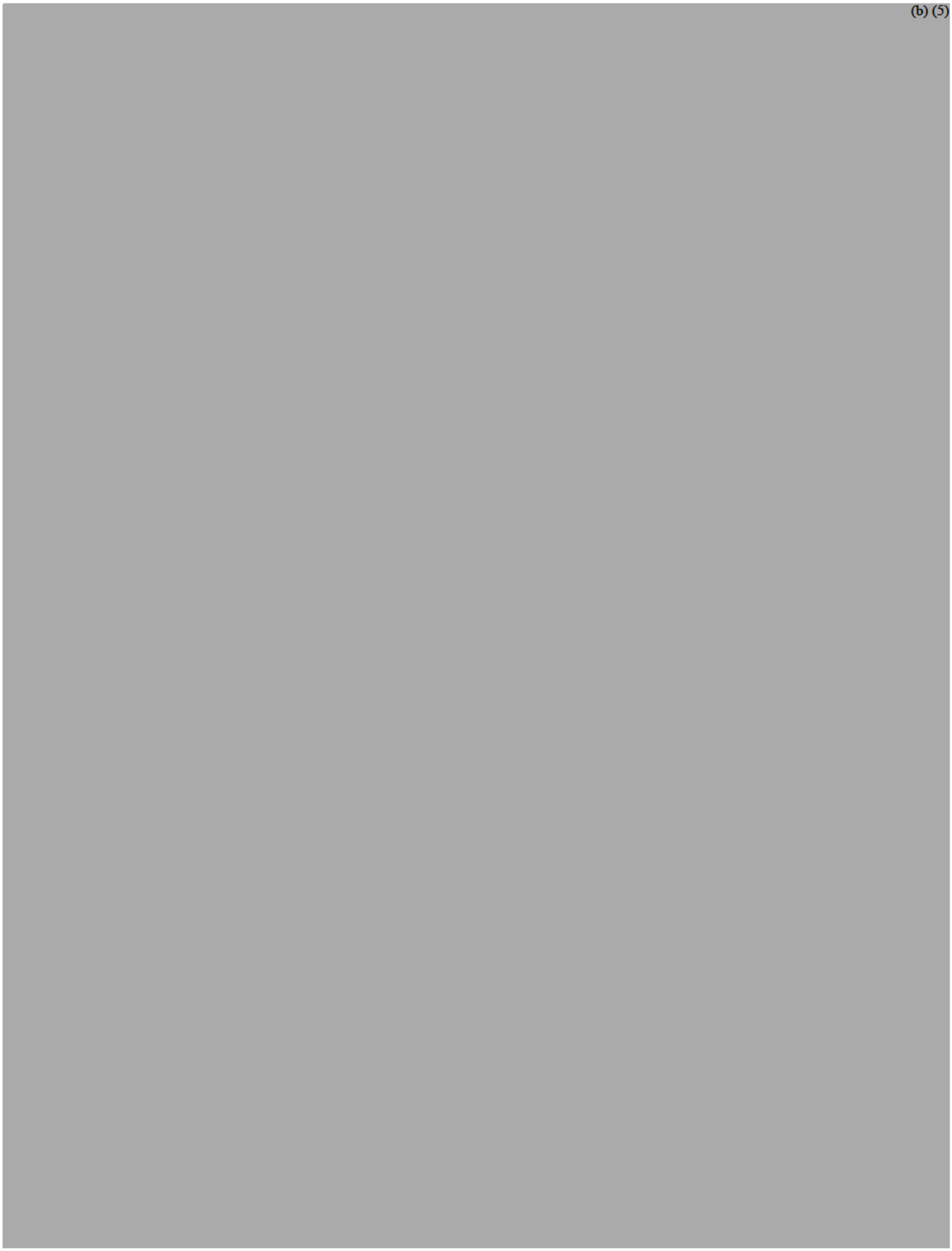
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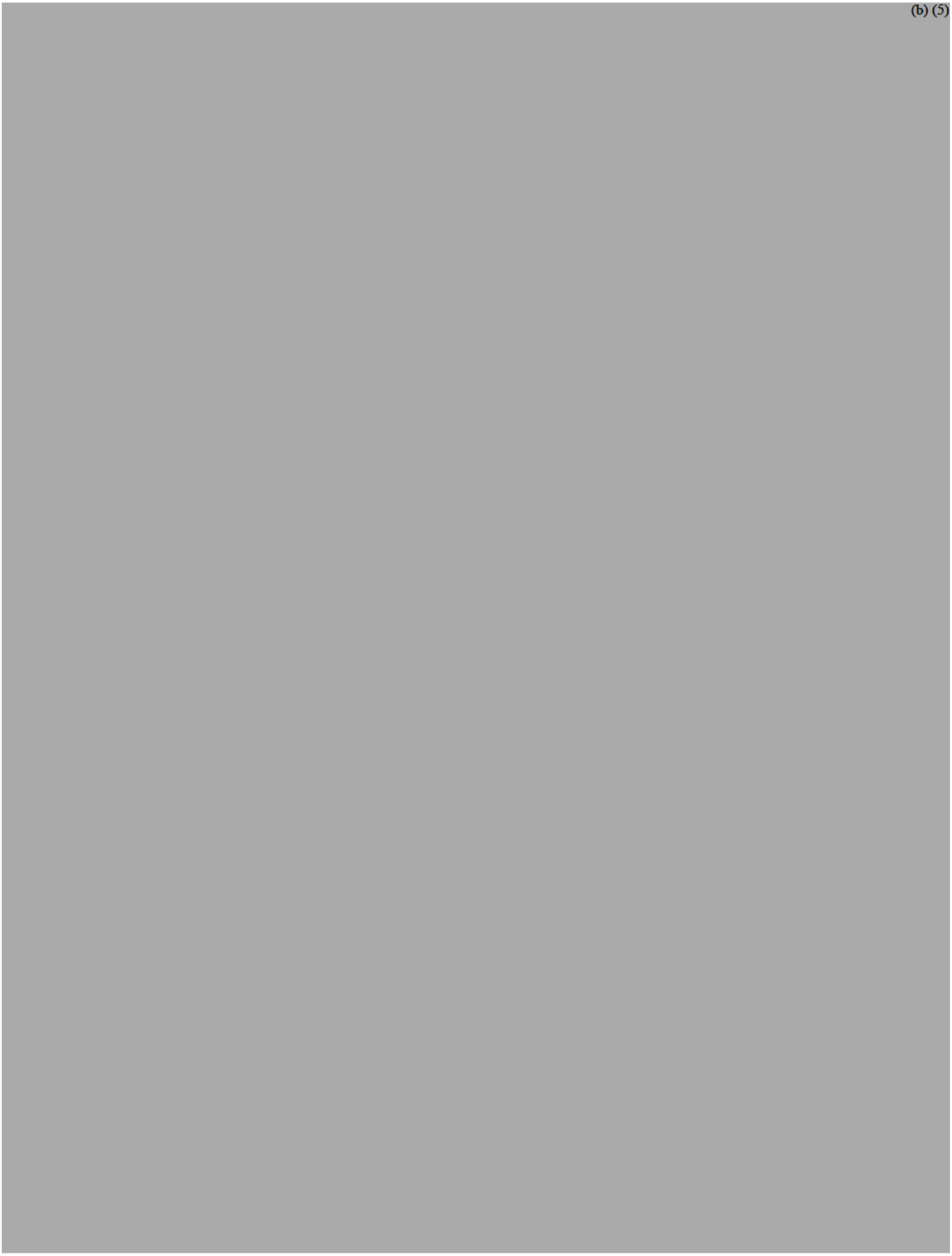
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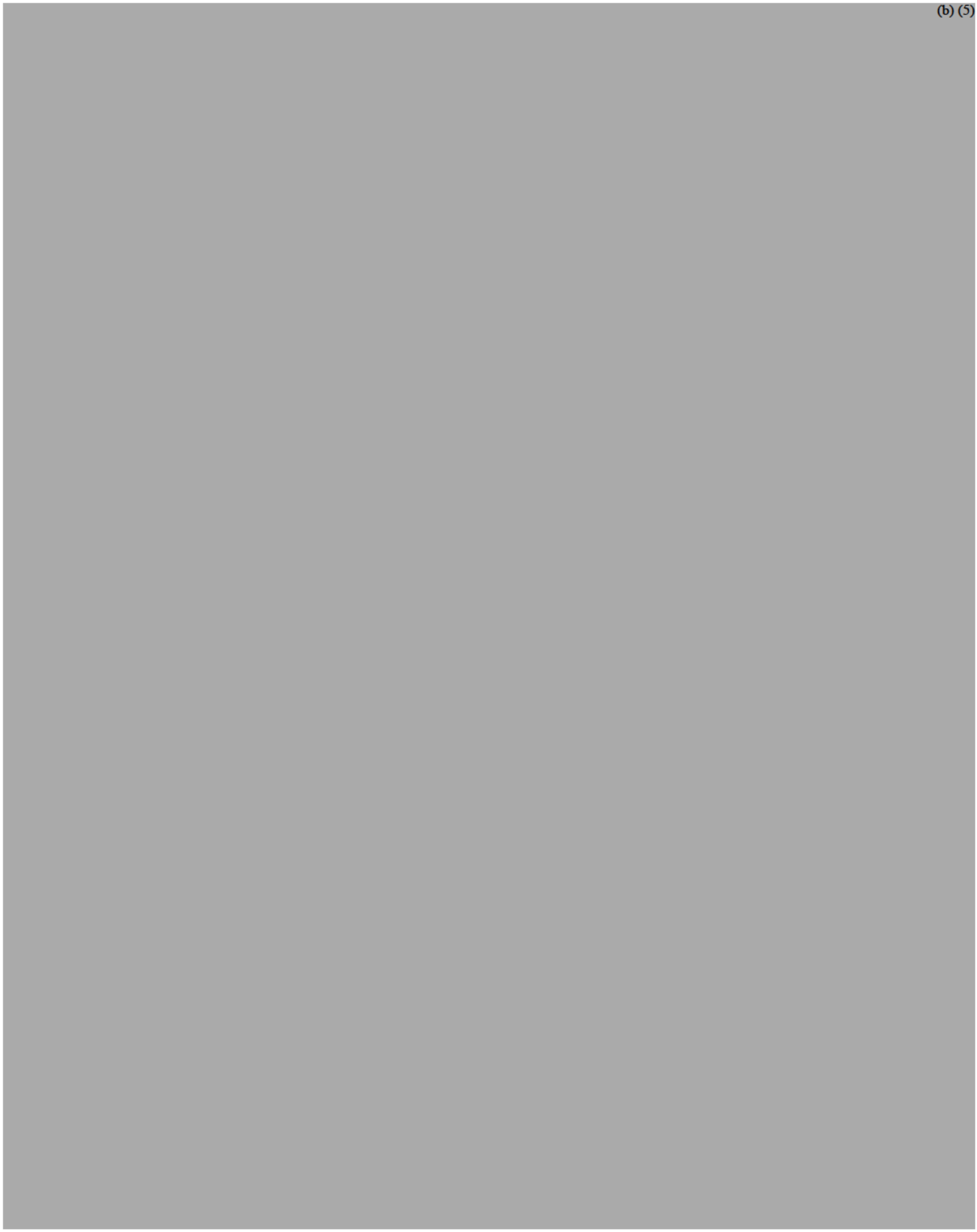
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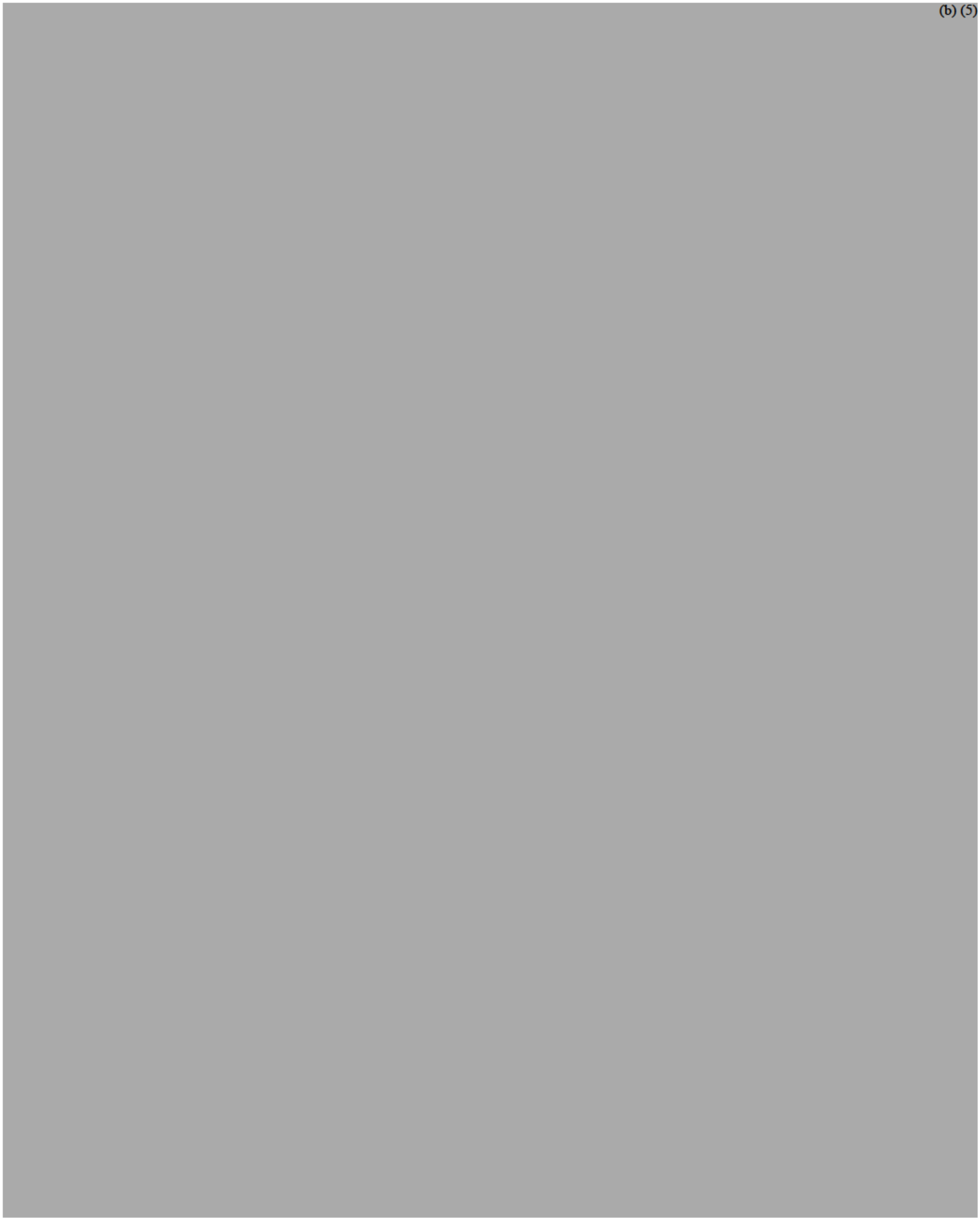
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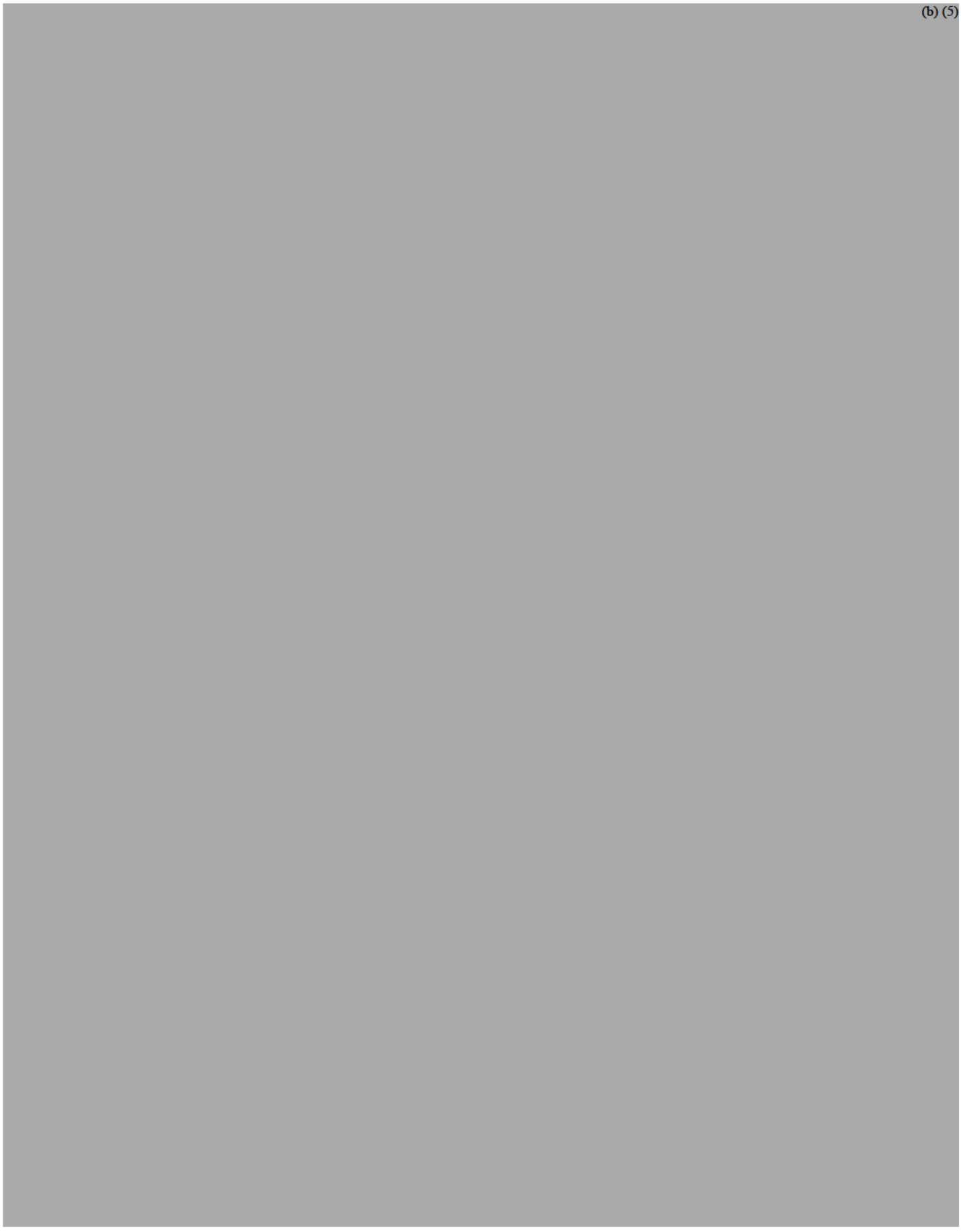
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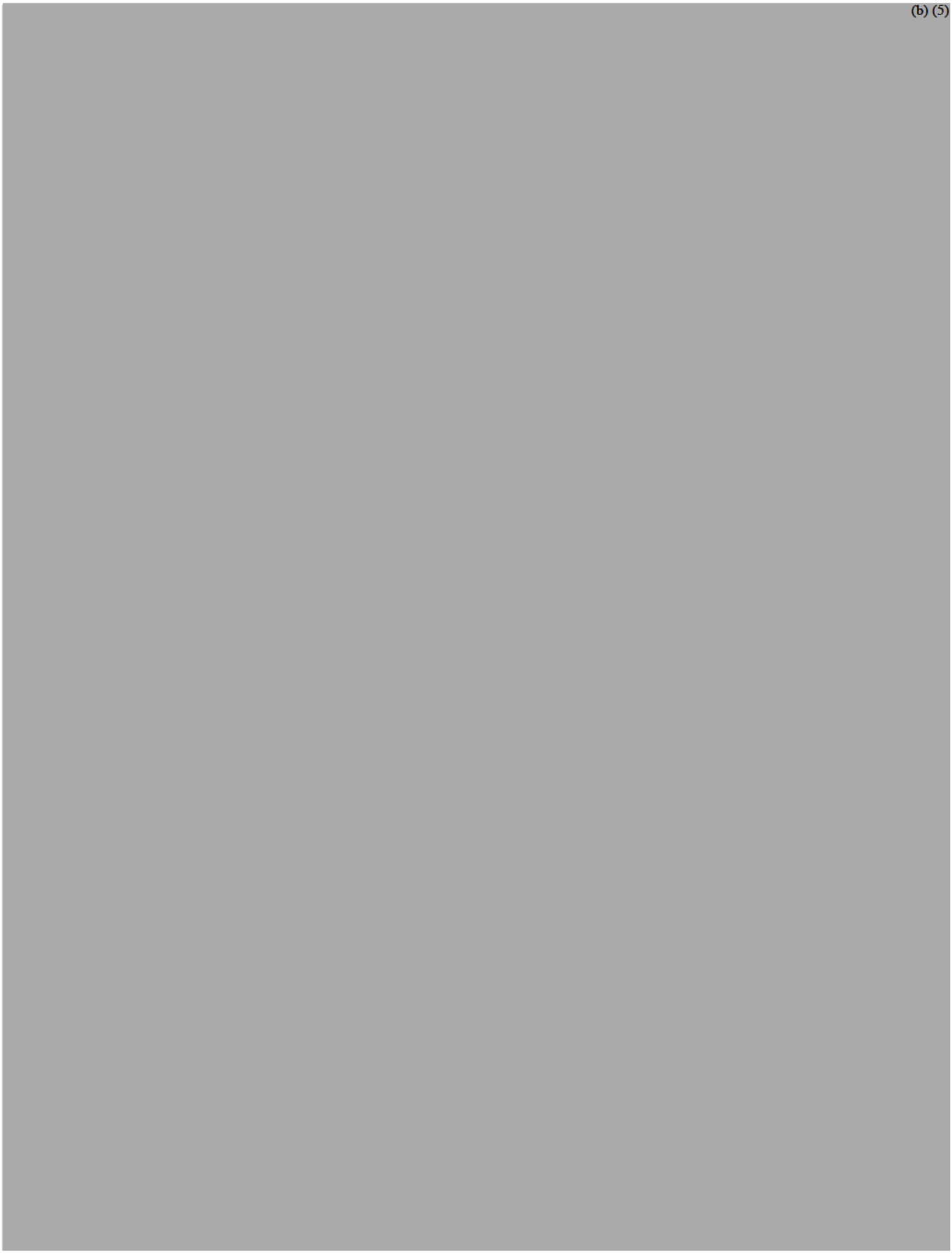
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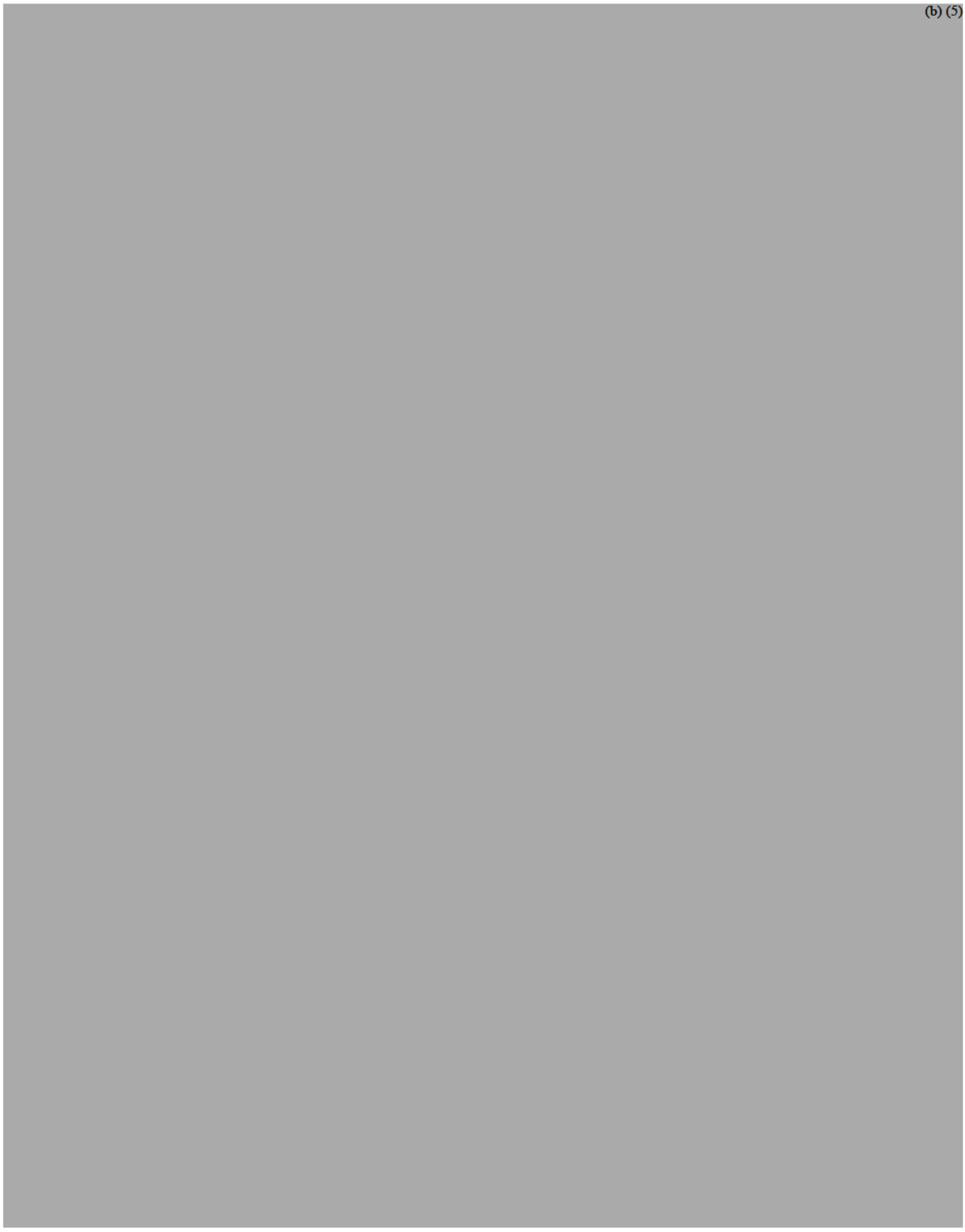
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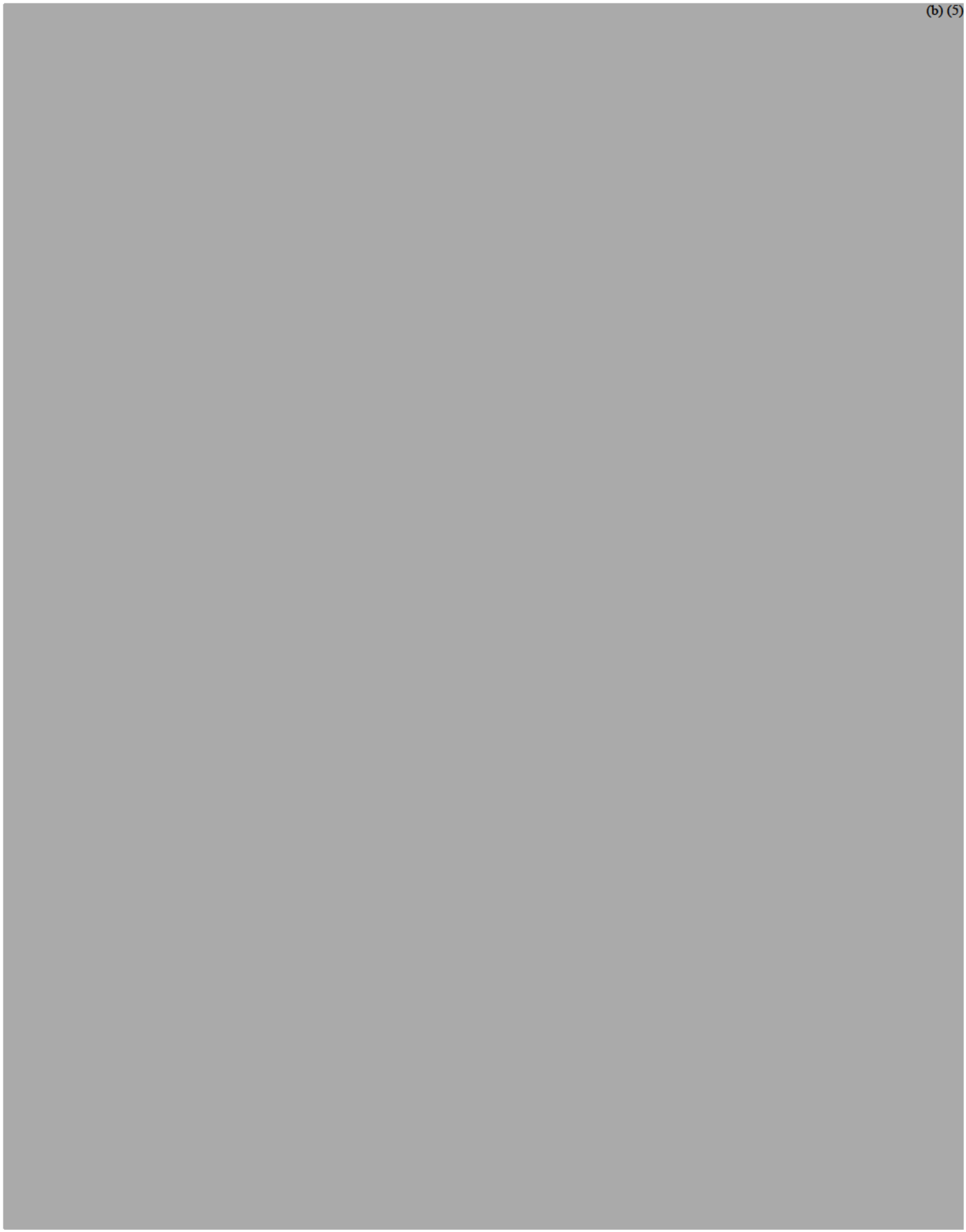
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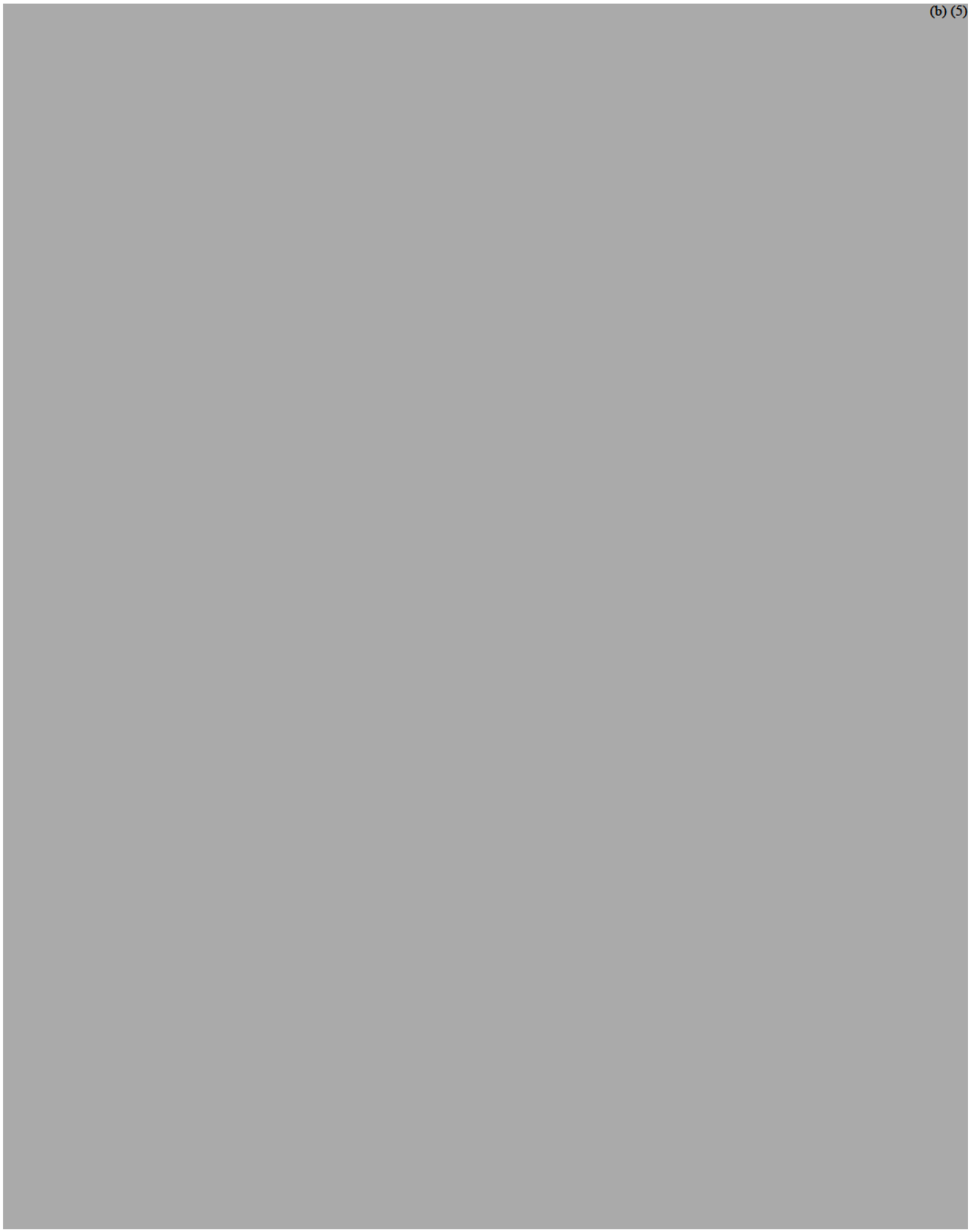
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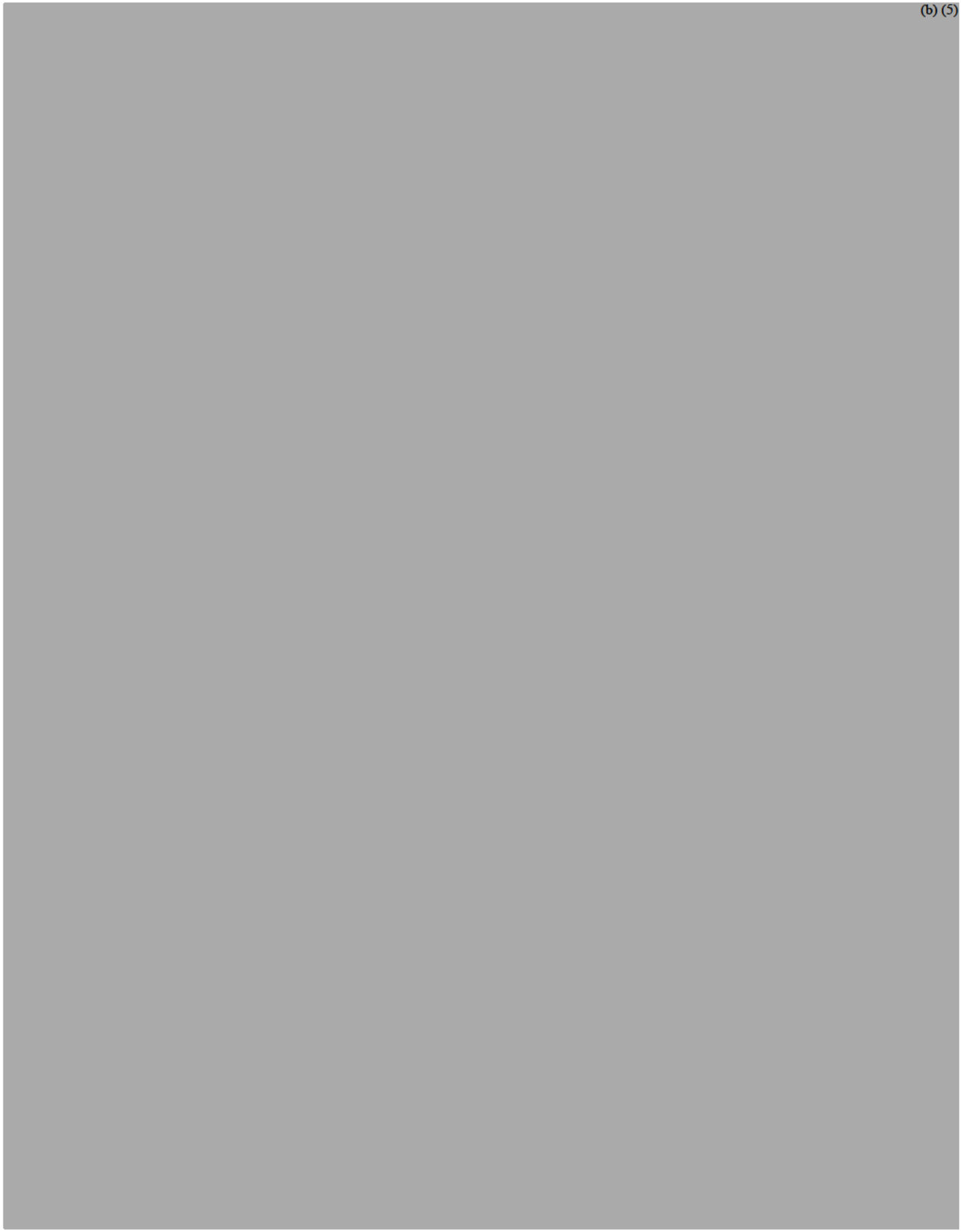
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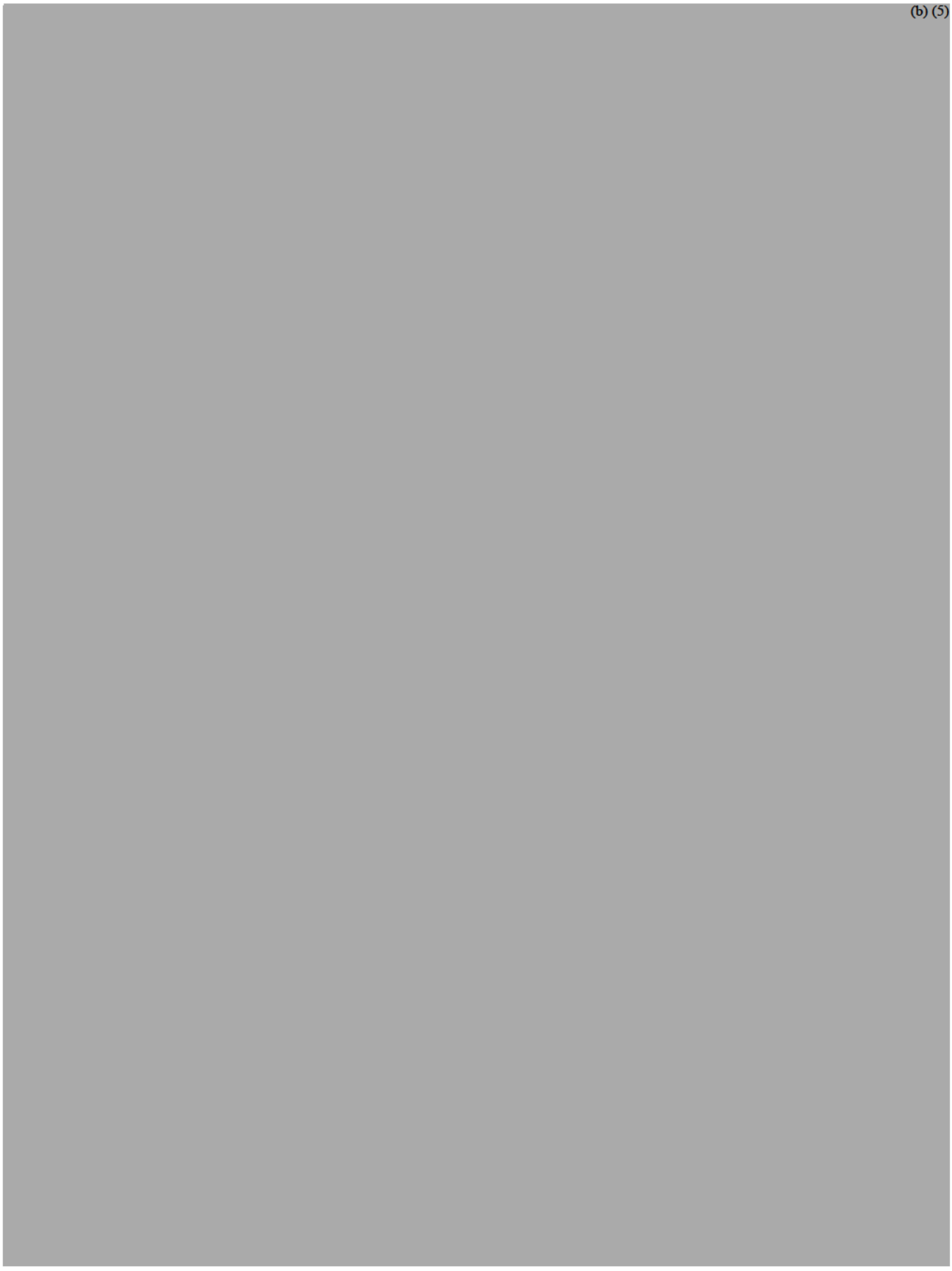
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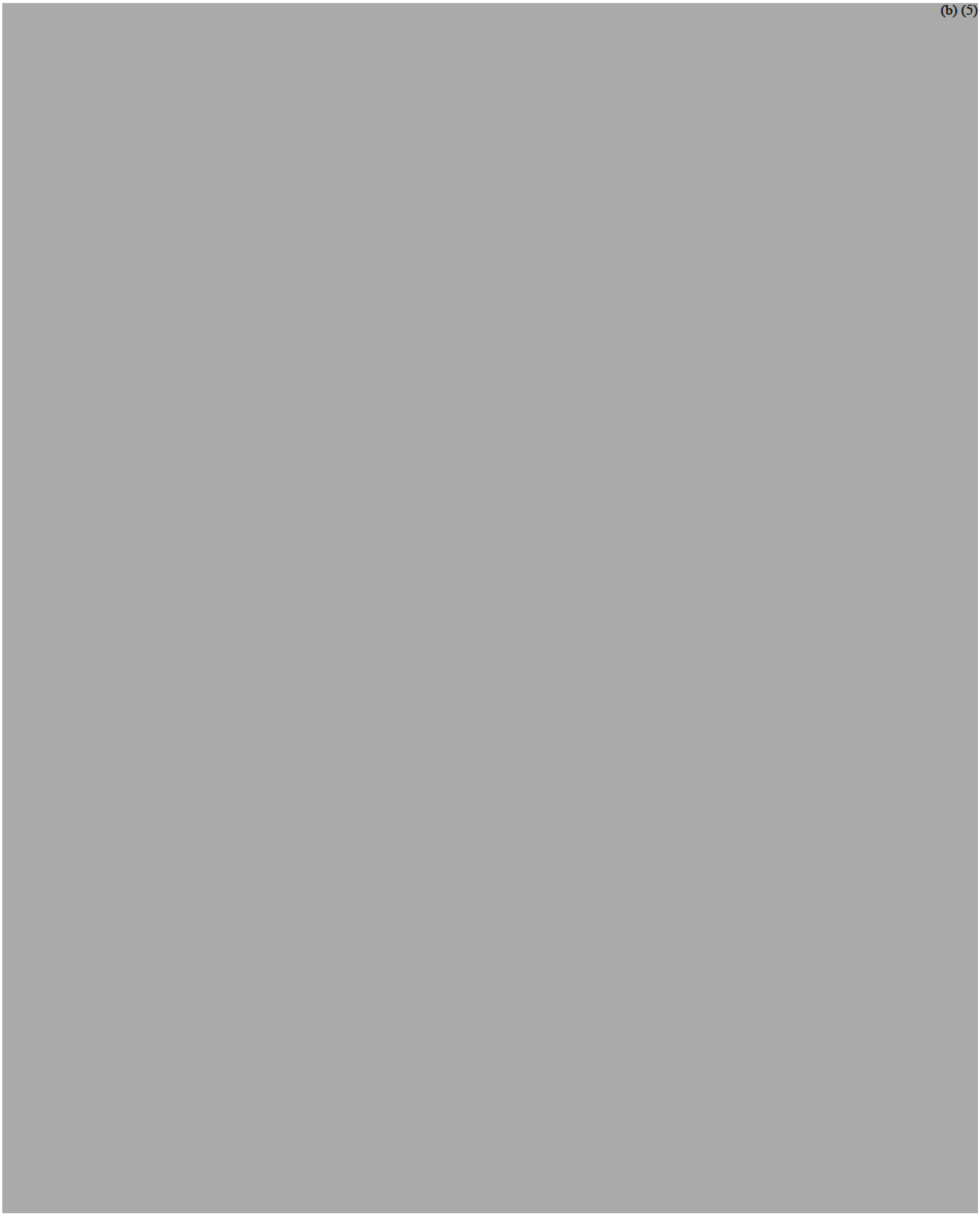
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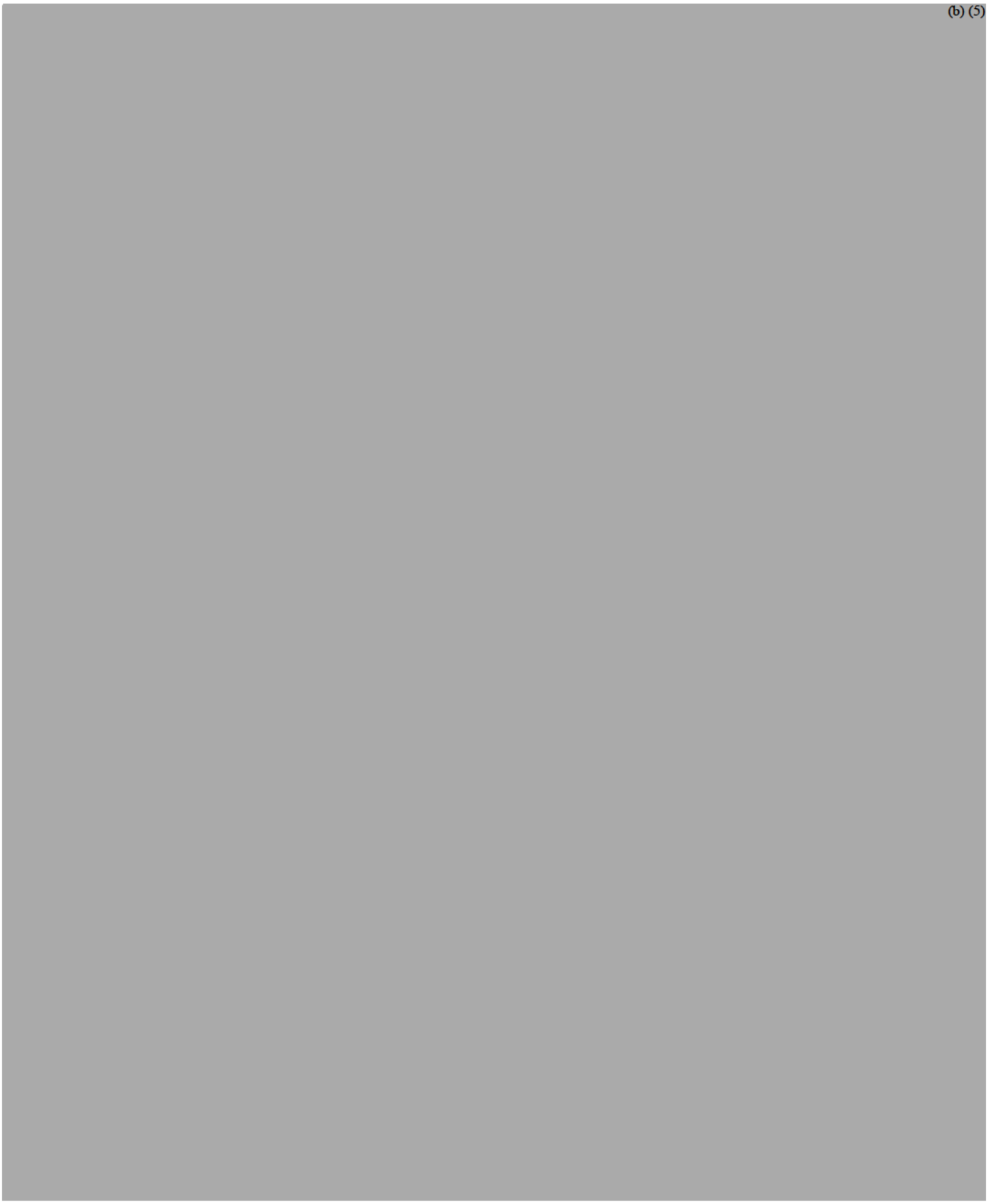
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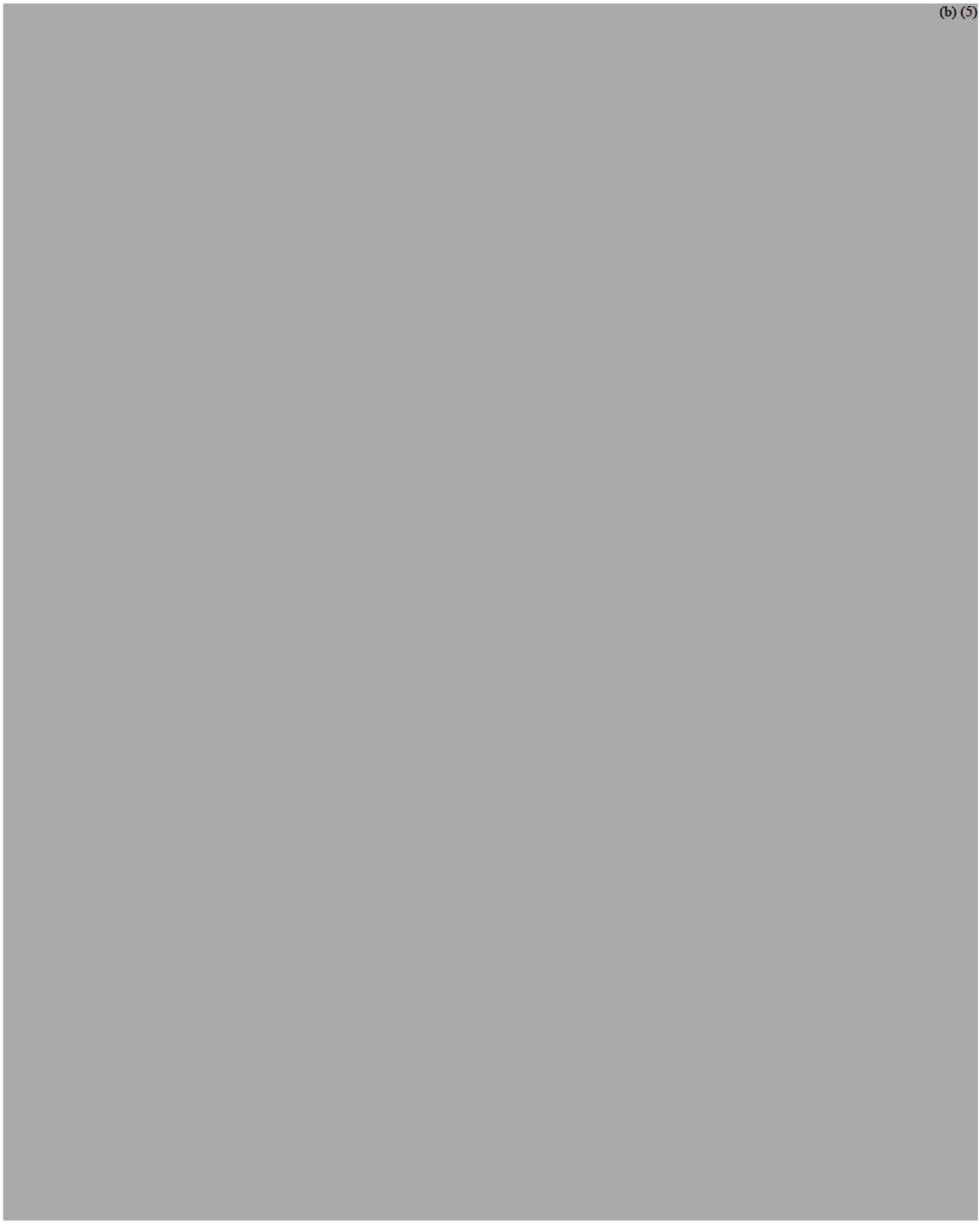
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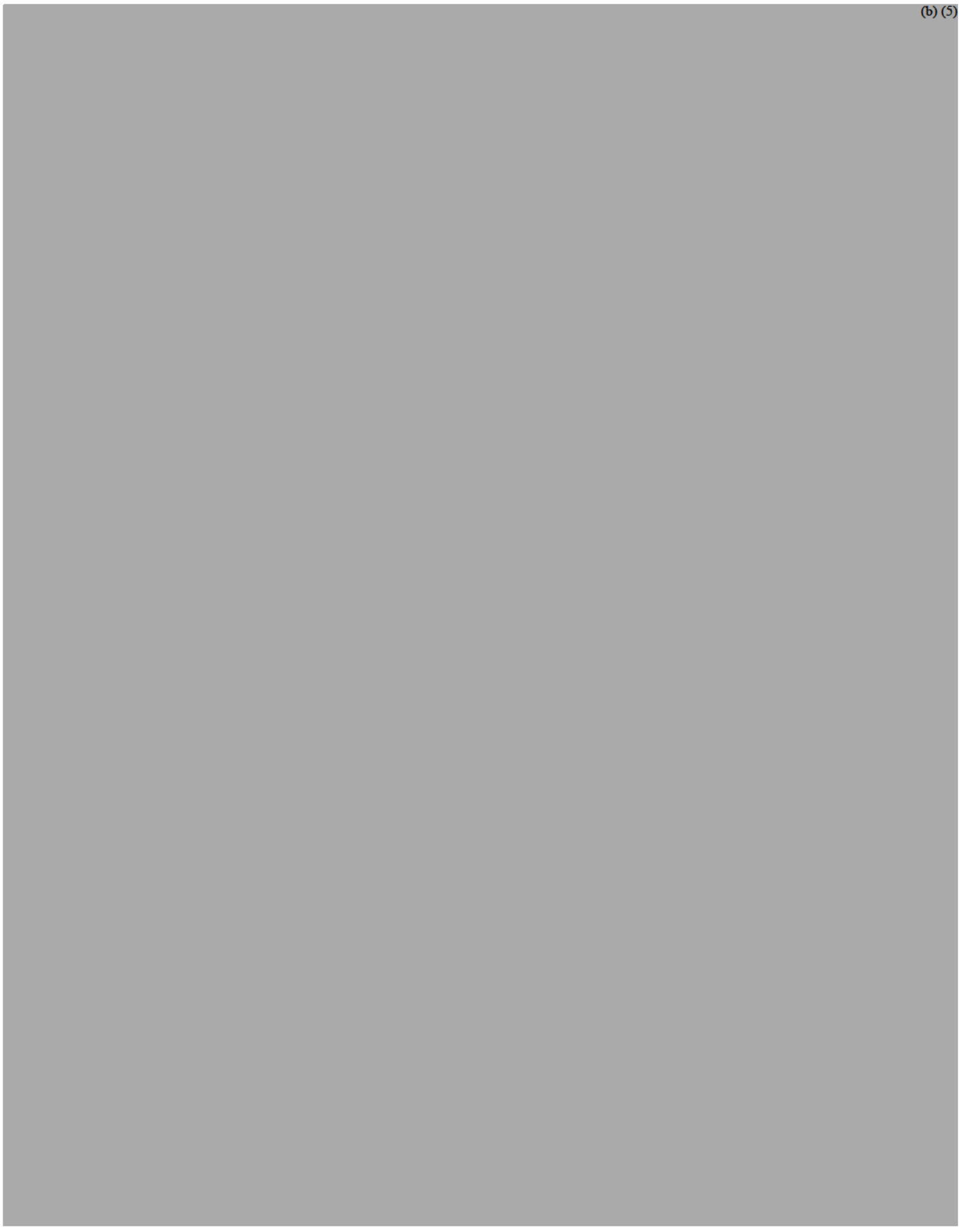
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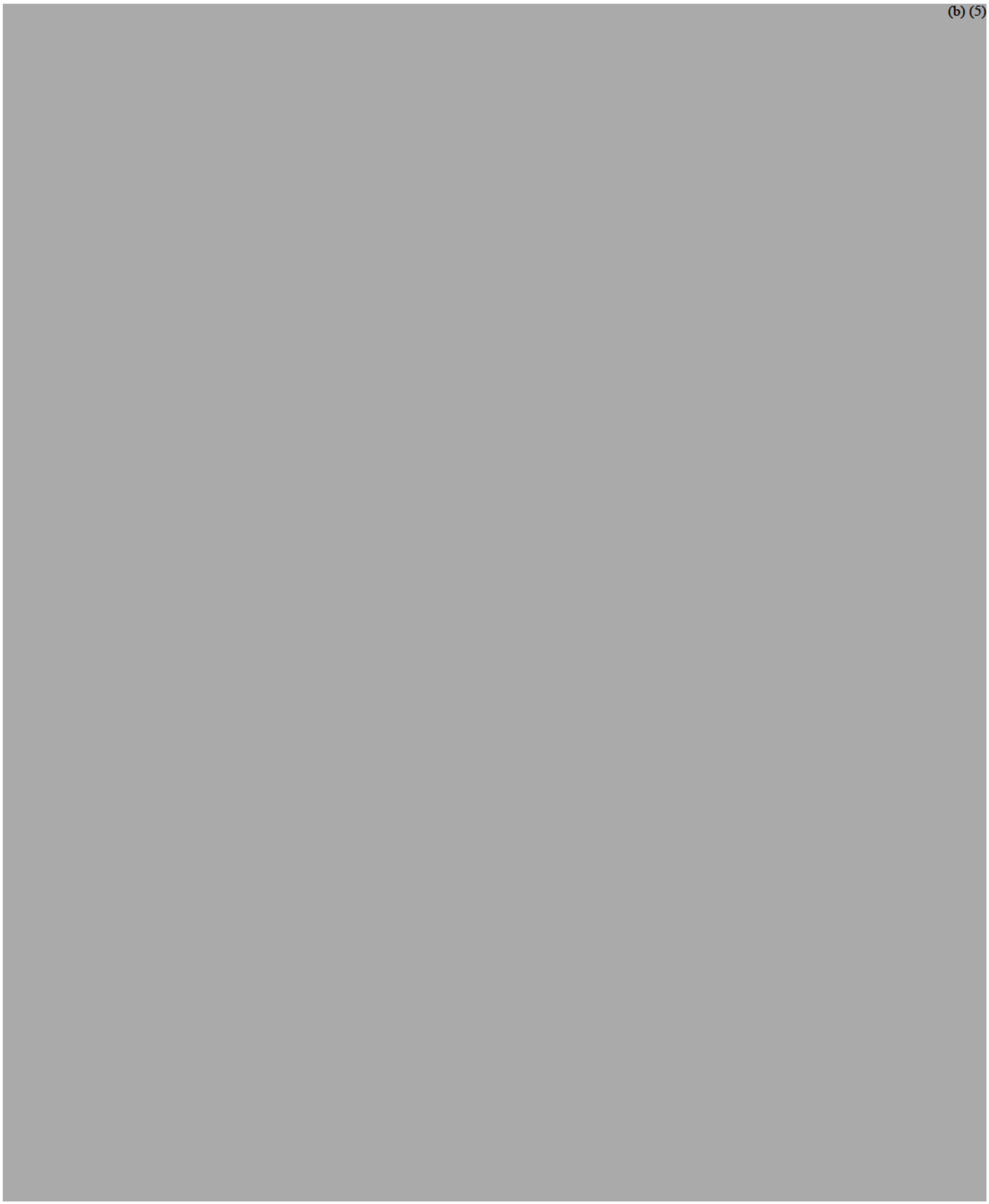
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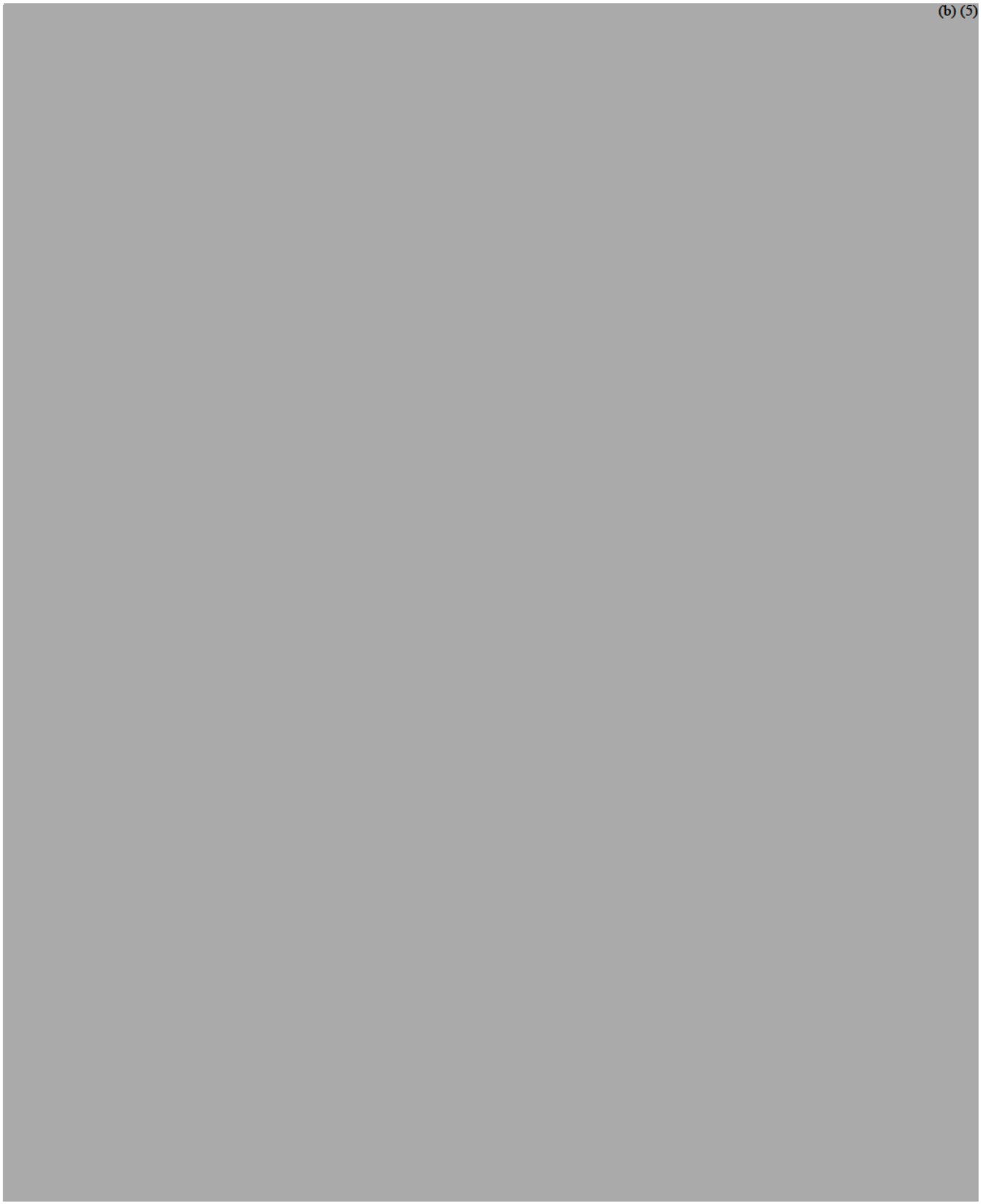
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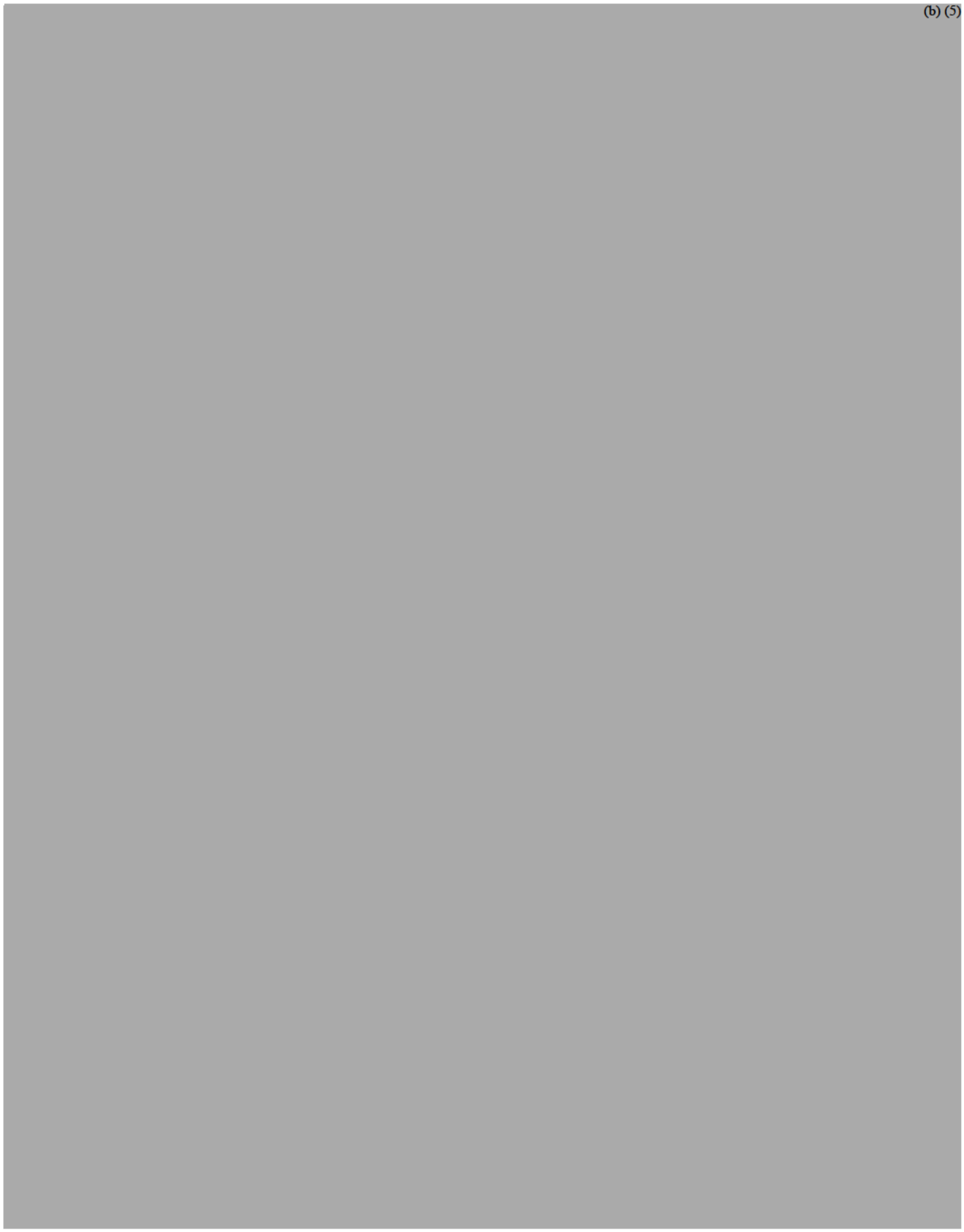
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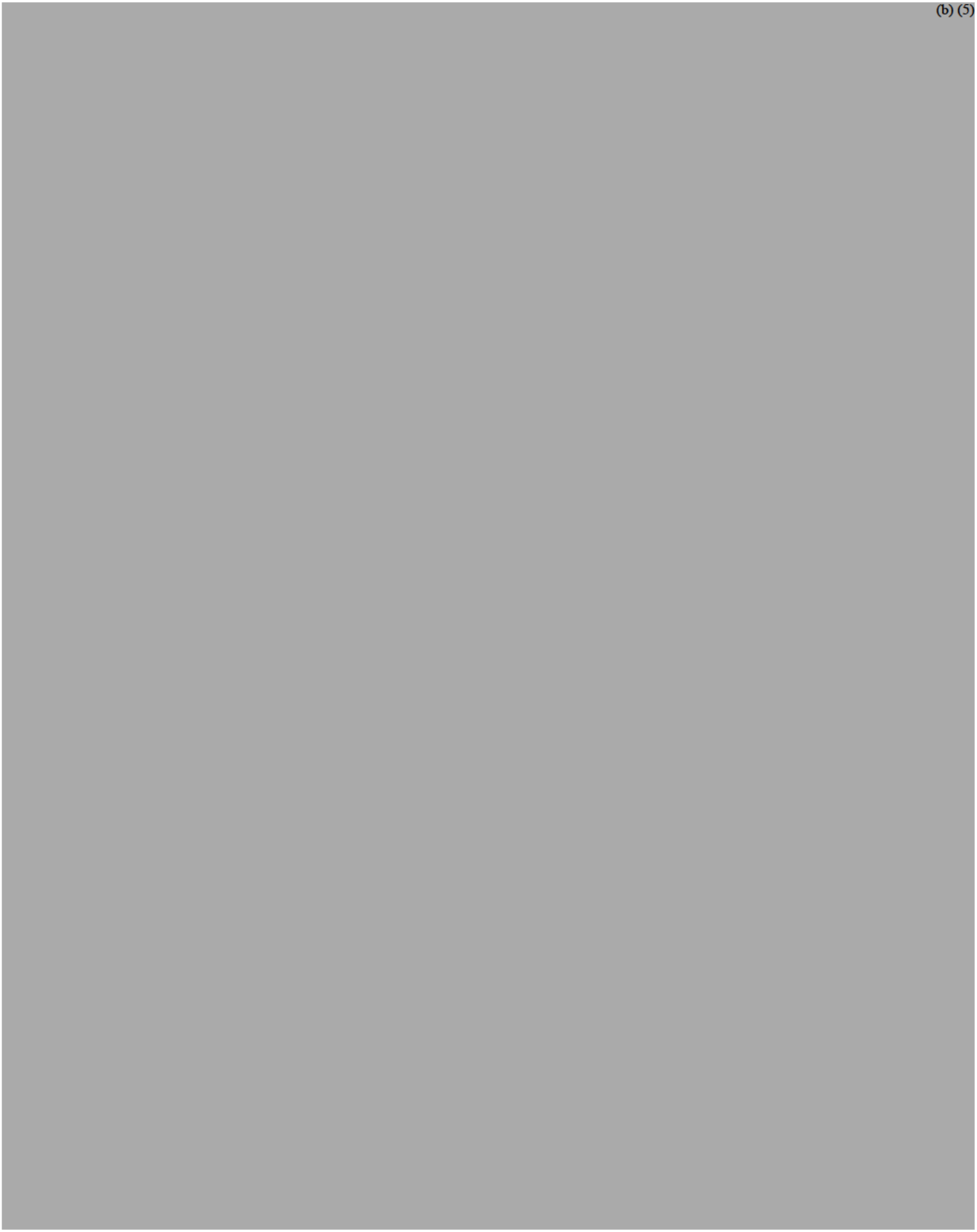
Appendix I:

Funding for Chronic Diseases and Organ Systems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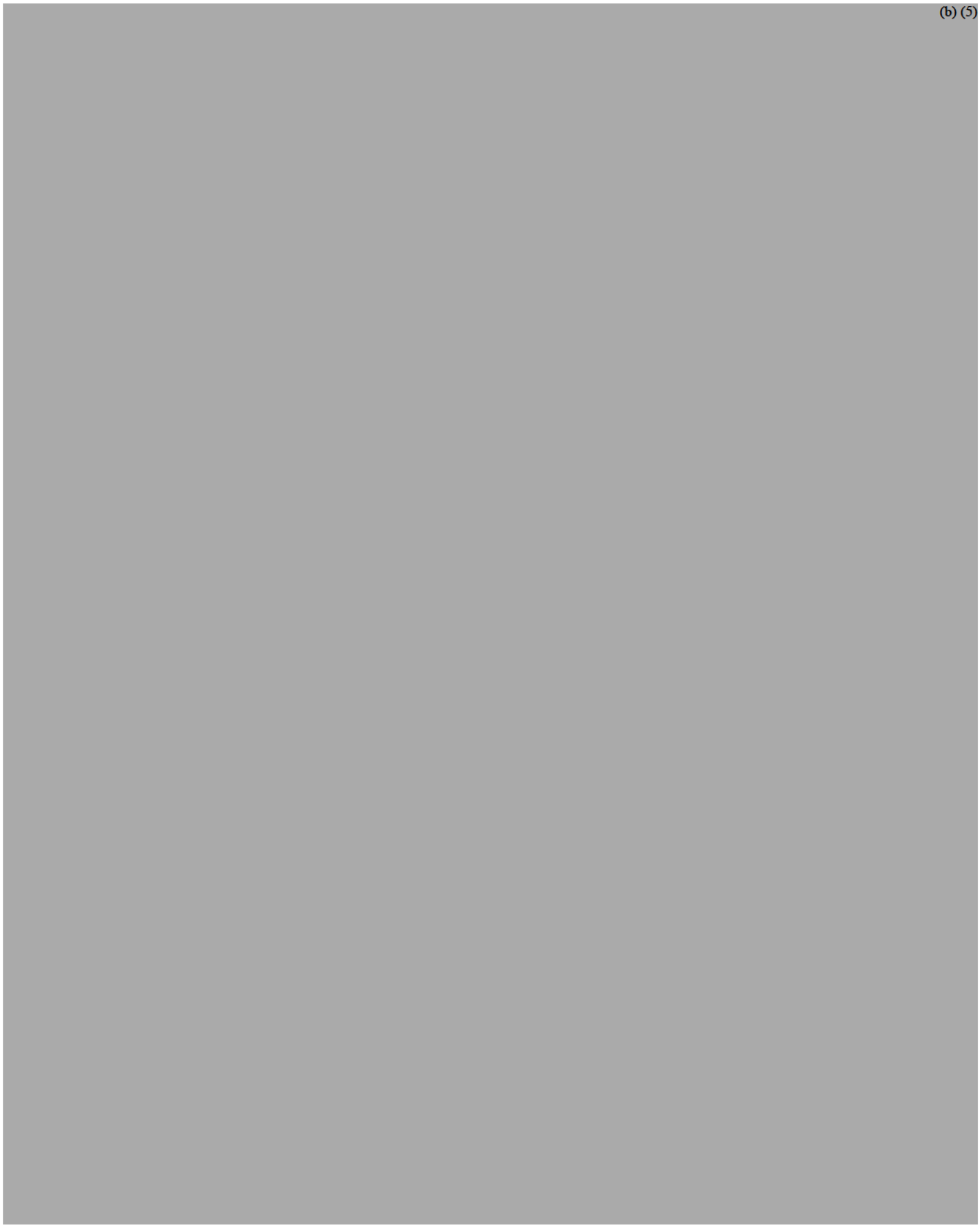
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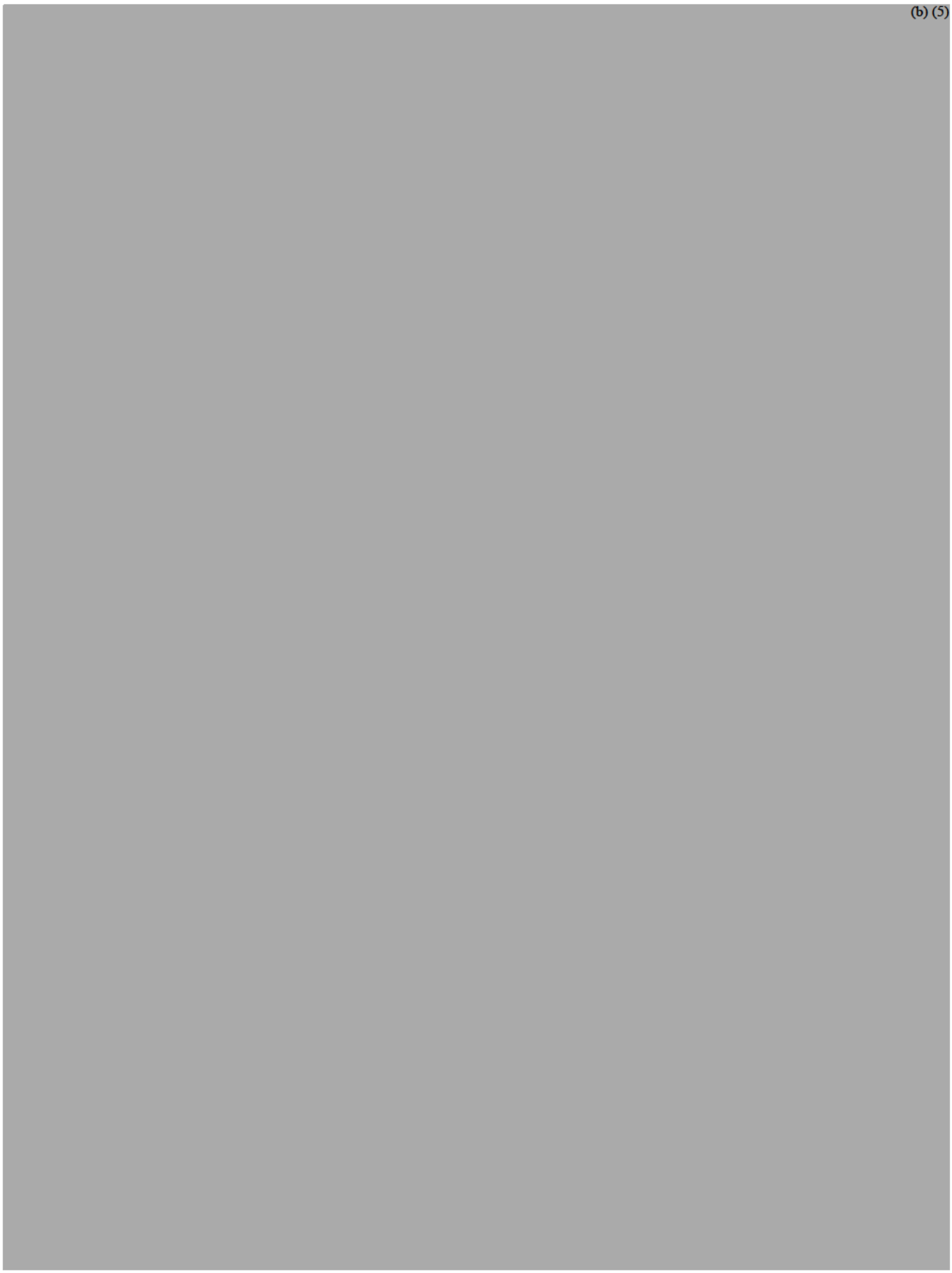
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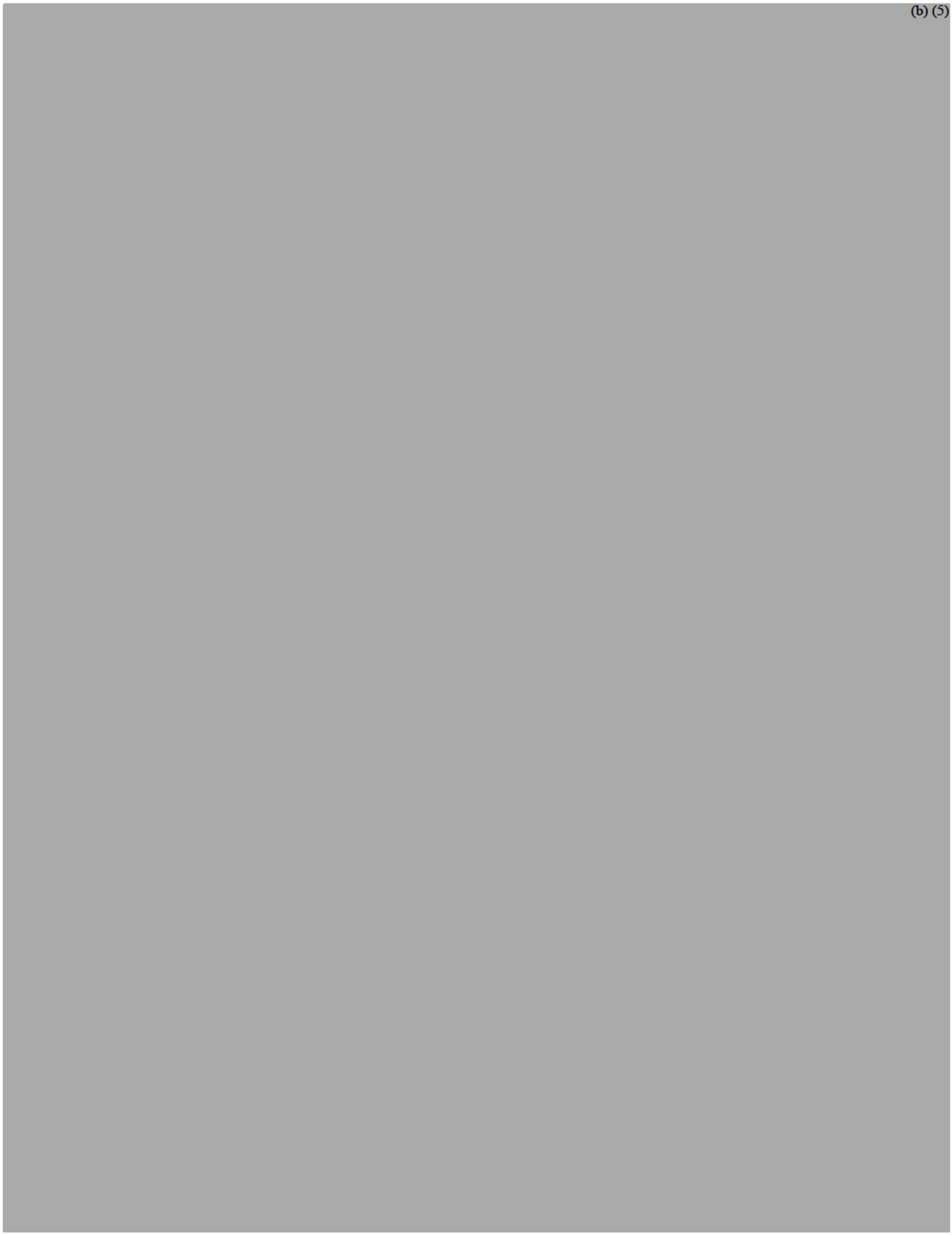
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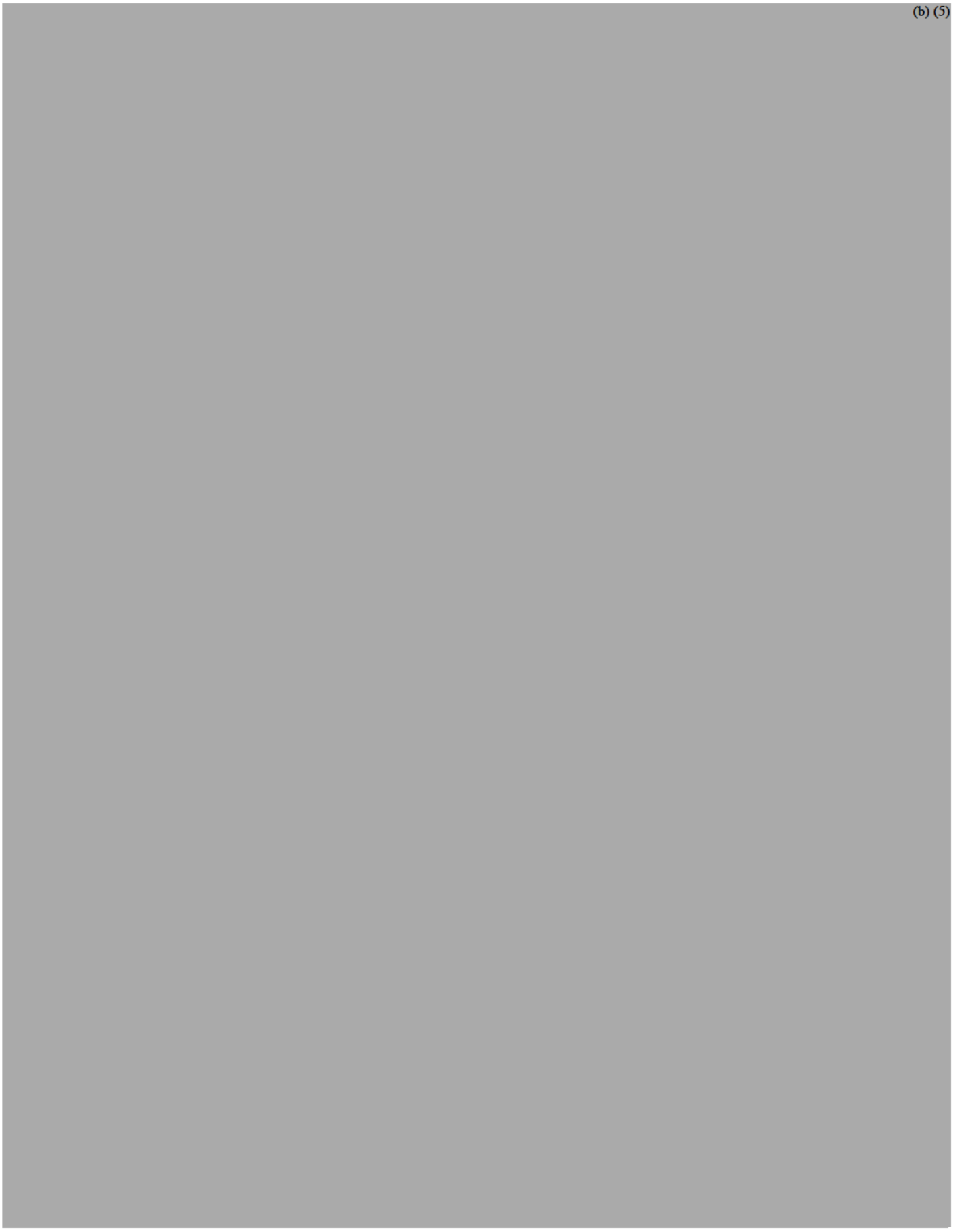
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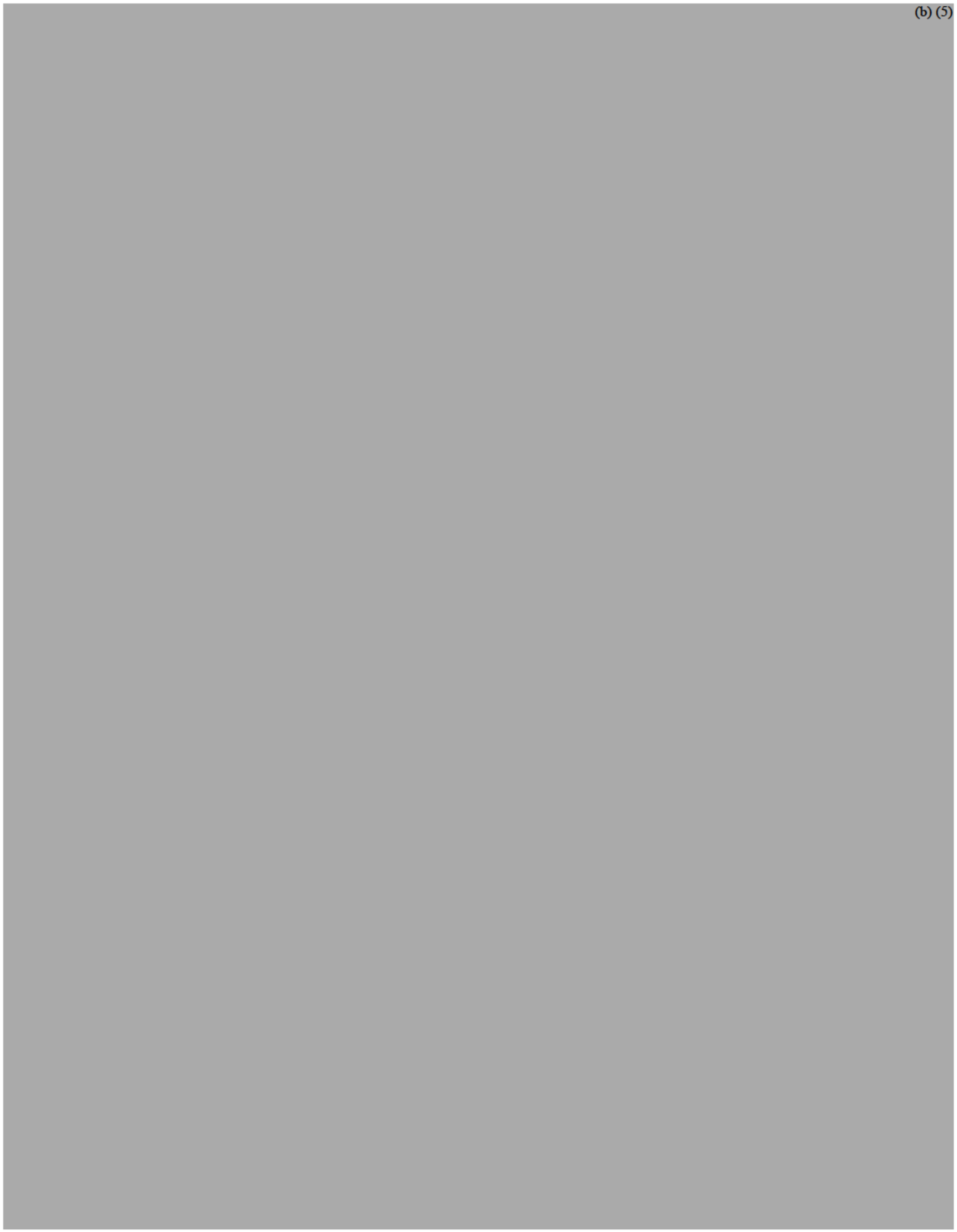
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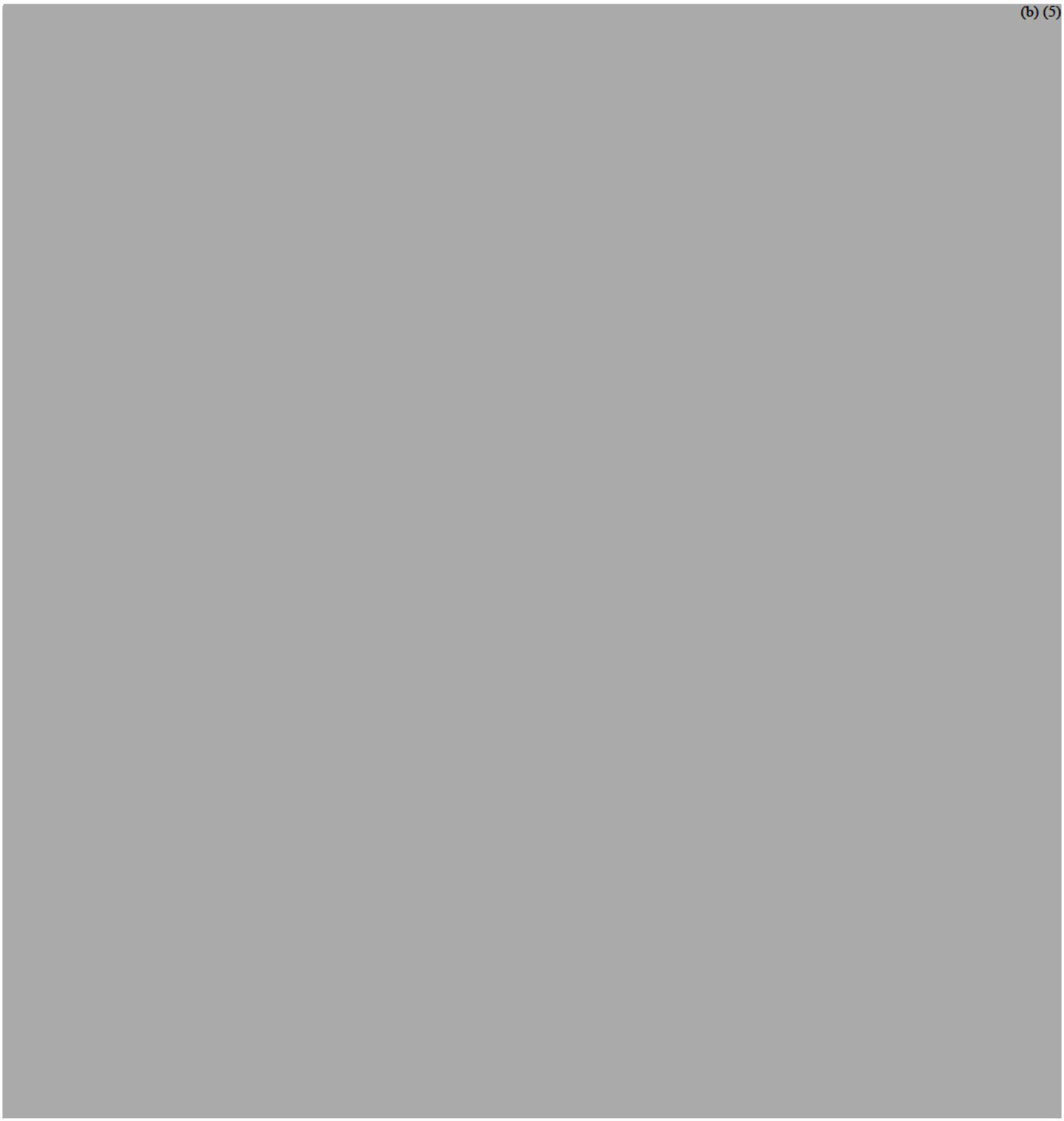
Appendix J:
EUREKA Prize Competitions

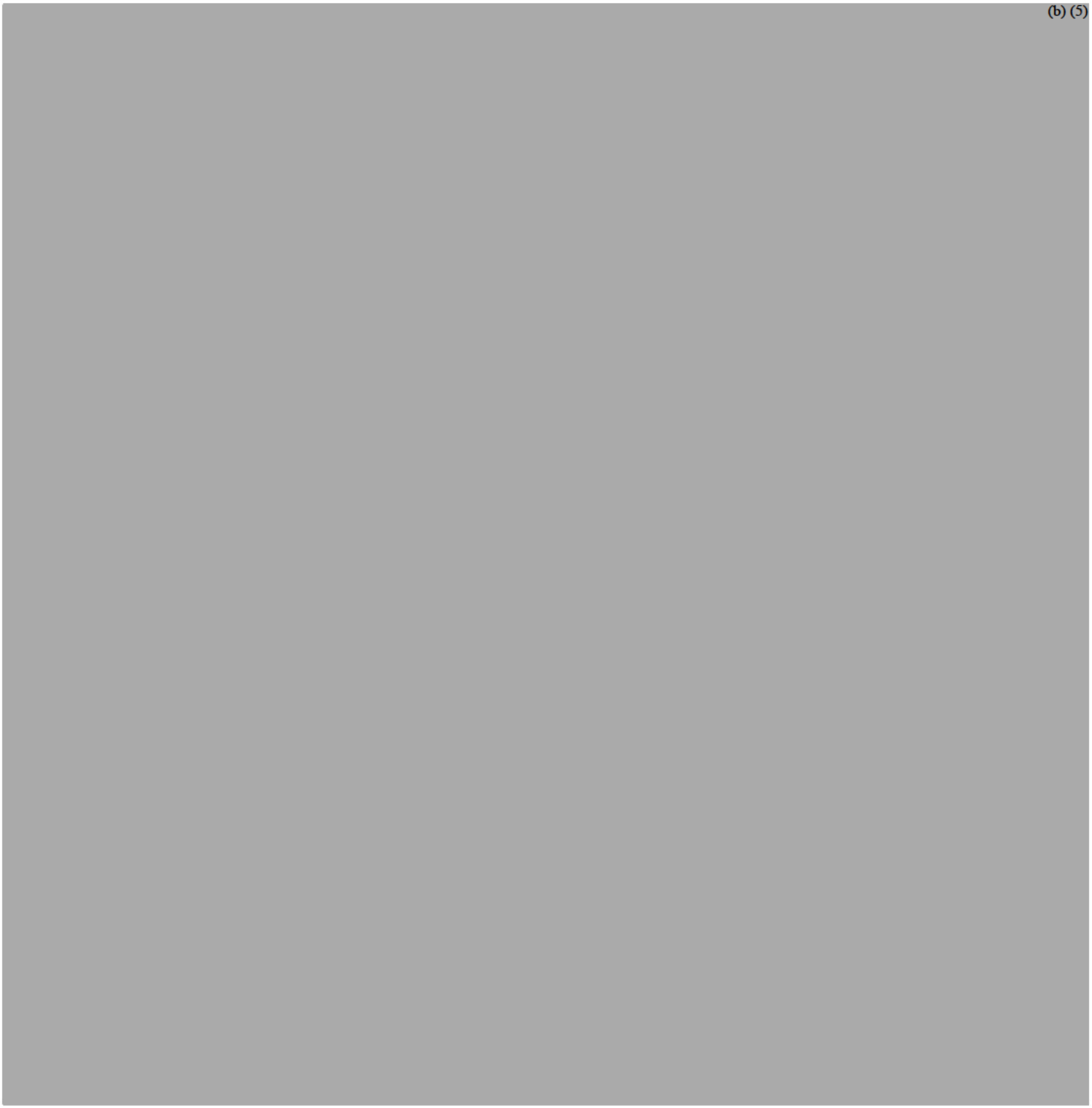
(b) (5)

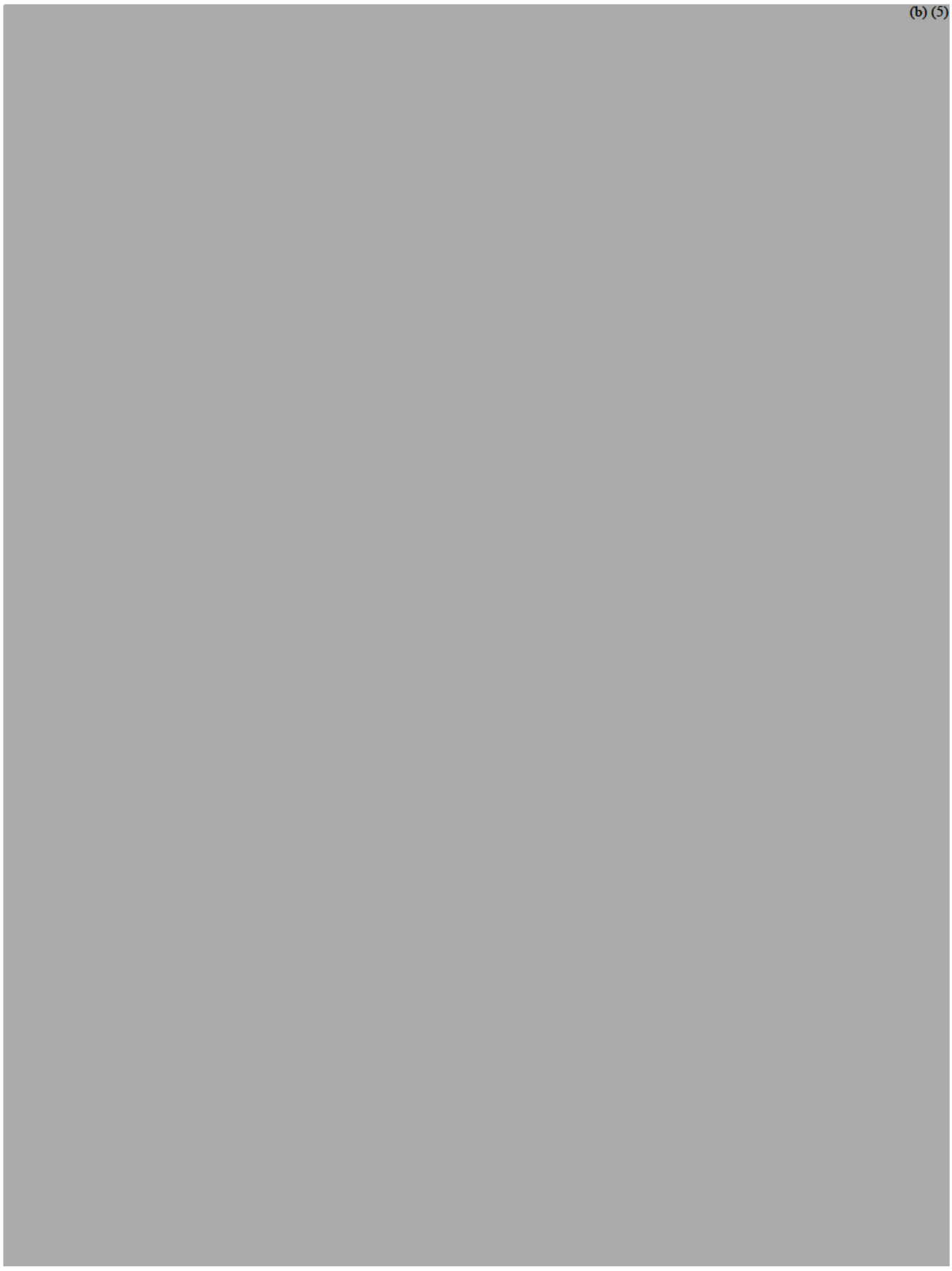



(b) (5)

Appendix K:
Acronyms

(b) (5)

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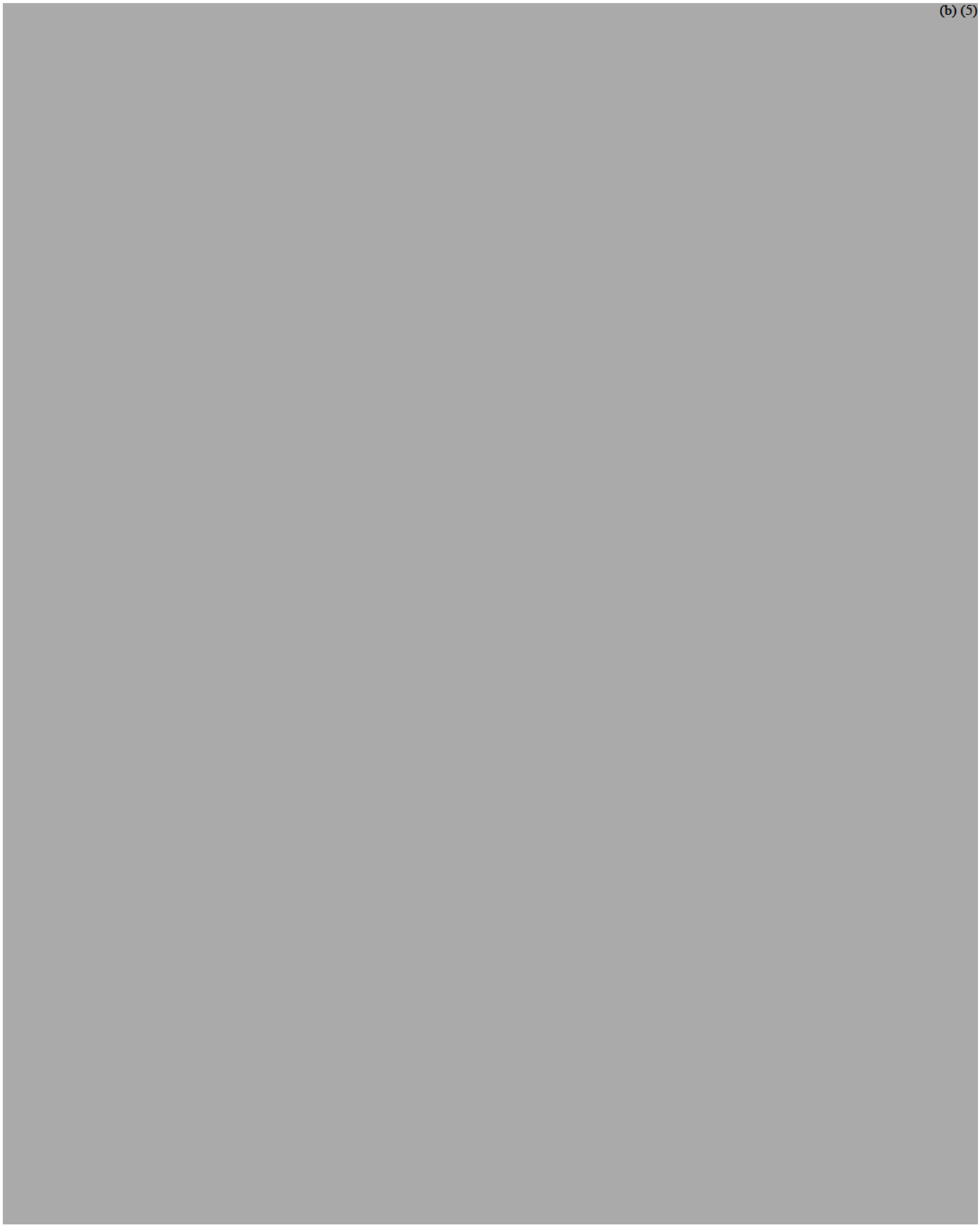
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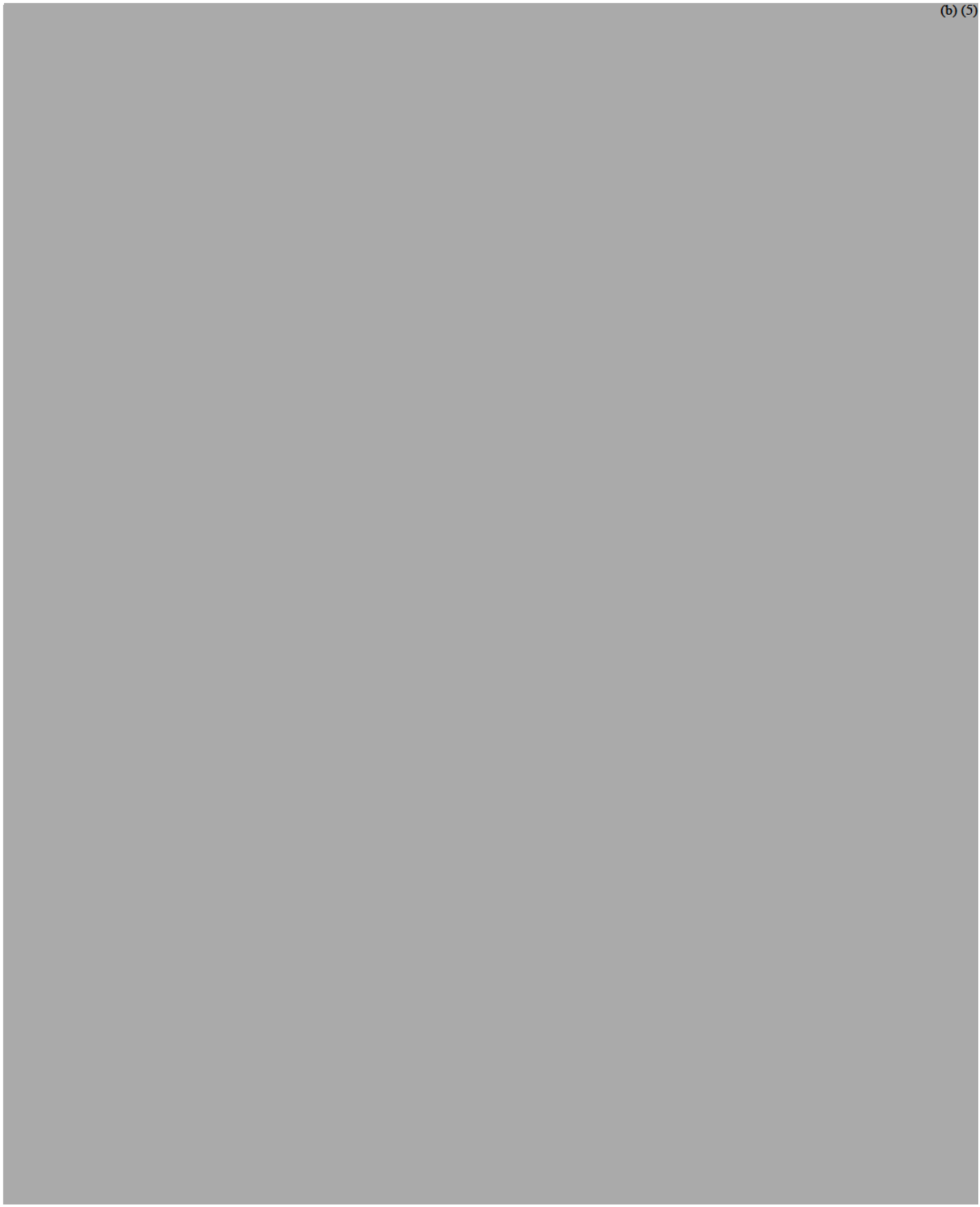
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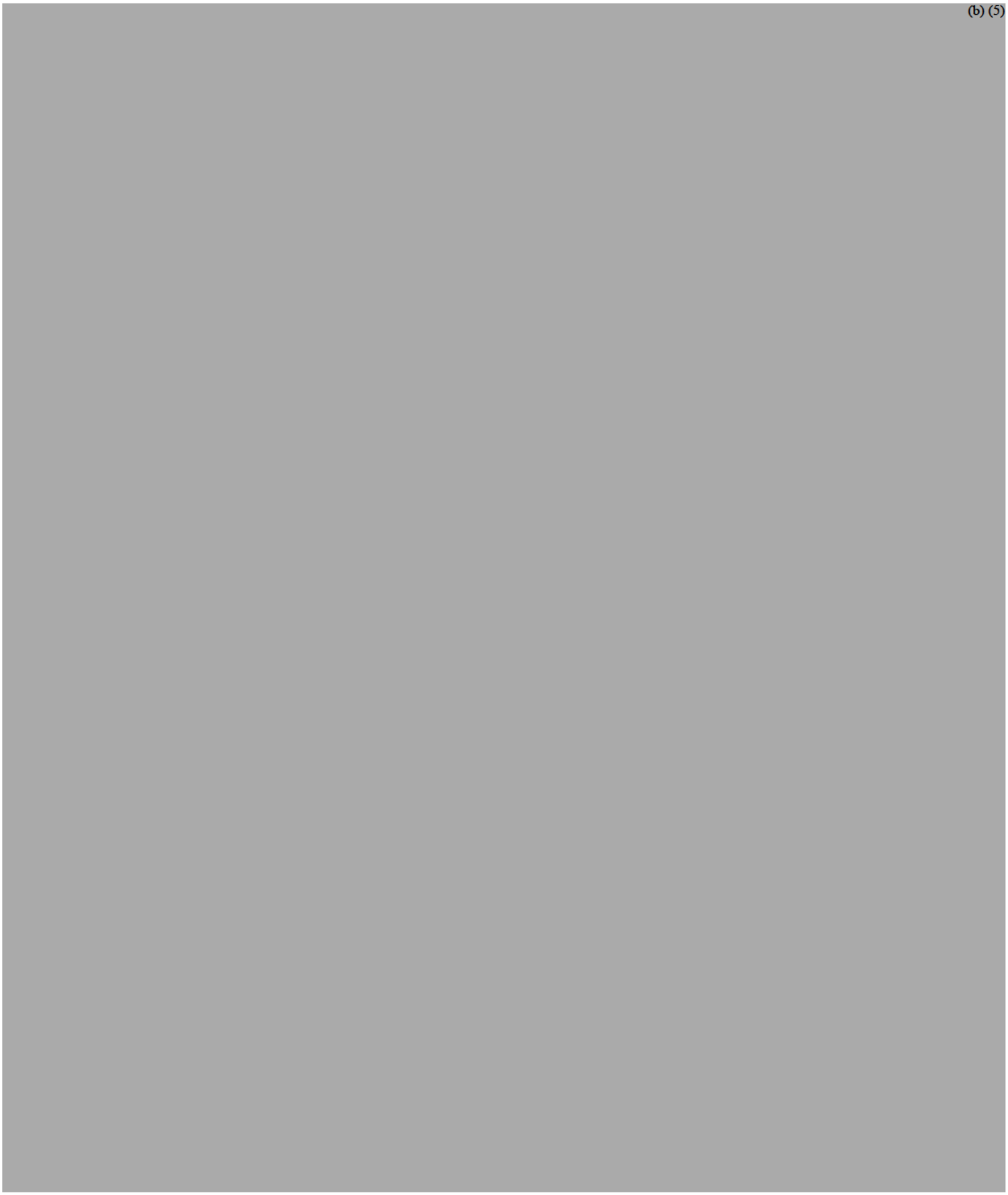
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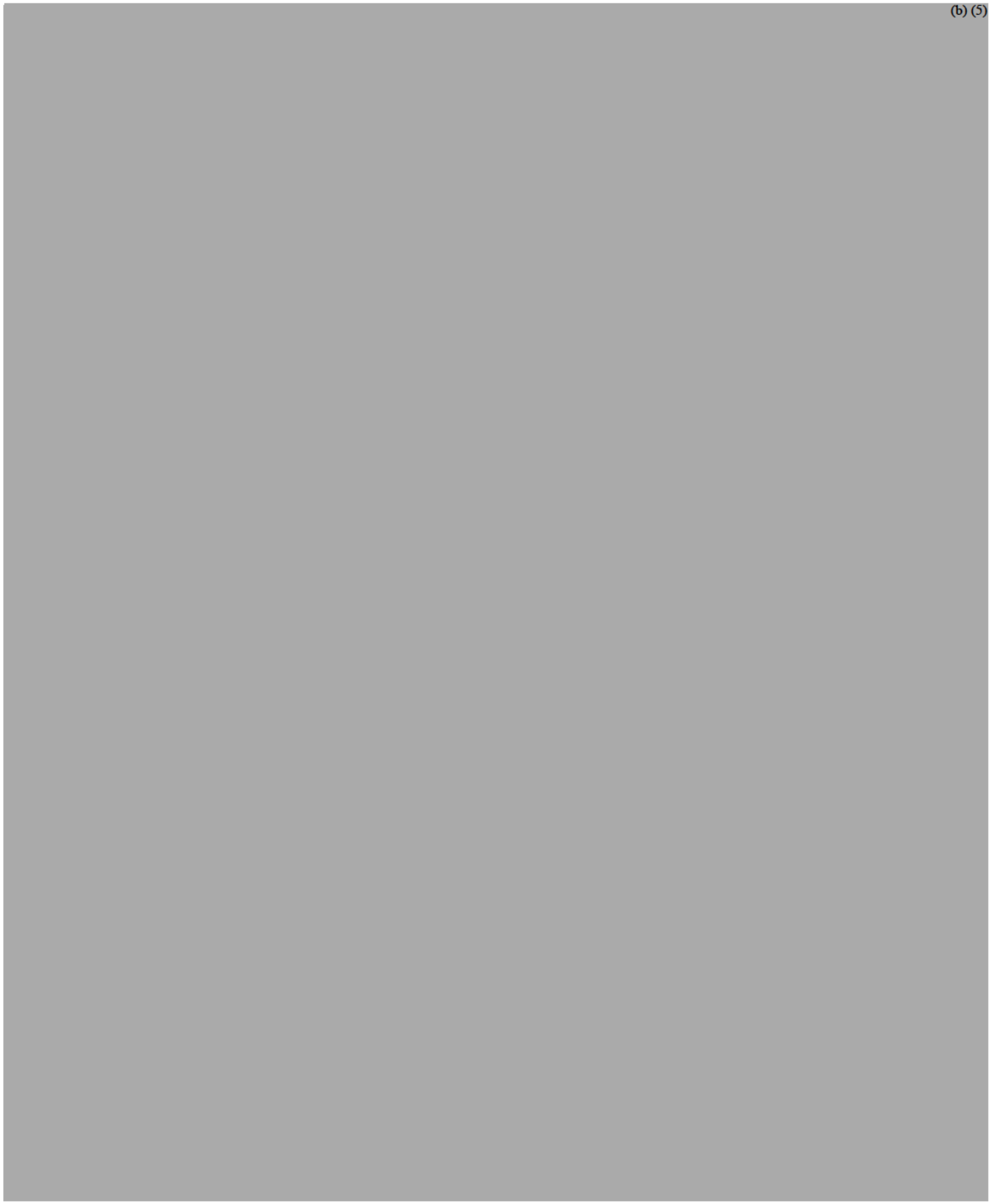
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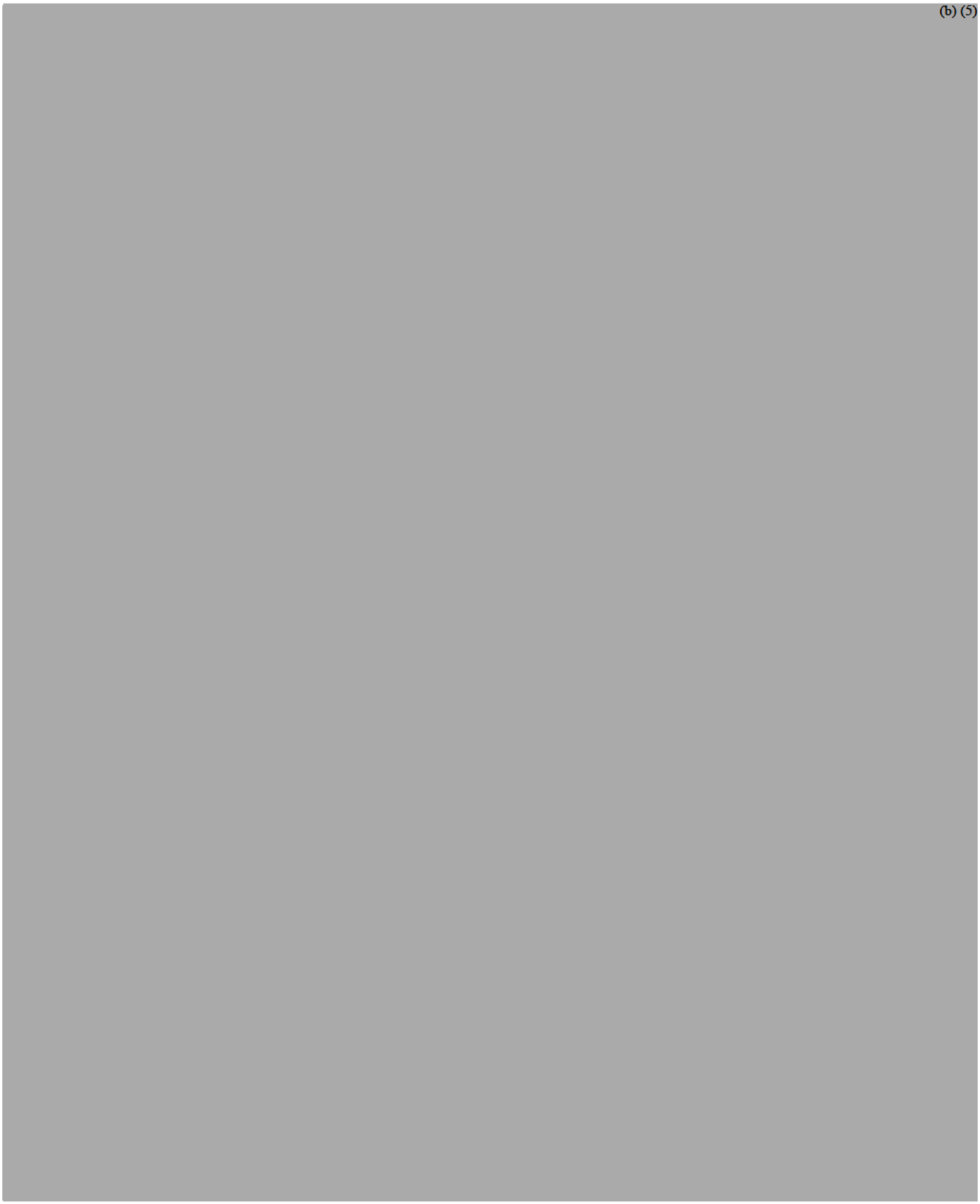
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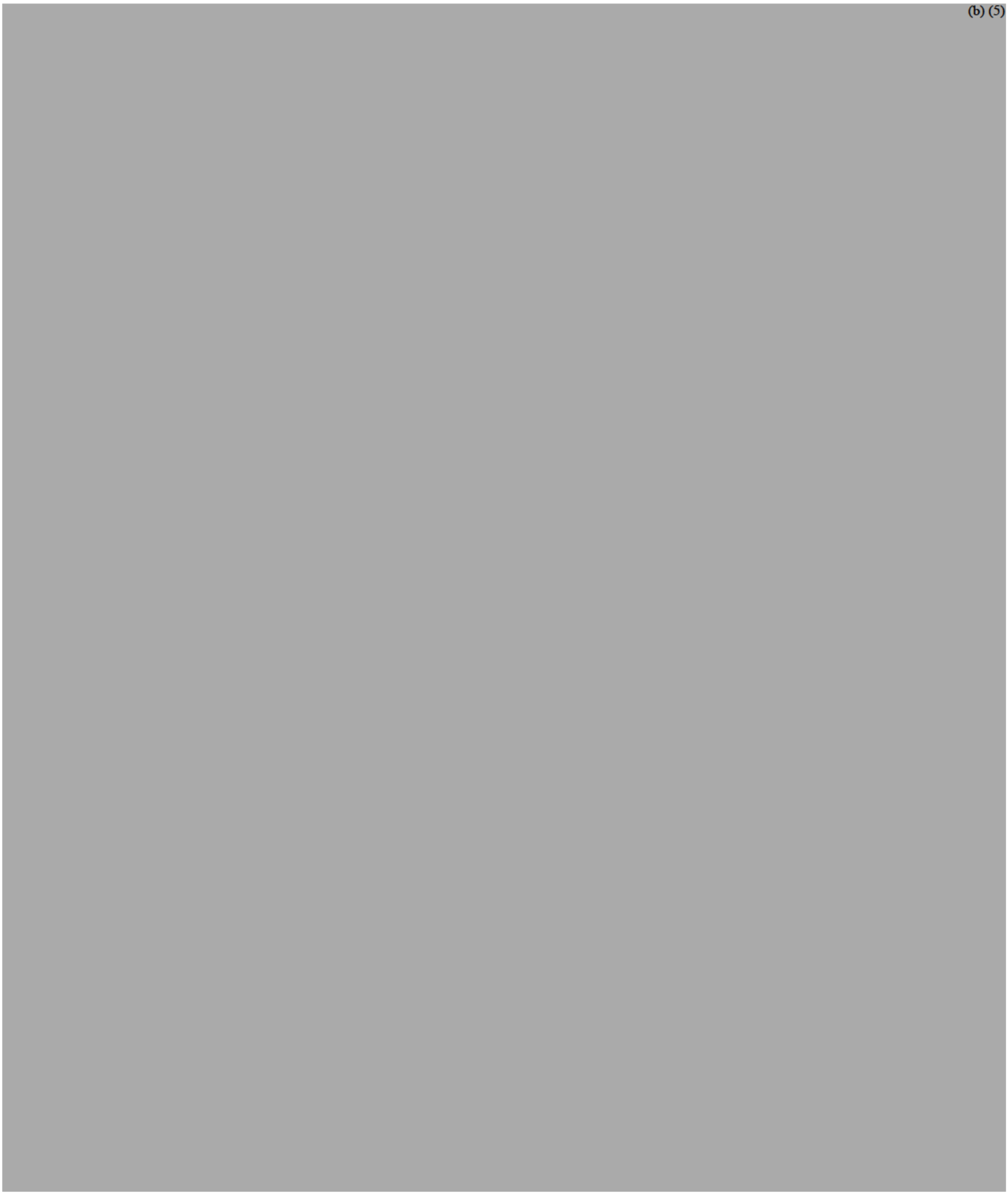
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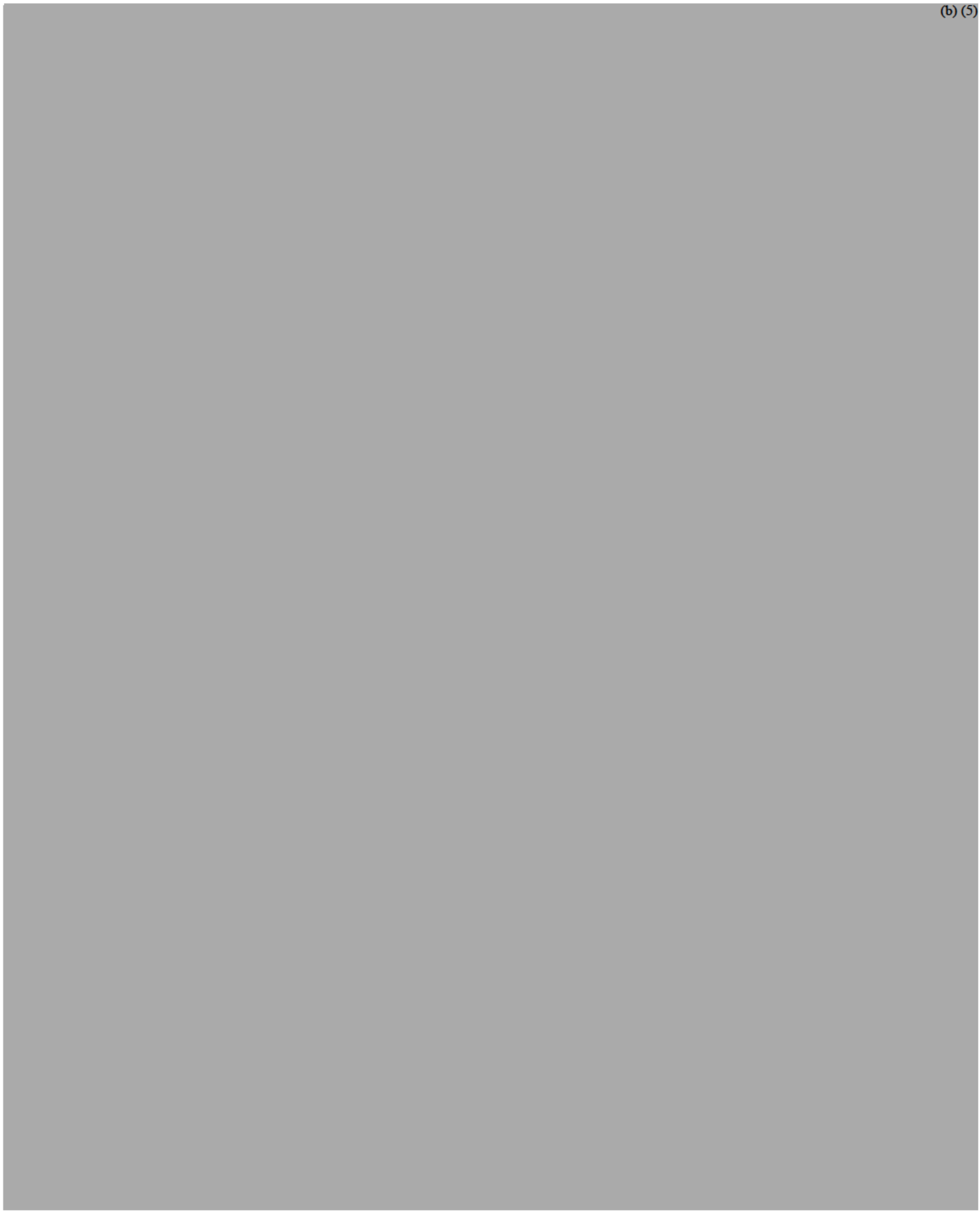
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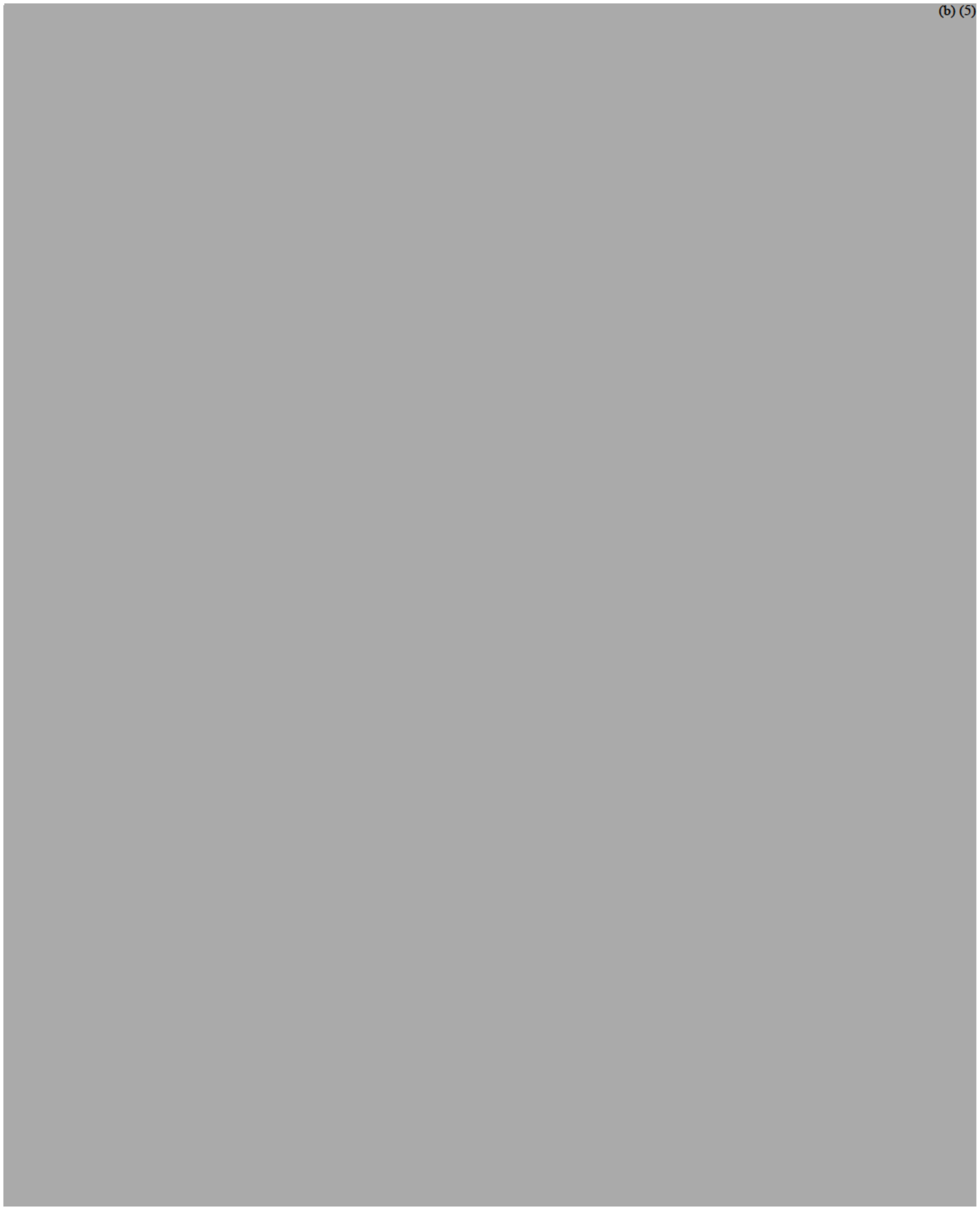
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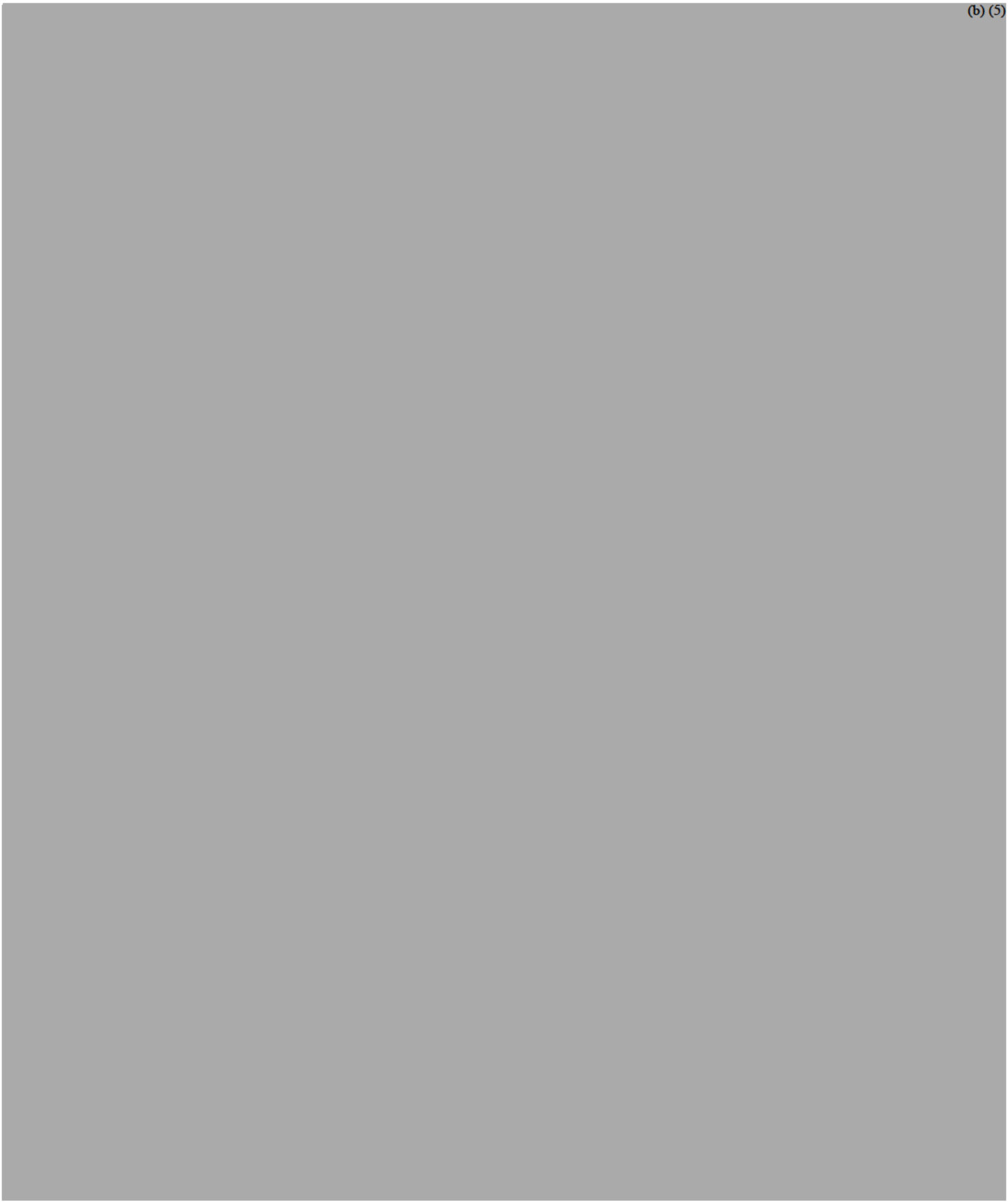
Acronym	Meaning
HIRN	Human Islet Research Network
HIV	human immunodeficiency virus
HIV-STIC	HIV Services and Treatment Implementation in Corrections
HLA	human leukocyte antigen
HMP	Human Microbiome Project
HNBP	Healthy Native Babies Project
HO	heterotopic ossification
HOPE	HIV Organ Policy Equity
HPFH	hereditary persistence of fetal hemoglobin
HPTN	HIV Prevention Trials Network
HPV	human papillomavirus
HRI	heme-regulated inhibitor
HRS	Health and Retirement Study
HRSA	Health Resources and Services Administration
HSCT	hematopoietic stem cell transplant
HSIL	High Grade Squamous Intraepithelial Lesion
HSR	health services research
HSRProj	Health Services Research Projects
HSRR	Health Services and Sciences Research Resources
HSV-1	Herpes Simplex Virus
HTS	high-throughput screening
HuBMAP	Human BioMolecular Atlas Program
HZO	herpes zoster ophthalmicus
I statements	Insufficient Evidence statements
IACC	Interagency Autism Coordinating Committee
IADRP	International Alzheimer's and Related Dementias Research Portfolio
IBD	inflammatory bowel disease
IBS	irritable bowel syndrome
IBSOS	IBS Outcome Study
IC/BPS	interstitial cystitis/bladder pain syndrome
ICAC	Inner-City Asthma Consortium
ICBP	Integrative Cancer Biology Program
ICC	intrahepatic cholangiocarcinoma
ICD	International Classification of Disease Coding
ICEMR	International Centers of Excellence for Malaria Research
ICO	Institute/Center/Office
ICPC	International Cancer Proteogenome Consortium
ICs	Institutes and Centers
ICT	information and communication technology
ID	intellectual disabilities

(b) (5)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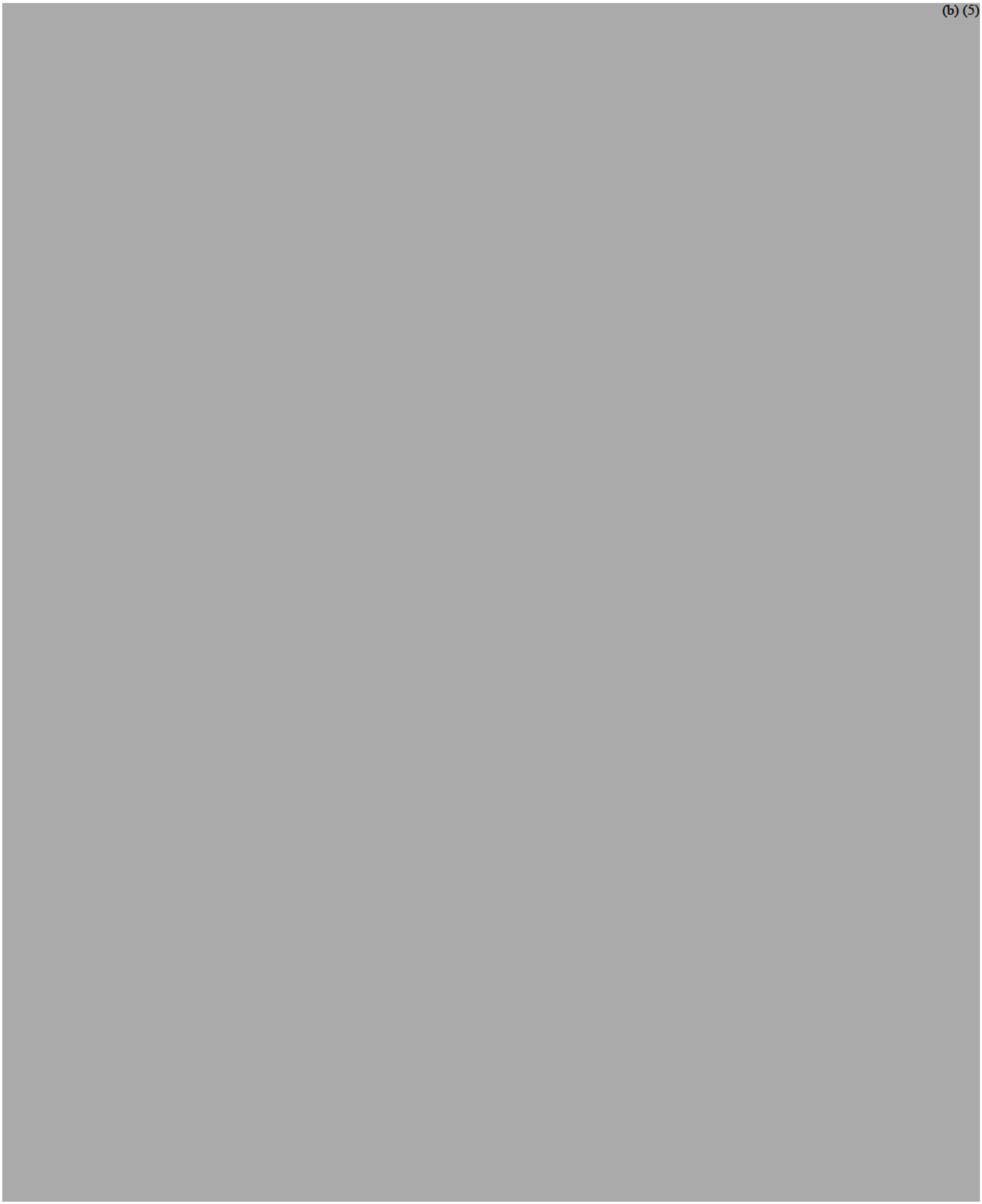
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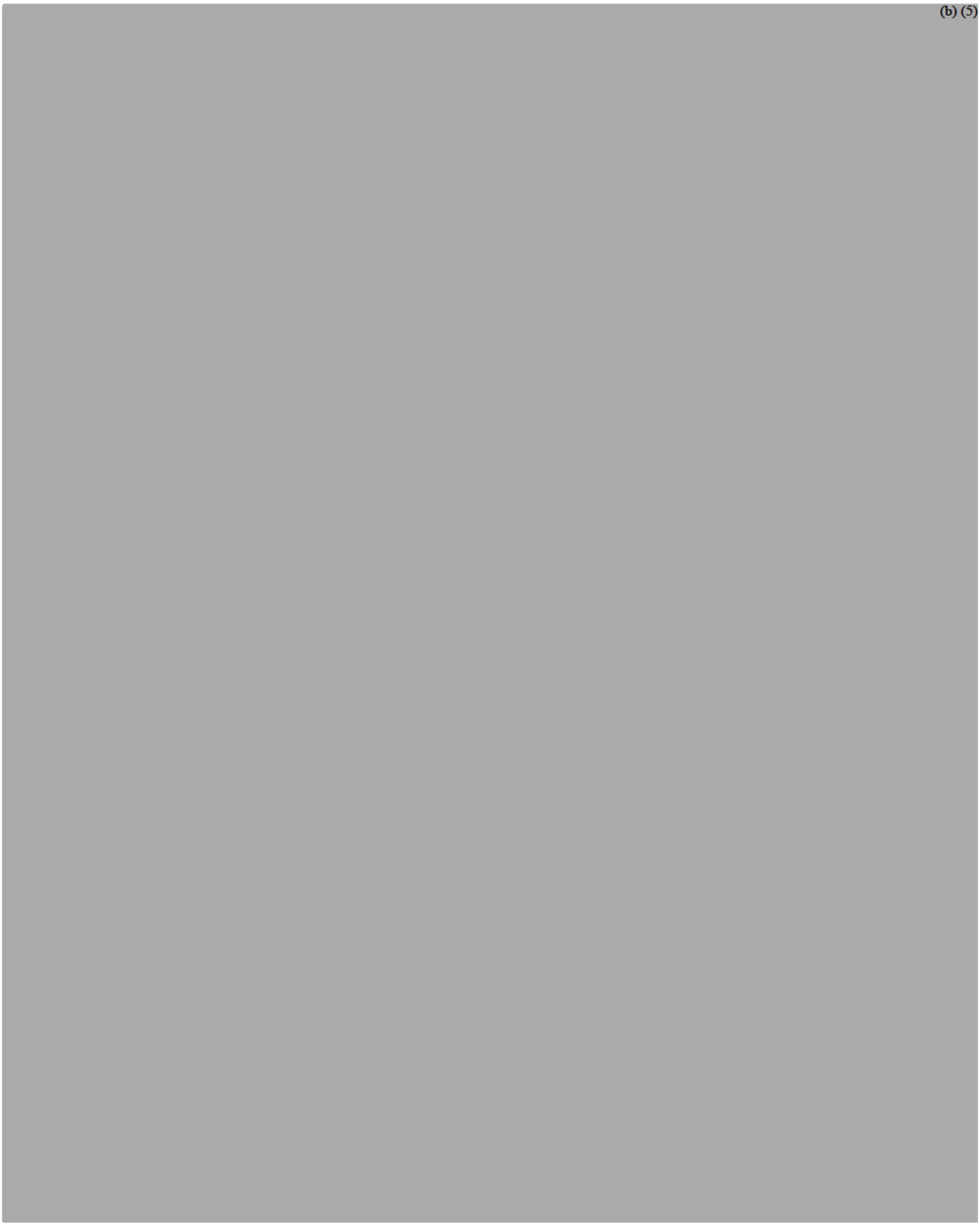
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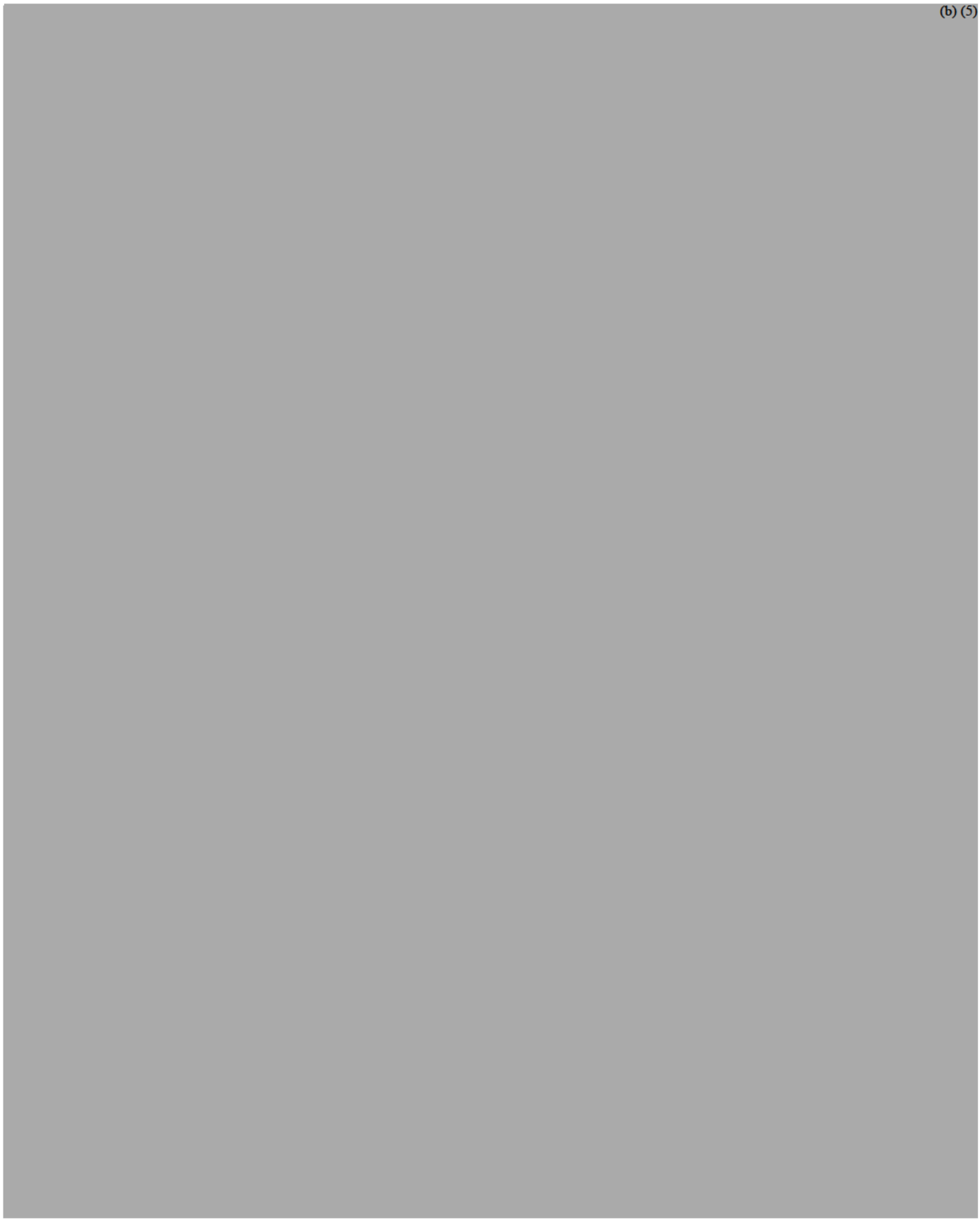
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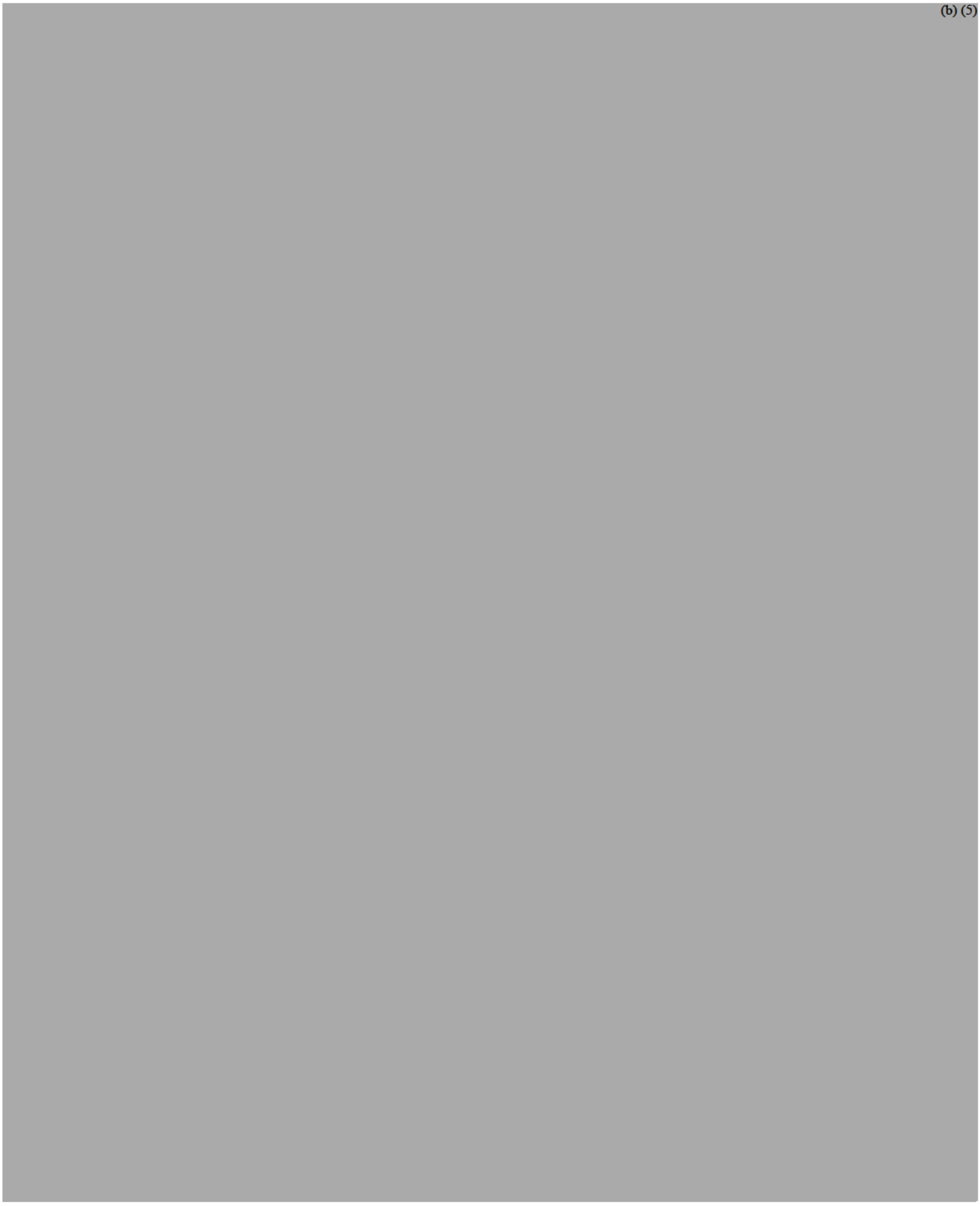
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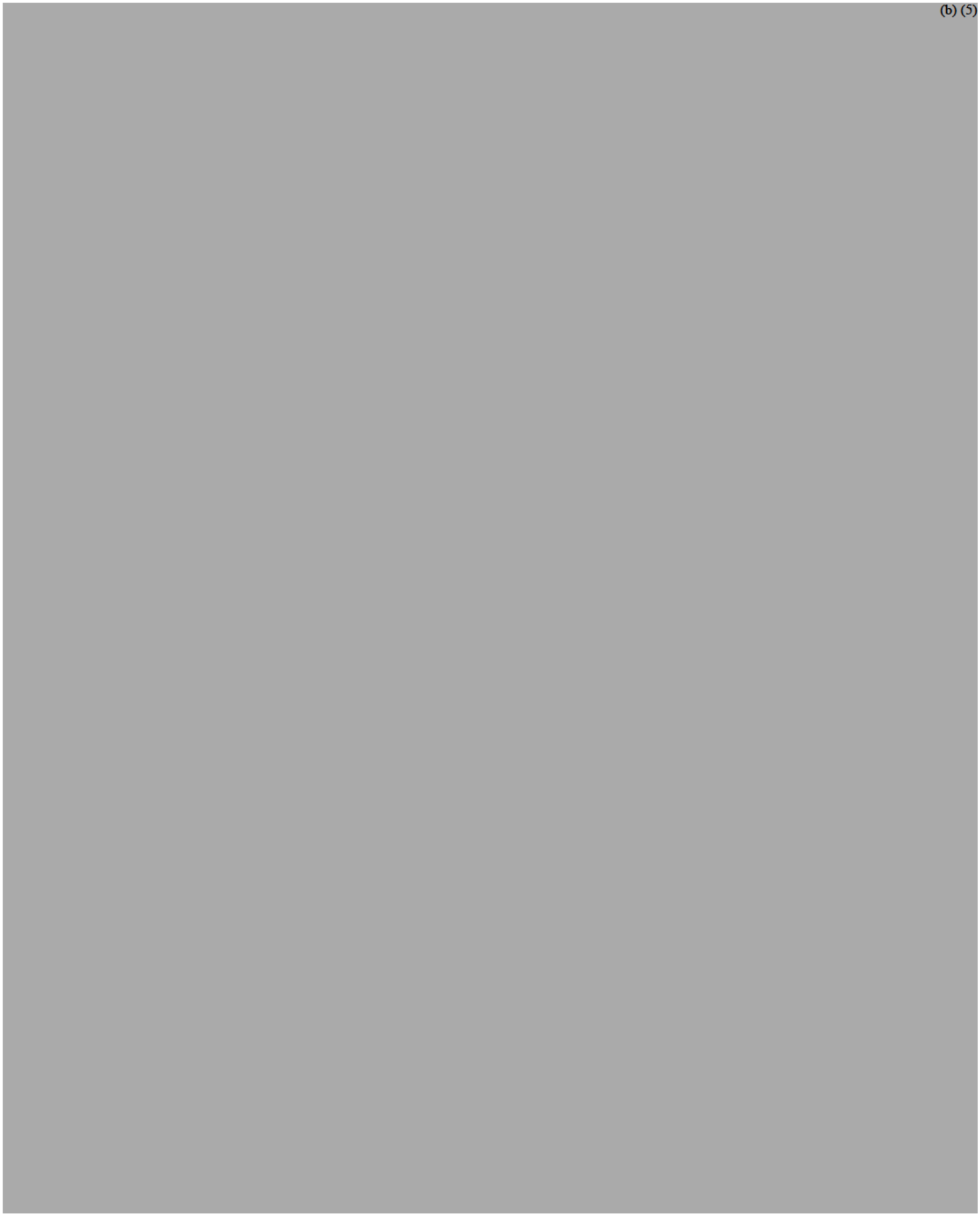
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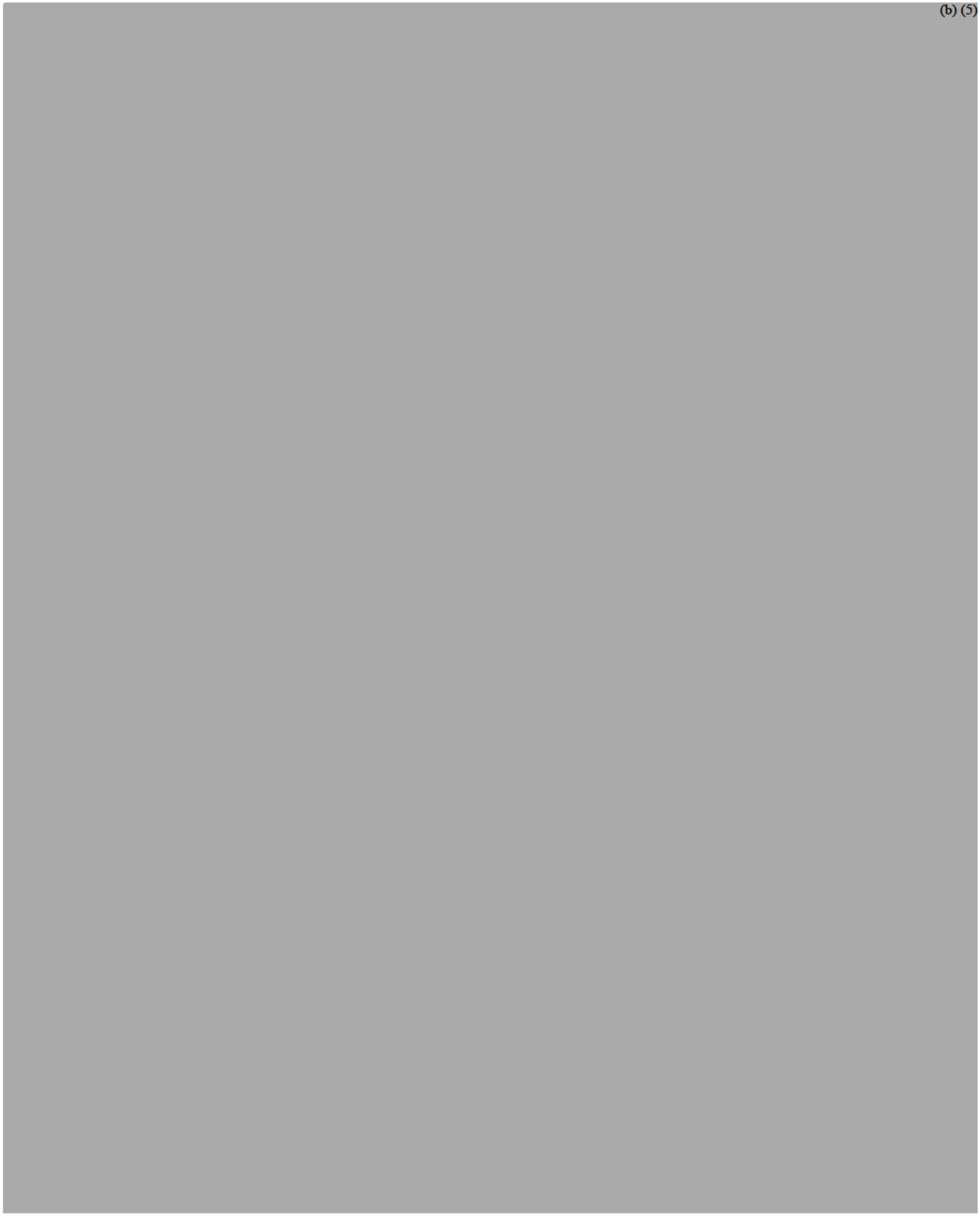
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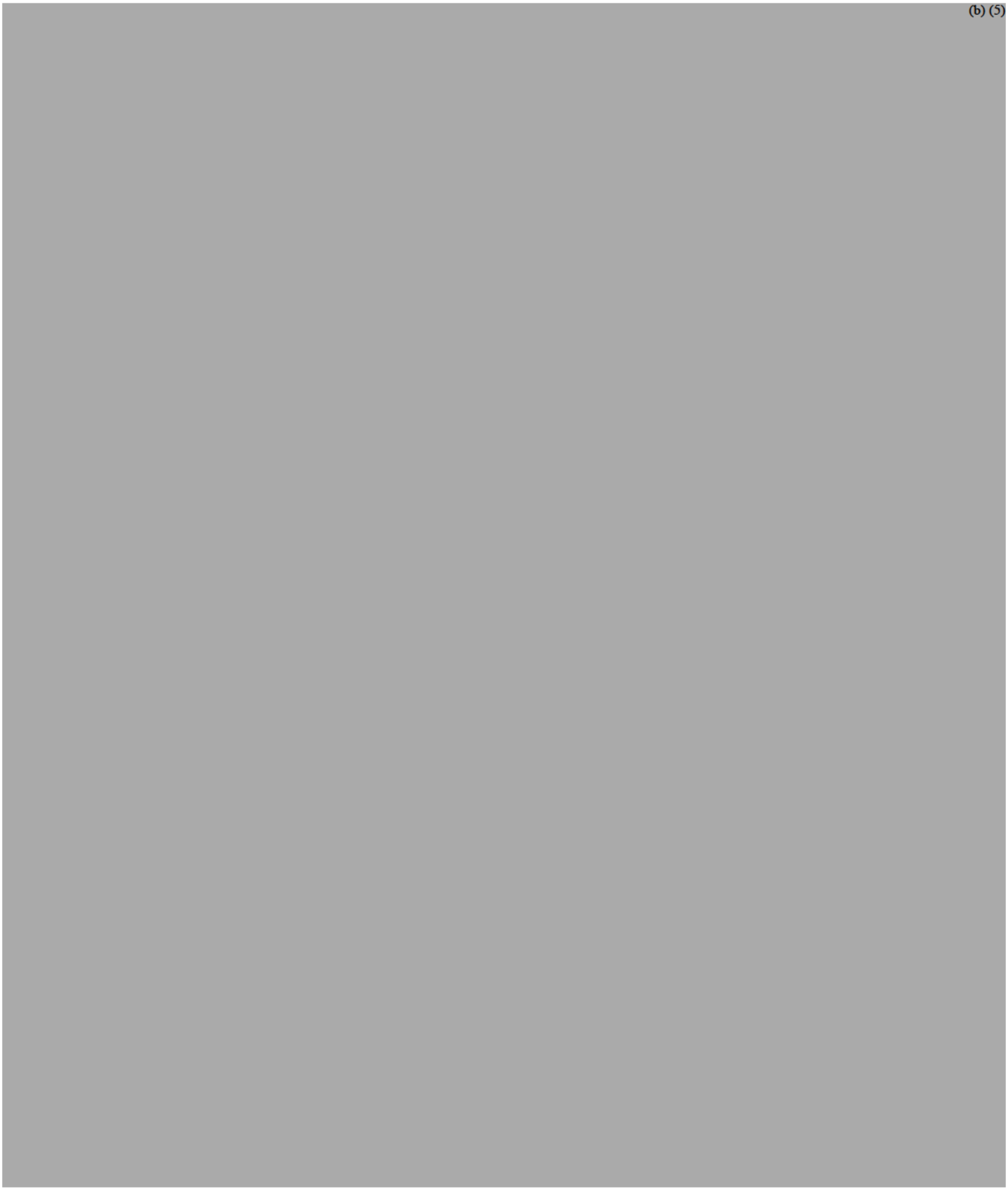
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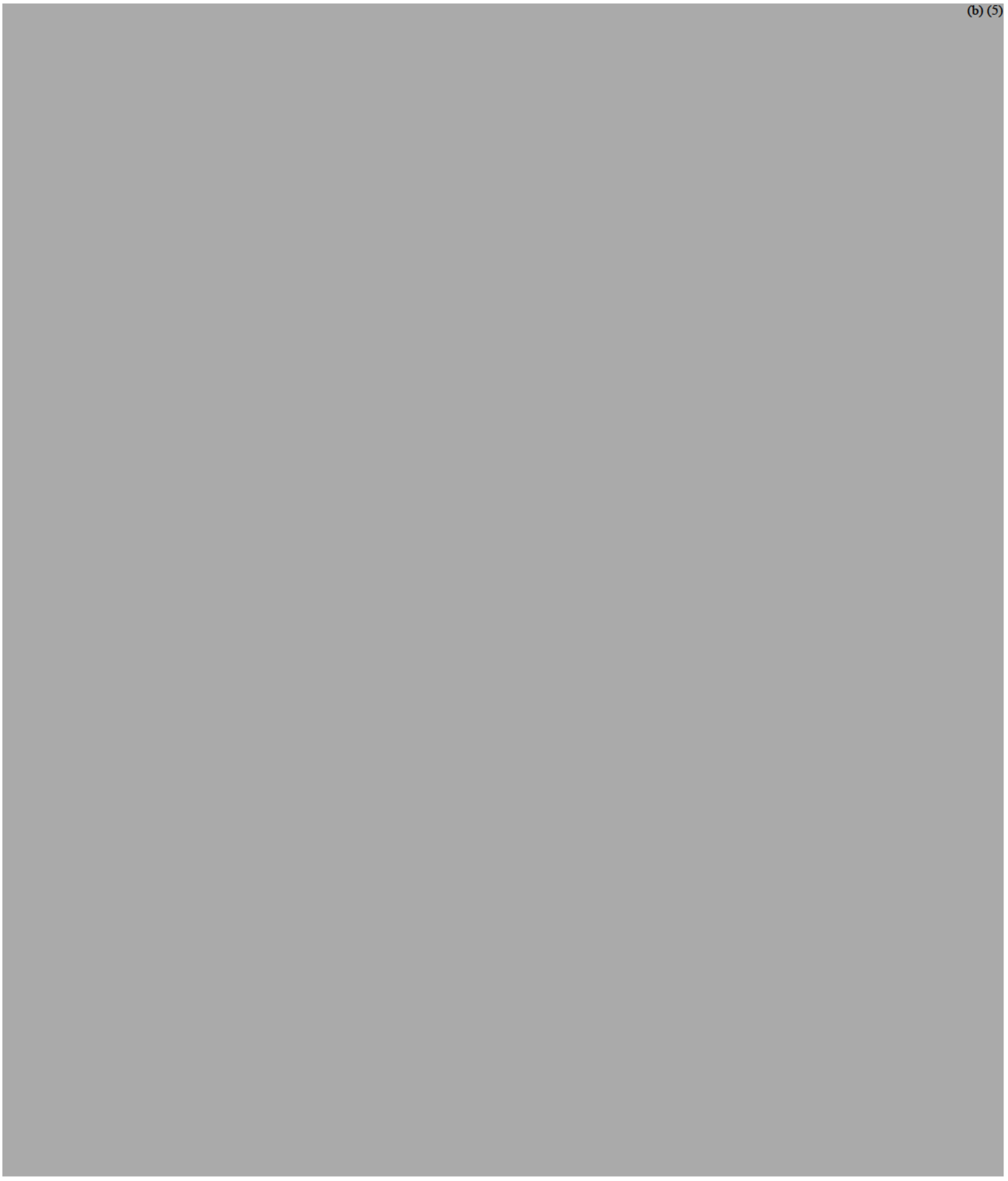
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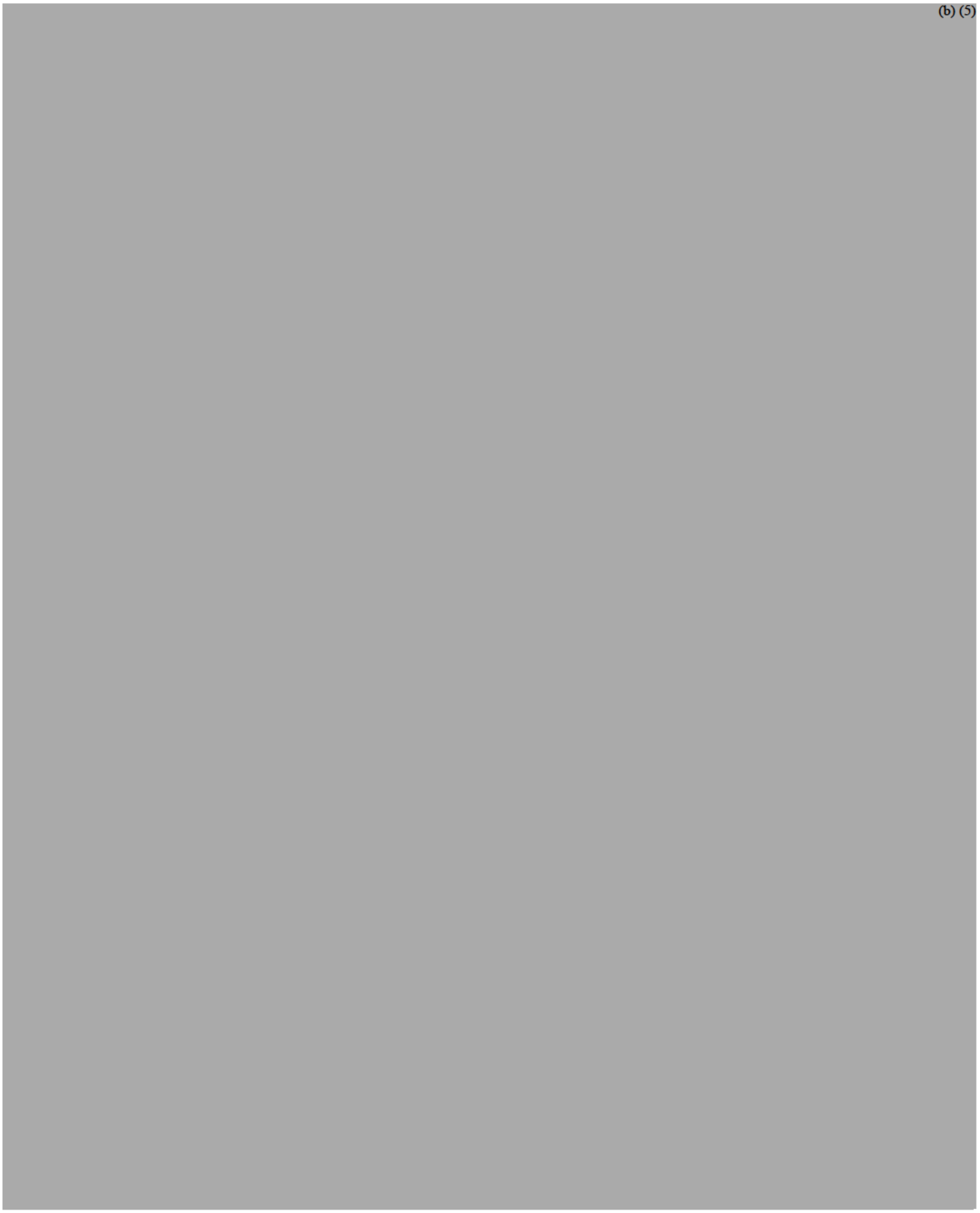
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(b) (5)

Tab B

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

National Institutes of Health
Bethesda, Maryland 20892

The Honorable Lamar Alexander
Chairman, Committee on Health,
Education, Labor and Pensions
United States Senate
Washington, D.C. 20510

Dear Mr. Chairman:

I am pleased to inform you that the Triennial Report of the Director, National Institutes of Health (NIH), Fiscal Years 2016, 2017 and 2018 has been posted on the NIH website at https://report.nih.gov/biennialreport/.

This report is required by Section 403 of the Public Health Service Act, and we hope that the information in this report achieves that goal and serves as a useful reference for understanding NIH activities and operations.

This report provides:

- An assessment of the state of biomedical and behavioral research;
- An overview of the NIH structure, operations, policies, and priorities;
- Summaries and highlights of NIH research activities in areas specified by Congress;
- Reviews of the NIH center of excellence programs that were established by congressional mandate; and
- Myriad hyperlinks allowing the reader to locate more information on NIH programs and activities.

If you have any questions, please contact the NIH Office of Legislative Policy and Analysis at 301-496-3471. We also welcome any feedback on the report.

Sincerely yours,

Francis S. Collins, M.D., Ph.D.
Director

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

National Institutes of Health
Bethesda, Maryland 20892

The Honorable Patty Murray
Ranking Member, Committee on Health,
Education, Labor and Pensions
United States Senate
Washington, D.C. 20510

Dear Senator Murray:

I am pleased to inform you that the Triennial Report of the Director, National Institutes of Health (NIH), Fiscal Years 2016, 2017, and 2018 has been posted on the NIH website at https://report.nih.gov/biennialreport/.

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Sincerely yours,

Francis S. Collins, M.D., Ph.D.
Director

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

National Institutes of Health
Bethesda, Maryland 20892

The Honorable Richard Shelby
Chairman, Committee on Appropriations
United States Senate
Washington, D.C. 20510

Dear Mr. Chairman:

I am pleased to inform you that the Triennial Report of the Director, National Institutes of Health (NIH), Fiscal Years 2016, 2017, and 2018 has been posted on the NIH website at https://report.nih.gov/biennialreport/.

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Sincerely yours,

Francis S. Collins, M.D., Ph.D.
Director

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

National Institutes of Health
Bethesda, Maryland 20892

The Honorable Patrick Leahy
Vice Chairman, Committee on Appropriations
United States Senate
Washington, D.C. 20510

Dear Mr. Vice Chairman:

I am pleased to inform you that the Triennial Report of the Director, National Institutes of Health (NIH), Fiscal Years 2016, 2017, and 2018 has been posted on the NIH website at https://report.nih.gov/biennialreport/.

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Sincerely yours,

Francis S. Collins, M.D., Ph.D.
Director

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

National Institutes of Health
Bethesda, Maryland 20892

The Honorable Roy Blunt
Chairman, Subcommittee on Labor, Health, and
Human Services, Education, and Related Agencies
Committee on Appropriations
United States Senate
Washington, D.C. 20510

Dear Mr. Chairman:

I am pleased to inform you that the Triennial Report of the Director, National Institutes of Health (NIH), Fiscal Years 2016, 2017, and 2018 has been posted on the NIH website at https://report.nih.gov/biennialreport/.

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Sincerely yours,

Francis S. Collins, M.D., Ph.D.
Director

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

National Institutes of Health
Bethesda, Maryland 20892

The Honorable Patty Murray
Ranking Member, Subcommittee on Labor, Health, and
Human Services, Education, and Related Agencies
Committee on Appropriations
United States Senate
Washington, D.C. 20510

Dear Senator Murray:

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Sincerely yours,

Francis S. Collins, M.D., Ph.D.
Director

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

National Institutes of Health
Bethesda, Maryland 20892

The Honorable Frank Pallone, Jr.
Chairman, Committee on Energy
and Commerce
U.S. House of Representatives
Washington, D.C. 20515

Dear Mr. Chairman:

I am pleased to inform you that the Triennial Report of the Director, National Institutes of Health (NIH), Fiscal Years 2016, 2017, and 2018 has been posted on the NIH website at https://report.nih.gov/biennialreport/.

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Sincerely yours,

Francis S. Collins, M.D., Ph.D.
Director

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

National Institutes of Health
Bethesda, Maryland 20892

The Honorable Greg Walden
Ranking Member, Committee on Energy
and Commerce
U.S. House of Representatives
Washington, D.C. 20515

Dear Representative Pallone:

I am pleased to inform you that the Triennial Report of the Director, National Institutes of Health (NIH), Fiscal Years 2016, 2017, and 2018 has been posted on the NIH website at https://report.nih.gov/biennialreport/.

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Sincerely yours,

Francis S. Collins, M.D., Ph.D.
Director

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

National Institutes of Health
Bethesda, Maryland 20892

The Honorable Anna Eshoo
Chairwoman, Subcommittee on Health
Committee on Energy and Commerce
U.S. House of Representatives
Washington, D.C. 20515

Dear Ms. Chairwoman:

I am pleased to inform you that the Triennial Report of the Director, National Institutes of Health (NIH), Fiscal Years 2016, 2017, and 2018 has been posted on the NIH website at https://report.nih.gov/biennialreport/.

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Sincerely yours,

Francis S. Collins, M.D., Ph.D.
Director

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

National Institutes of Health
Bethesda, Maryland 20892

The Honorable Michael Burgess
Ranking Member, Subcommittee on Health
Committee on Energy and Commerce
U.S. House of Representatives
Washington, D.C. 20515

Dear Representative Burgess:

I am pleased to inform you that the Triennial Report of the Director, National Institutes of Health (NIH), Fiscal Years 2016, 2017, and 2018 has been posted on the NIH website at https://report.nih.gov/biennialreport/.

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Sincerely yours,

Francis S. Collins, M.D., Ph.D.
Director

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

National Institutes of Health
Bethesda, Maryland 20892

The Honorable Nita Lowey
Chairwoman, Committee on Appropriations
U.S. House of Representatives
Washington, D.C. 20515

Dear Ms. Chairwoman:

I am pleased to inform you that the Triennial Report of the Director, National Institutes of Health (NIH), Fiscal Years 2016, 2017, and 2018 has been posted on the NIH website at https://report.nih.gov/biennialreport/.

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Sincerely yours,

Francis S. Collins, M.D., Ph.D.
Director

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

National Institutes of Health
Bethesda, Maryland 20892

The Honorable Kay Granger
Ranking Member, Committee
on Appropriations
U.S. House of Representatives
Washington, D.C. 20515

Dear Representative Granger:

For your information the Triennial Report of the Director, National Institutes of Health (NIH), Fiscal Years 2016, 2017, and 2018 has been posted on the NIH website at https://report.nih.gov/biennialreport/.

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Sincerely yours,

Francis S. Collins, M.D., Ph.D.
Director

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

National Institutes of Health
Bethesda, Maryland 20892

The Honorable Rosa DeLauro
Chairwoman, Subcommittee on Labor, Health and
Human Services, Education, and Related Agencies
Committee on Appropriations
U.S. House of Representatives
Washington, D.C. 20515

Dear Ms. Chairwoman:

I am pleased to inform you that the Triennial Report of the Director, National Institutes of Health (NIH), Fiscal Years 2016, 2017, and 2018 has been posted on the NIH website at https://report.nih.gov/biennialreport/.

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Francis S. Collins, M.D., Ph.D.
Director

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

National Institutes of Health
Bethesda, Maryland 20892

The Honorable Tom Cole
Ranking Member, Subcommittee on Labor, Health and
Human Services, Education, and Related Agencies
Committee on Appropriations
U.S. House of Representatives
Washington, D.C. 20515

Dear Representative Cole:

I am pleased to inform you that the Triennial Report of the Director, National Institutes of Health (NIH), Fiscal Years 2016, 2017, and 2018 has been posted on the NIH website at https://report.nih.gov/biennialreport/.

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Sincerely yours,

Francis S. Collins, M.D., Ph.D.
Director

From: Doepel, Laurie (NIH/NIAID) [E]
Sent: Fri, 6 Mar 2020 16:33:31 +0000
To: Lane, Cliff (NIH/NIAID) [E]
Subject: RE: Draft CONFIDENTIAL Trip Report
Attachments: Trip Report China 2020 ld.docx

Cliff,

Sorry for the delay. Wonderfully informative and comprehensive, and fascinating to read. Minor copyedits for your consideration, feel free to ignore them.

Many thanks for sharing your incredible photos, observations and insights!

Laurie

From: Lane, Cliff (NIH/NIAID) [E] <(b) (6)
Sent: Thursday, March 5, 2020 1:44 PM
To: Doepel, Laurie (NIH/NIAID) [E] <(b) (6)
Subject: Draft CONFIDENTIAL Trip Report

Are you back to work?

Only – if so - please take a look at the attached trip report and feel free to edit for clarity. I have to admit I have not yet done a careful proof-read myself.

If not – take a look and enjoy the additional photos!

Cliff

From: Laurie Doepel <(b) (6)
Date: Thursday, March 5, 2020 at 10:17 AM
To: "Lane, Cliff (NIH/NIAID) [E]" <(b) (6)
Subject: RE: China Mission Group Photo

Cliff,

Thank you, these are really nice photos—ones for the history books. And what an impressive, cogent report.

Hope you are holding up under the increasing competing demands for your wisdom and expertise.

Best wishes,

From: GIERSING, Birgitte
Sent: Thu, 3 Sep 2020 11:49:16 +0000
To: Graham, Barney (NIH/VRC) [E];Sinead Delany-Moretlwe;Bernard Fritzell;(SPmig) Shabir Madhi;Karron, Ruth;klaus.cichutek;Marian Wentworth;Papania, Mark (CDC/DDPHSIS/CGH/GID);Yshao;Jerome Kim;Peter Smith;Claudio Lanata;(b) (6);dracravioto;Kaslow, David;Bekeredjian-Ding, Isabelle;Gagandeep Kang
Cc: SPARROW, Erin Grace;Pabillon-Green, Karen;FRIEDE, Martin Howell;Isabel Frost
Subject: RE: Draft slide deck: PDVAC virtual session on TB
Attachments: Consolidated final PDVAC TB Sept 2020.pdf

Dear PDVAC
Please find attached the final slides for the TB PDVAC presentation today.
Kind regards,
Gitte

From: GIERSING, Birgitte
Sent: 02 September 2020 23:31
To: Graham, Barney (NIH/VRC) [E] (b) (6); Sinead Delany-Moretlwe (b) (6); Bernard Fritzell (b) (6); (SPmig) Shabir Madhi (b) (6); Karron, Ruth (b) (6); klaus.cichutek (b) (6) Marian Wentworth (b) (6); Papania, Mark (CDC/DDPHSIS/CGH/GID) (b) (6); Yshao (b) (6); Jerome Kim (b) (6); Peter Smith (b) (6); Claudio Lanata (b) (6); (b) (6) dracravioto (b) (6); Kaslow, David (b) (6); Bekeredjian-Ding, Isabelle (b) (6); Gagandeep Kang (b) (6)
Cc: SPARROW, Erin Grace (b) (6); Pabillon-Green, Karen (b) (6); FRIEDE, Martin Howell (b) (6); Isabel Frost (b) (6)
Subject: Draft slide deck: PDVAC virtual session on TB

Dear PDVAC members,
Please find attached the DRAFT slides for the meeting tomorrow. The modelling slides still need some tidying up, and I need to add my overview slides – final deck to follow in the morning.
Best,
Gitte

From: GIERSING, Birgitte
Sent: 02 September 2020 23:17
To: SPARROW, Erin Grace (b) (6); Graham, Barney (NIH/VRC) [E] (b) (6); Sinead Delany-Moretlwe (b) (6); Bernard Fritzell (b) (6); (SPmig) Shabir Madhi (b) (6); Karron, Ruth (b) (6); klaus.cichutek (b) (6); G Kang (b) (6) Marian Wentworth (b) (6); Papania, Mark (CDC/DDPHSIS/CGH/GID) (b) (6) Yshao (b) (6); Jerome Kim (b) (6); Peter Smith (b) (6); Claudio Lanata (b) (6); (b) (6); dracravioto (b) (6); Kaslow, David (b) (6); GRIFFIN, Geraldine Margaret

(b) (6); Pabillon-Green, Karen (b) (6); Bekeredjian-Ding, Isabelle (b) (6); FRIEDE, Martin Howell (b) (6); (b) (6); (b) (6); Gagandeep Kang (b) (6); GEBRESELASSIE, Nebiat (b) (6); Frank Cobelens (b) (6); Alexander Schmidt (b) (6); Taryn Rogalski-Salter (b) (6); Ann Ginsberg (b) (6); Richard White (b) (6); (b) (6); Mark Hatherill (b) (6); Helinski, Michelle (b) (6); Deepali Patel (b) (6); FALZON, Dennis (b) (6); ZIGNOL, Matteo (b) (6); (b) (6); Isabel Frost (b) (6); Nicola Viebig (b) (6); (b) (6); (b) (6); (b) (6)

Subject: Logistics: PDVAC virtual session on TB

Dear all,

We're looking forward to the PDVAC session on TB vaccine development tomorrow. Please find the final agenda and list of participants attached.

We have a very full agenda, so **please read the following to help us manage the meeting effectively** by zoom (dial in details below):

- When entering the call, you will be in a waiting room until we admit you onto the call. Please dial in a couple of minutes early if possible to help us co-ordinate this.
- Apologies but there will not be the opportunity for everyone to introduce themselves. We plan to start promptly at 3pm Geneva, and will do one roll call. We will not be able to announce you if join the call after this initial roll call.
- Everyone will be muted upon entering the call. Please raise your hand or use the chat function if you'd like to speak outside of requests for comments/questions from the chair.
- The meeting will be recorded to assist with drafting the minutes.
- At the end of the meeting (5pm Geneva), all participants apart from the PDVAC committee will be asked to disconnect for the closed session.

All the best,
Gitte

-----Original Appointment-----
From: SPARROW, Erin Grace (b) (6)
Sent: 01 July 2020 12:03
To: SPARROW, Erin Grace; Graham, Barney (NIH/VRC) [E]; Sinead Delany-Moretlwe; Bernard Fritzell; (SPmig) Shabir Madhi; Karron, Ruth; klaus.cichutek; G Kang; Marian Wentworth; Papania, Mark (CDC/DDPHSIS/CGH/GID); Yshao; Jerome Kim; Peter Smith; Claudio Lanata; (b) (6) dracravioto; Kaslow, David; GIERSING, Birgitte; GRIFFIN, Geraldine Margaret; Pabillon-Green, Karen; Bekeredjian-Ding, Isabelle; FRIEDE, Martin Howell; (b) (6) (b) (6)
Cc: GEBRESELASSIE, Nebiat; Frank Cobelens; Alexander Schmidt; Taryn Rogalski-Salter; Ann Ginsberg; Richard White; (b) (6); Mark Hatherill; Helinski, Michelle; Deepali Patel; Gagandeep Kang; FALZON, Dennis; ZIGNOL, Matteo; (b) (6); Isabel Frost; Nicola Viebig; (b) (6); (b) (6); (b) (6)
Subject: Confirmed: PDVAC virtual session on TB

When: 03 September 2020 15:00-17:30 (UTC+01:00) Amsterdam, Berlin, Bern, Rome, Stockholm, Vienna.
Where:

Dear All,

Please find the zoom details for the PDVAC session on TB vaccines below and attached the agenda and list of participants. Please note that the final 30 minutes will be a closed discussion for PDVAC members only.

Topic: PDVAC virtual session 3 September - TB vaccines
Time: Sep 3, 2020 03:00 PM Zurich

Join Zoom Meeting
https://zoom.us/j (b) (6) ?pwd=czk0YlpDd2NjMW5ybm91QzdQb1RMUT09

Meeting ID: (b) (6)
Passcode: (b) (6)

Find your local number: https://zoom.us/u/acQreLzV6E

Thanks,
Erin

An update on Tuberculosis vaccine development activities

WHO's Product Development for Vaccines Development Committee

Virtual session 6

3 September 2020

PDVAC committee members

David Kaslow, PATH (chair)

Klaus Cichutek
Paul-Ehrlich-Institute (PEI)
Langen, Germany

Sinead Delany-Moretlwe
University of Witwatersrand (Wits)
Johannesburg, South Africa

Bernard Fritzell
Independent
Bordeaux, France

Barney Graham
NIAID, Vaccine Research Center
Bethesda, USA

Gagandeep Kang Christian Medical College,
Vellore, India

Ruth Karron
Johns Hopkins Bloomberg School of Public Health (JHSPH)
Baltimore, USA

Jerome Kim
International Vaccine Institute (IVI)
Seoul, Korea

Alejandro Cravioto (ex-officio SAGE chair)
University of Mexico
Puerto Vallarta, Mexico

Claudio Lanata
Instituto de Investigación Nutricional
Lima, Peru

Shabir Madhi
Witwatersrand University
Johannesburg, South Africa

Beno Y. Nyam
National Agency for Food and Drug Administration and Control
Lagos, Nigeria

Mark Papania
Centers for Disease Control and Prevention
Atlanta, USA

Peter Smith
London School of Hygiene and Tropical Medicine
London, UK

Yiming Shao
Chinese Center for Disease Control and Prevention (CDC)
Beijing, China

Marian W. Wentworth Management Sciences for Health (MSH)
Medford, USA

Three priority development goals for TB vaccines

World Health Organization

A safe, effective and affordable TB vaccine for adolescents and adults

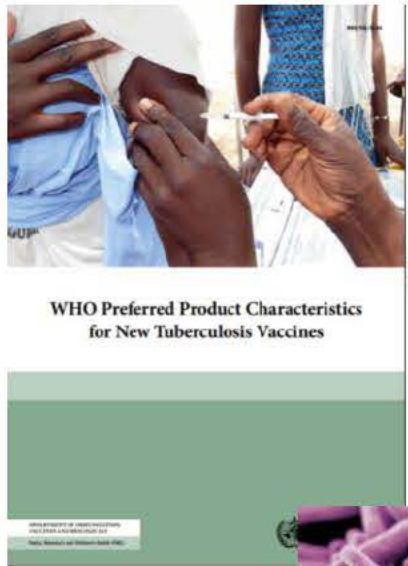
Given the substantial disease burden in adolescents and adults, and the critical role that those with active pulmonary TB disease play in transmission of Mtb infection, the *prevention of pulmonary TB disease in adolescents and adults* is the priority strategic target in TB vaccine development.

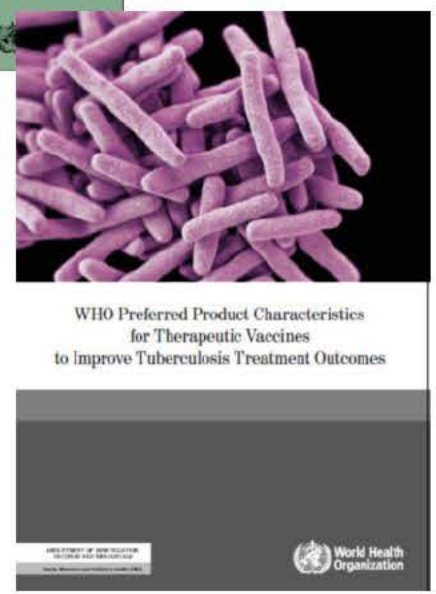
Affordable TB vaccine for neonates and infants with improved safety and efficacy as compared to BCG

There is a need to *improve upon the BCG vaccines currently in use* by i) providing improved and longer duration of protection, ii) easing the safe administration to infants with HIV infection or other causes of immune suppression and/or iii) improving the manufacturing process to secure sustainable supply.

A therapeutic vaccine to improve tuberculosis treatment outcomes

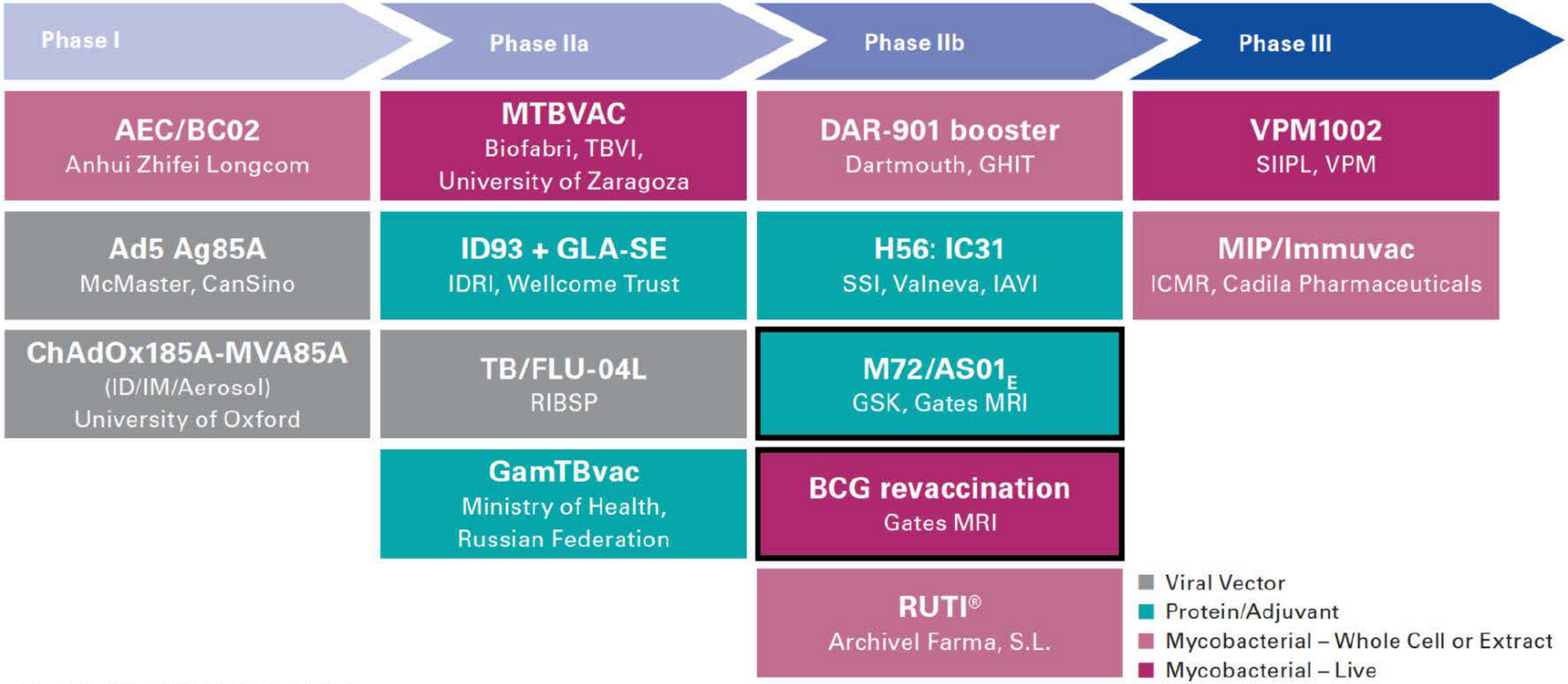
Such a vaccine should *improve outcomes of drug therapy* by increasing the cure rate at the end of drug treatment and/or decreasing the frequency of recurrences following initial cure.





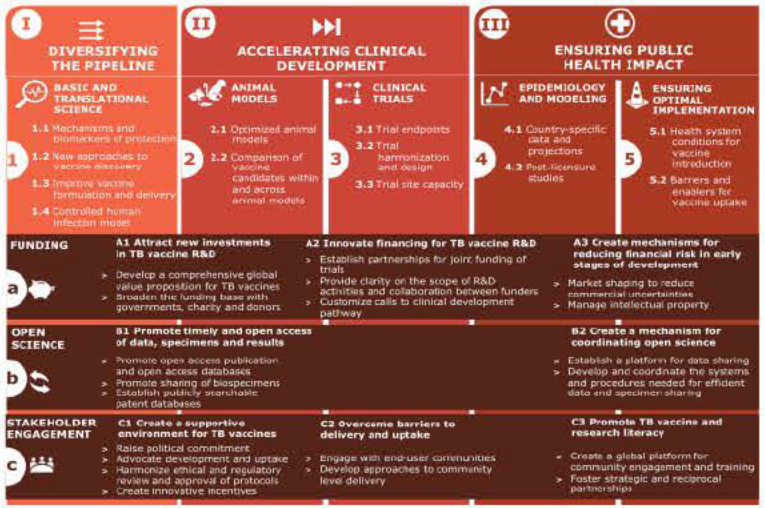
Overview of the TB vaccine pipeline

World Health Organization

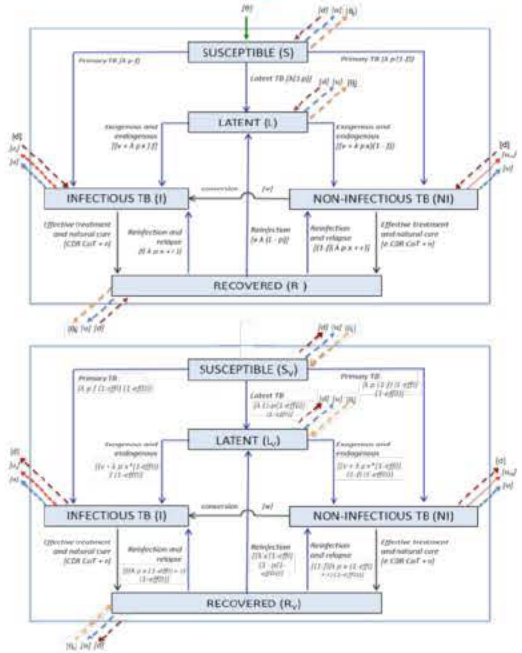


Slide courtesy of Nebait Gebreselassie

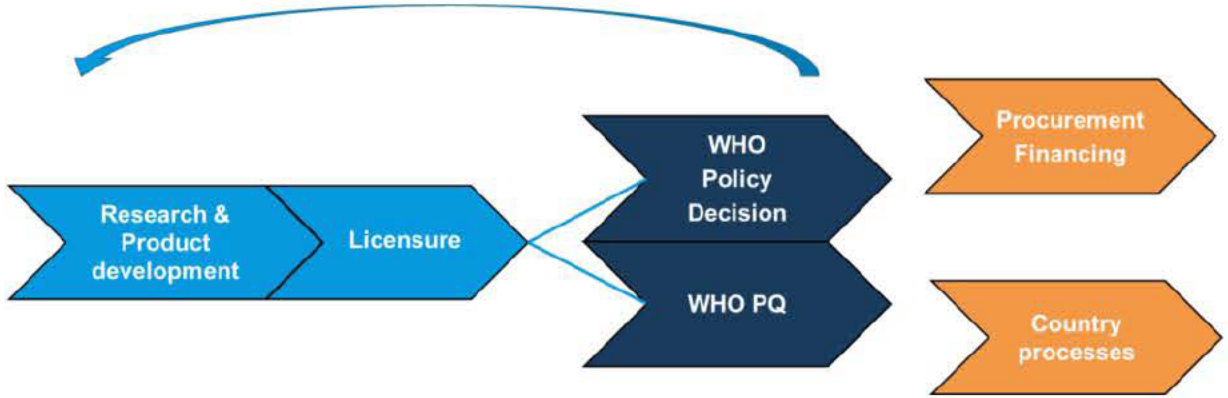
Other enabling activities for TB vaccine development



TB Vaccine roadmap



TB Vaccine impact modelling and assessment of value



Integrating the pathway for decision making from product development to policy, uptake and impact

Agenda

World Health Organization

Time (Geneva CEST)	Topic	Duration	Detail	Moderators, speakers
15.00 – 15.05	Welcome and roll call			David Kaslow / Birgitte Giersing
15.05 – 15.10	The context for this PDVAC meeting	5’	• Rationale for the topic selection • Overview of pipeline • Objectives of the meeting	Birgitte Giersing
15.10 – 15.50	Update on Gates MRI TB Vaccine Development Activities	(25’ + 15’)	• Update on current status on phase IIb BCG revaccination study in South Africa; discussion related to additional studies and data required for policy change. • Review of M72/AS01 study plans, licensure and potential policy recommendation strategy; identification of critical areas for WHO/PDVAC input	Alex Schmidt (Gates MRI)
15.50 – 16.20	Review of the Global Roadmap for R&D for TB vaccines	(15 + 15)	• Purpose and process for developing the TB vaccine Roadmap • Review of the proposed 3 themes to advance TB vaccines, and how the activities relate to the 3 WHO development goals; are there gaps?	Frank Cobelens (AIGHD)
16.20 – 16.45	Modelling the potential value of TB vaccines	(15 + 10)	• Overview of the vaccine health and impact model framework and components, and the M72/AS01 and BCG revaccination specific modelling projects	Richard White (LSHTM)
16.45- 17.00	Discussion	15’	• Open session	All

Objectives for this session

World Health Organization

- Understand the **current status, future plans and critical issues** related to the M72/AS01 product development plan and the potential BCG revaccinations strategy;
- Review the **proposed workstreams of the TB vaccine roadmap development** and assess how they align with progressing the 3 WHO TB vaccine development goals;
- Introduce the ongoing WHO-funded **Full Value Assessment of TB Vaccines** project and assess how this progresses the WHO's Full Value of Vaccines Assessment approach, and what if any, high priority follow-up work is advised
- Introduce the ongoing BMGF-funded **M72/AS01 and BCG revaccination specific modelling project**, and advise if and how it could be more useful to global and country stakeholders
- Assess the **immediate TB vaccine development related needs and priorities**, from PDR/PDVAC

Questions for PDVAC

World Health Organization

- Are there critical activities that would benefit from PDR/PDVAC leadership and engagement, either related to M72/AS01 and BCG revaccination specifically, or enabling TB vaccine development more generally?
- Does PDVAC have recommendations on the draft TB vaccine roadmap?
- Does PDVAC support WHO co-authorship of the roadmap?
- Are there any recommendations for high priority follow up work to the WHO-funded Full Value Assessment of TB Vaccines project
- Are there suggestions with respect to how the BMGF-funded M72/AS01 and BCG revaccination modelling project could be more useful to global and country stakeholders

BILL & MELINDA GATES MEDICAL RESEARCH INSTITUTE

Update on Gates MRI TB Vaccine Development Activities

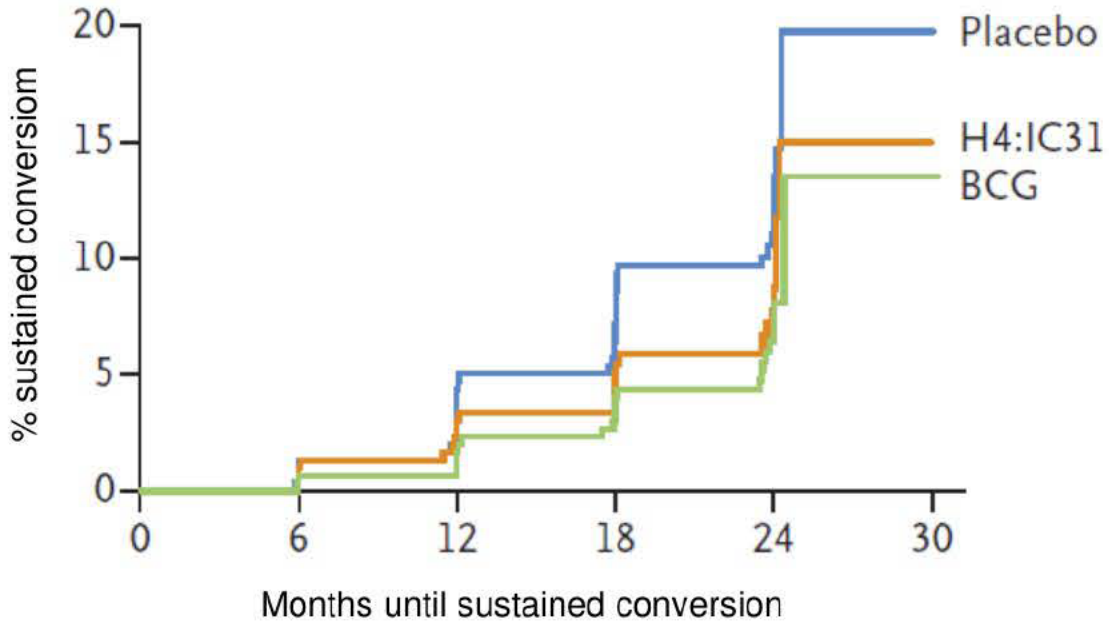
Alexander Schmidt, Taryn Rogalski-Salter,
Robin Mogg, Nicole Frahm & Marie Green

PDVAC, September 3, 2020

GATES MRI BCG REVACCINATION STUDY

AERAS C-040-404 STUDY

- N=990, 1:1:1, primary endpoint: initial QFT-conversion, secondary EP: sustained QFT-conversion
- BCG: 45% (95%CI 6.4-68.1%) vaccine efficacy for sustained QFT conversion



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Prevention of *M. tuberculosis* Infection with H4:IC31 Vaccine or BCG Revaccination

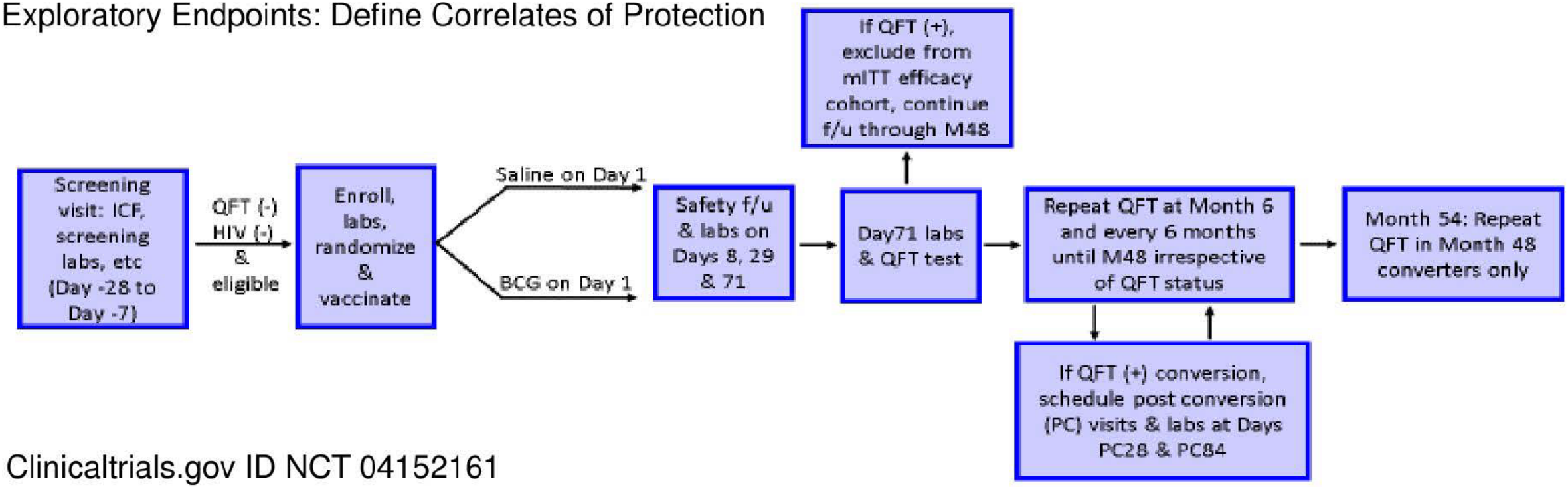
E. Nemes, H. Geldenhuys, V. Rozot, K.T. Rutkowski, F. Ratangee, N. Bilek, S. Mabwe, L. Makhethe, M. Erasmus, A. Toefy, H. Mulenga, W.A. Hanekom, S.G. Self, L.-G. Bekker, R. Ryall,* S. Gurunathan, C.A. DiazGranados, P. Andersen, I. Kromann, T. Evans, R.D. Ellis, B. Landry, D.A. Hokey, R. Hopkins, A.M. Ginsberg, T.J. Scriba, and M. Hatherill, for the C-040-404 Study Team†

DOI: 10.1056/NEJMoa1714021

GATES MRI BCG ReVax STUDY

Goal: generate data that can potentially support policy changes for BCG revaccination

- Randomized, placebo controlled, observer-blind, Phase 2b study with two arms (BCG vaccine and saline placebo)
- 1,800 QFT-negative participants 10-18 years of age are randomized 1:1 to receive a single intradermal injection
- Primary Endpoint: Sustained QFT conversion (initial conversion and IGRA positive 3 & 6 months thereafter)
- Exploratory Endpoints: Define Correlates of Protection



Clinicaltrials.gov ID NCT 04152161

alexander.schmidt@gatesmri.org

BCG ReVax STUDY STATUS

- Five sites in South Africa (SATVI, CAPRISA, Wits RHI, Desmond Tutu HRF, Be Part)
- First participant randomized November 6, 2019
- Screening and randomization paused due to COVID-19-related restrictions from March 19, 2020
- Enrolment resumed starting in July 2020 (site-by-site)
- Approx. 400 of 1,800 participants enrolled
- Enrolment completion anticipated for Q3 2021
- Primary endpoint analysis will occur when a total of 118 sustained *Mtb* infection events have occurred in the mITT efficacy population (anticipated in late 2023, or early 2024)

BCG Immune Correlates Program (CoP for POSI)
- using biospecimens from Aeras C-040-404 trial -

CELLULAR IMMUNITY

- Antigen-specific T cells and NK cells (McElrath)
  - Intracellular cytokine staining
- Donor-unrestricted T cells (DURTs, MAITs) (McElrath)
  - Tetramer staining
- scRNAseq (Shalek)

HUMORAL IMMUNITY

- Antibody titer, subclass and avidity (Tomaras)
  - Binding antibody multiplex assay
- Antibody function (Alter)
  - Systems serology
- Antibody-mediated mycobacterial growth inhibition (Alter)

INNATE / TRAINED IMMUNITY

- Whole blood composition (Nemes)
  - DLC-ICE
- scATACseq (Barreiro)
- EpiToF (Utz/Khatri)

OMICS ANALYSES

Bulk RNAseq (Scriba)

WHAT IS NEEDED TO ADVANCE BCG REVACCINATION?

Anticipated data availability:

- Candidate Correlate of Protection (CoP) data for prevention of sustained infection (POSI) (based on Aeras revaccination study biospecimens) in 2023.
  - / Candidate CoP to be confirmed with biospecimens from Gates MRI BCG ReVax study.
- Candidate CoP data for prevention of Disease (POD) (based on M72 Phase 2b trial) in 2023.
  - / To be confirmed with biospecimens from M72/AS01 Phase 3 study.
  - / Best case assumption is that we can identify a CoP for progression from sustained infection to disease.
- BCG ReVax primary endpoint data (sustained IGRA-conversion) in 2024

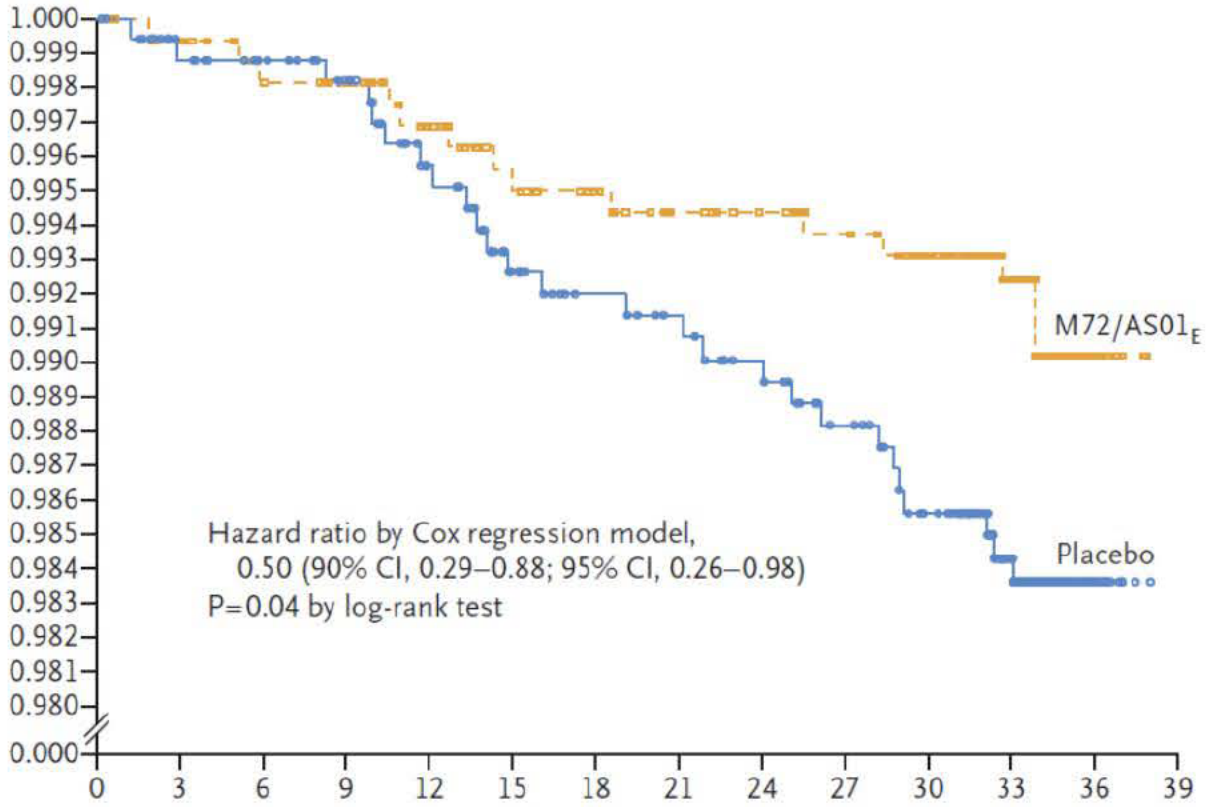
- Other BCG developers may replicate BCG ReVax study in a second geography
- POD clinical endpoint efficacy trial is unlikely to be conducted (too large, too expensive)

M72/AS01 VACCINE DEVELOPMENT

M72/AS01$_E$ & PREVENTION OF DISEASE

PHASE 2B TRIAL IN A QFT-POSITIVE POPULATION

- 49.7% (95% CI 2.1 to 74.2%) vaccine efficacy
- Acceptable safety profile



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Phase 2b Controlled Trial of M72/AS01$_E$ Vaccine to Prevent Tuberculosis

O. Van Der Meeren, M. Hatherill, V. Nduba, R.J. Wilkinson, M. Muyoyeta, E. Van Brakel, H.M. Ayles, G. Henostroza, F. Thienemann, T.J. Scriba, A. Diacon, G.L. Blatner, M.-A. Demoitié, M. Tameris, M. Malahleha, J.C. Innes, E. Hellström, N. Martinson, T. Singh, E.J. Akite, A. Khatoon Azam, A. Bollaerts, A.M. Ginsberg, T.G. Evans, P. Gillard, and D.R. Tait

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Final Analysis of a Trial of M72/AS01$_E$ Vaccine to Prevent Tuberculosis

D.R. Tait, M. Hatherill, O. Van Der Meeren, A.M. Ginsberg, E. Van Brakel, B. Salaun, T.J. Scriba, E.J. Akite, H.M. Ayles, A. Bollaerts, M.-A. Demoitié, A. Diacon, T.G. Evans, P. Gillard, E. Hellström, J.C. Innes, M. Lempicki, M. Malahleha, N. Martinson, D. Mesia Vela, M. Muyoyeta, V. Nduba, T.G. Pascal, M. Tameris, F. Thienemann, R.J. Wilkinson, and F. Roman

DOI: 10.1056/NEJMoa1803484 & DOI: 10.1056/NEJMoa1909953

M72/AS01$_E$ PRODUCT DEVELOPMENT

Generate data to support licensure of the vaccine and recommendations for effective use

- GSK licensed M72/AS01$_E$ to the Gates MRI, paving the way for continued vaccine development and potential use in LMICs
- GSK will ensure an efficient transfer of the asset technology
- Gates MRI will lead product development and sponsor future clinical trials
- GSK will provide AS01 adjuvant for the development program
- Gates MRI will actively reach out to and collaborate with the many partners and stakeholders committed to accelerating the end of the TB epidemic.

KEY TOPICS & QUESTIONS FOR M72

- Phase 3 study
  - Does M72/AS01E protect IGRA-positive individuals from disease (and for how long)?
  - Does M72/AS01E protect IGRA-negative individuals from infection (and/or disease)?
  - Primary endpoint, age range, IGRA status, participating countries, how to enrich for high risk?
- Data needed for first dossier in South Africa
  - Lower bound of 95% CI? Submission with interim data (95%CI LB>0?), followed by primary analysis data (95%CI LB>15%?)
- Delivery considerations
  - Target age groups (depending of VE in IGRA-negative individuals)
  - Delivery channels, payors?
- What needs to be included in the Phase 3 study design, and what implementation research is needed to support WHO policy recommendation, PQ and financing?

CRITICAL PATH

Clinical & Regulatory:

- Generate Safety & Immunogenicity data to support inclusion of PLHIV in Phase 3 VE trial
- Develop Phase 3 protocol jointly with stakeholders, SMEs & NRAs
- Select countries and prepare sites for Phase 3 VE trial
- Reach agreement on protocol design & initial registration package with health authorities
- Conduct Phase 3 vaccine efficacy study

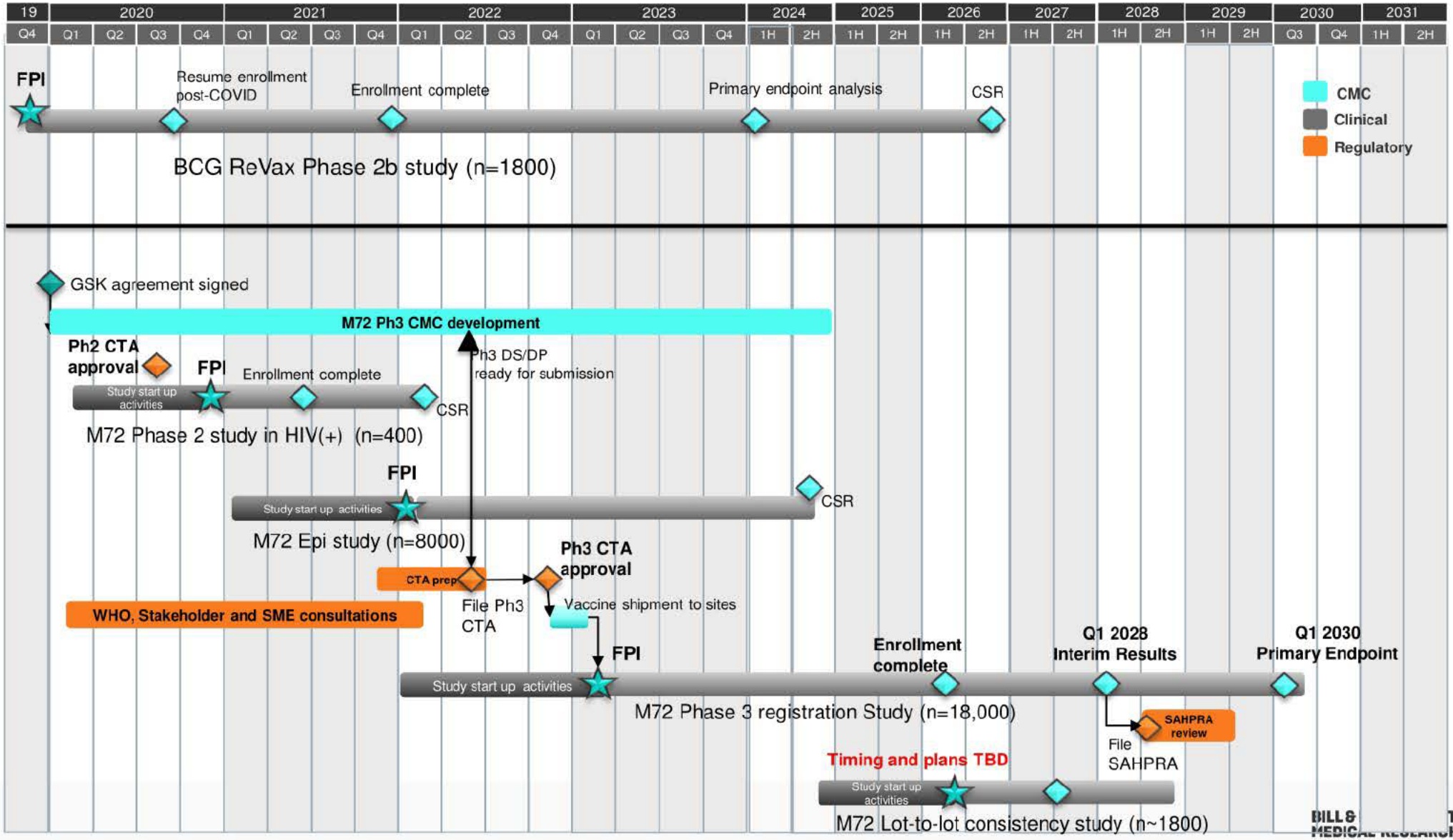
Technical Development:

- Develop M72 antigen manufacturing process to support Phase 3 and commercialization.
- Develop adjuvant manufacturing process to support Phase 3 and commercialization
- Manufacture new drug product & supply Phase 3
- Identify Commercial Manufacturer / Marketing Authorization Holder and transfer M72 manufacturing

INITIAL ASSUMPTIONS ON DEVELOPMENT TIMELINES

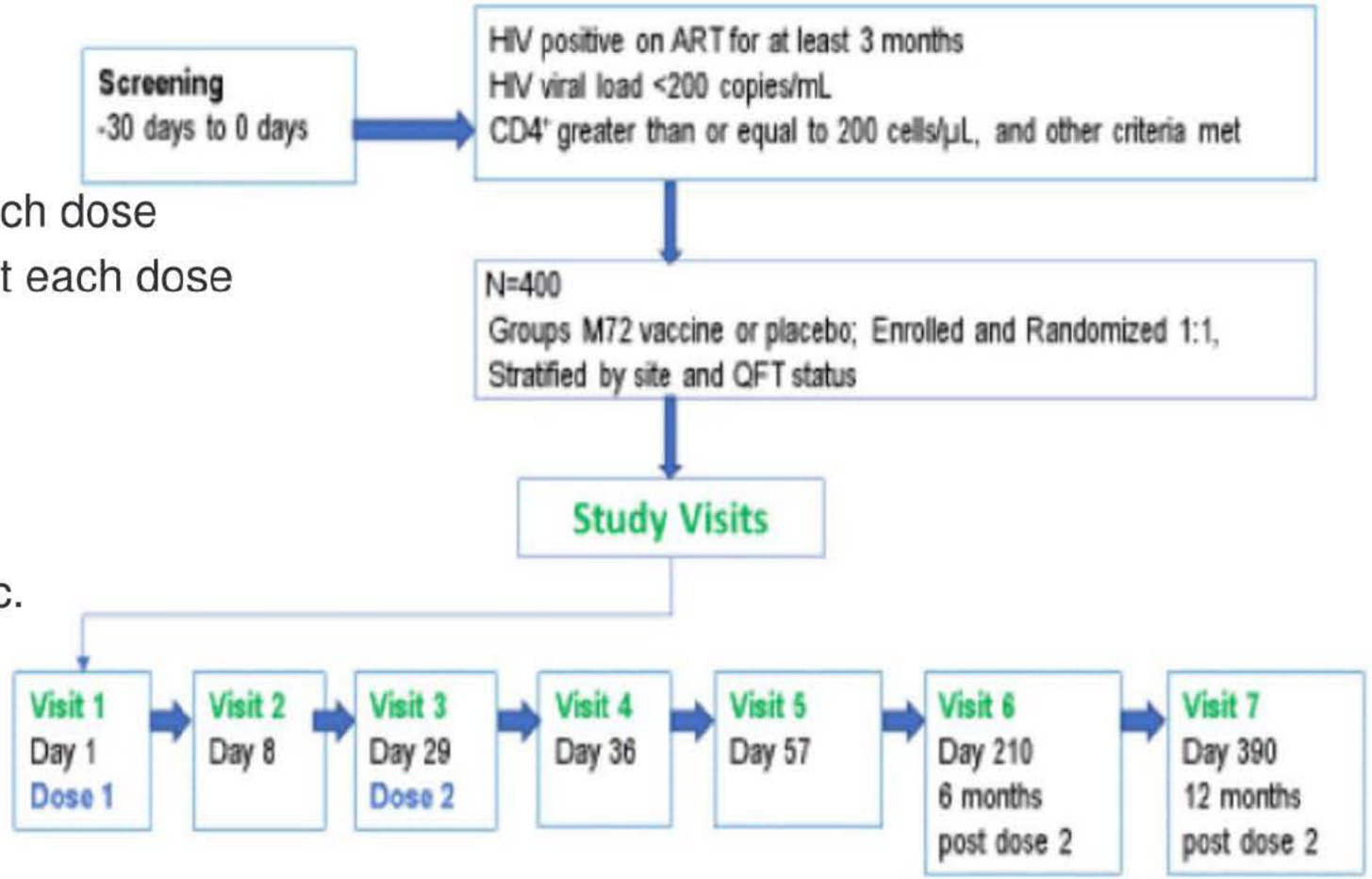
BCG ReVax

M72/AS01E



PHASE 2 STUDY IN PLHIV

- Observer-blind, 1:1 randomized study
- Primary objectives
  - Solicited AEs through 7 days post each dose
  - Unsolicited AEs through 28 days post each dose
  - All SAEs through end of study
- Secondary objectives:
  - M72-specific humoral and cellular immunogenicity
- Exploratory objectives: HIV RNA, CD4 etc.
- Study start anticipated for Nov 2020
- Sites in Durban, Cape Town, Johannesburg & Worcester
- SAHPRA approval received
- Awaiting IRB approvals
- Enrollment anticipated to start November 2020



EPI STUDY IN PREPARATION FOR PHASE 3

Scientific Objectives	Endpoints
Primary	
• To assess prevalence of LTBI	• Interferon gamma (IFNg) release assay positivity by age and by site
Secondary	
• To describe the incidence of TB	• Suspected TB cases by site, risk group, and overall • Lab-confirmed TB cases by site, risk group, & overall
Tertiary/Exploratory	
• To describe the association between IGRA IFNg concentration and progression to TB	• IGRA IFNg concentration at baseline & and risk of TB

EPI STUDY IN PREPARATION FOR PHASE 3

Operational goals:

- Build site capacity & train teams
- Establish operational feasibility for each site: QFT-positivity by age, quality of TB surveillance & study procedures
- Establish study cohorts; subset could be invited to participate in Phase 3 (e.g., IGRA-negatives & recent converters)

Design:

- Approx. 8,000 study participants, f/u 12 - 24 months; study to end at a given site once site is ready to start Phase 3 enrolment
- Approx. 50 sites
- IGRA status at baseline, follow-up every 2 months to identify suspected TB

PHASE 3 EFFICACY STUDY DESIGN FOR M72/AS01$_E$

- **Objectives:**
  - Unequivocally demonstrate VE for POD in QFT-positive participants
  - Support licensure for use irrespective of QFT status, i.e., include enough QFT-neg participants to establish safety, immunogenicity & initial assessment of VE in QFT-neg vaccinees. (Screening for QFT status in national programs is currently not feasible)
  - Support licensure including people living with HIV
- Trial simulations suggest that at least 14,000 subjects in very high incidence settings are needed to demonstrate VE in a randomized controlled trial (1:1 vs placebo)
- An interim analysis for VE could be explored to potentially accelerate submission of a first dossier

PHASE 3: KNOWLEDGE GAPS & CHALLENGES

- Significant uncertainty with regards to incidence of *Mtb* infection & TB disease
  - Highest possible TB incidence rate needed to increase probability of success
  - Clinical trials capacity needed in poor communities in LMICs
- Significant uncertainty with regards to true vaccine efficacy (VE)
  - Primary endpoint definition appears to have impact on VE and incidence rate in IGRA-positives
  - No data on VE in IGRA-negative populations
  - No data on VE in PLHIV
- How can we mitigate uncertainties?
  - Determine site-level QFT prevalence, build capacity, enrich for high incidence, event-triggered primary analysis, adaptive trial, IDMC oversight of unblinded data

PARAMETER ASSUMPTIONS FOR TRIAL SIMULATIONS

Trial Parameter	Value	Reference
Age range	16 – 30 year of age	
Proportion baseline QFT-pos	65%	
Incidence of Disease (D) in QFT-pos	0.4 – 0.6% per year	Van Der Meeren et al (2018), NEJM
True VE in QFT-pos	50 – 65%	Van Der Meeren et al (2018), NEJM
Participant follow-up time	5 years	Study defined
Accrual time	3 years	Assumed
Participant drop out rate	5% per year	
Incidence of Infection (INF) in QFT-neg	5% per year (i.e., sustained QFT-pos conversion)	Nemes et al (2018), NEJM
Incidence of D in QFT-neg	1.6% per year after sustained conversion (no disease among non-sustained converters)	Nemes et al (2017), American Journal of Respiratory and Critical Care Medicine
True VE in QFT-neg	VE(INF) = 25%; VE(D) = VE(INF)	No data

PHASE 3 DESIGN CONSIDERATIONS

How likely are we to succeed?

- Probability of success (i.e., study "power") based on (i) number of observed events; (ii) true VE; and (iii) lower bound of VE needed

Show 95% CI LB on VE >	# required events when true VE =								
	70%	65%	60%	55%	50%	45%	40%	35%	30%
0%	29	39	51	66	88	118	162	227	331
15%	39	54	74	104	150	222	347	585	1115
20%	44	62	88	127	191	300	508	975	2358

Equal randomization, Type I error = 1-sided 2.5%, 90% power

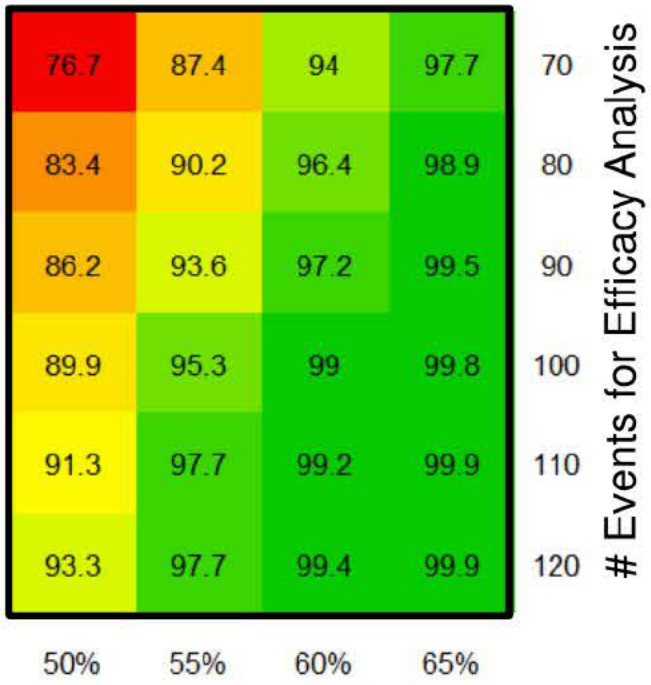
How long will it take to get the answer?

- Expected timing of analysis based on (i) sample size; (ii) underlying incidence; (iii) participant follow-up time; (iv) drop-out rate; and (v) study accrual rate

CLINICAL TRIAL SIMULATIONS INFORM PHASE 3 STUDY DESIGN

Point 1: # events needed to rigorously confirm vaccine efficacy against disease (VE(D)) depends on underlying true VE

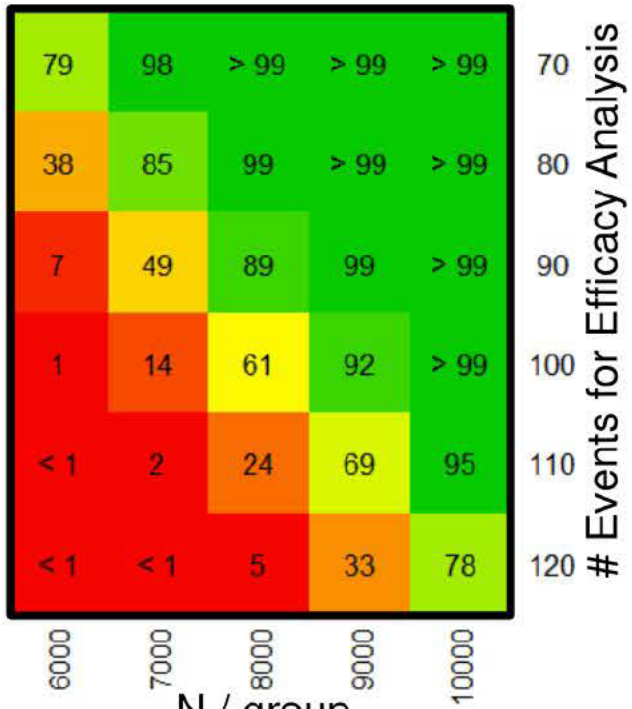
Probability of observing 95% CI LB for VE(D) > 0% in QFT-pos



- Probability of observing 95% CI LB for VE(D) > 0% in "all-comers" comparable to QFT-pos
- Increasing LB of CI for VE(D) from 0 to e.g., 15% significantly increases the # events required for Phase 3 success

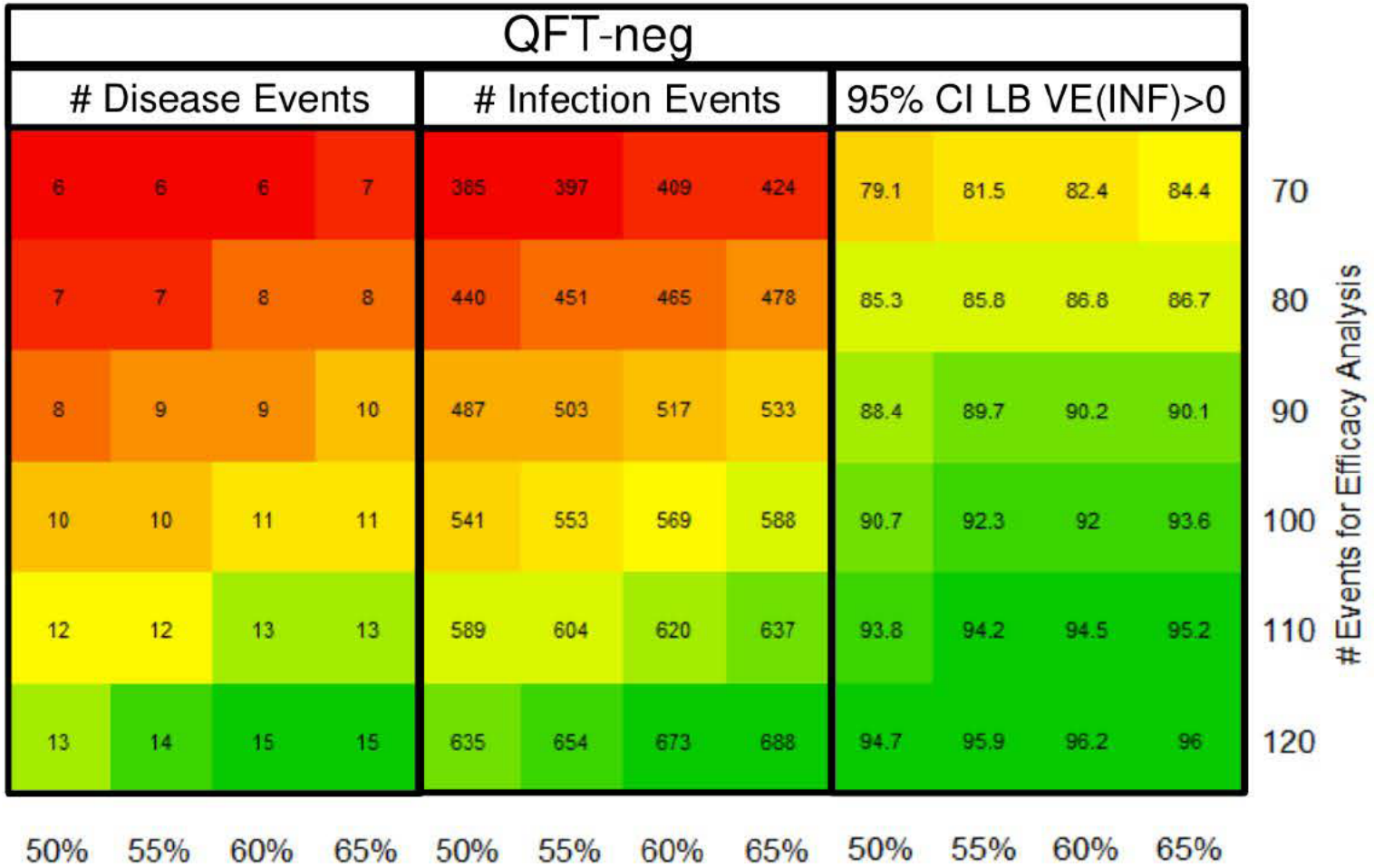
Point 2: High probability to accrue # events needed within 4 years of study start with 7000 – 10000 / group

Probability to perform analysis in ≤ 4 years



- Waiting an additional 6 months (e.g., to 4.5 years) increases probability to
- ≥ 80% for 100 events with N ≥ 7000 / group, 110 events with N ≥ 8000 / group, 120 events with ≥ 9000 / group

PHASE 3 TRIAL EXPECTATIONS: # OF EVENTS EXPECTED BY BASELINE QFT STATUS



Point 3: Limited power to assess VE(D) in QFT-neg participants due to low # of disease events expected

- Only ~10% of disease events expected to be from QFT-neg participants
- With 100 total disease events, expect over 500 infection events in QFT-neg participants
- With ≥ 90 - 100 total disease events, high probability to show 95% CI LB for VE(INF) > 0% [Assuming VE(INF) = 25% in QFT-neg]

M72/AS01$_E$ PHASE 3: NEXT STEPS

- Primary endpoint, case definition and trial design need thorough discussion with stakeholders, subject matter experts and LMIC national regulatory agencies
- TPT implementation & impact on trial design (inclusion of HHCs, IGRA-testing while on study) will need discussion
- Country selection prep has been initiated; epidemiology study to start late 2021 / early 2022
- Phase 3 study start anticipated in early 2023

WRAP-UP / CALL TO ACTION

- Gates MRI remains committed to accelerating the end of tuberculosis
- Developing effective vaccines is a cornerstone of this plan
  - / BCG REVAX
    - Results expected 2024
  - / M72/ASO1E
    - Efficacy study start expected in Q2 2023, interim VE data anticipated in 2028
    - Urgent need to define trial design & endpoints, trial population, participating countries & sites, and to prepare for recommendation should Phase 3 data be supportive
    - WHO participation in defining trial design is critical to the success of the program
    - Can PDVAC members participate in Phase 3 design & endpoint definition (SAB Q1 2021)?
    - Can PDVAC co-ordinate workstreams/stakeholders within WHO?
    - Is it possible to receive SAGE input prior to finalization of Phase 3 protocol? (Q2 2021)?

THANK YOU

	Draft Product Profile at First Registration	Draft Target Product Profile (life-cycle target)
Indication	Active immunization to prevent pulmonary TB disease	Active immunization to prevent pulmonary TB disease
Target Population	16-35 years of age: no restrictions	9 years of age and above; no restrictions
POD VE in QFT+ (LB)	50% (0%) at first submission 50% (15%) for recommendation	70%(25%)
POD VE in QFT- (LB)	0	50%
Duration of Protection	At least 3 years (median follow-up)	At least 10 years
Regimen	2 doses (10 µg) 4 weeks apart	2 doses (10 µg) 1 to 12 months apart
Indirect Protection	No data	Established
Safety	Acceptable safety profile	Acceptable safety profile
Presentation/formulation	Single dose vial for antigen and adjuvant respectively, needles not provided, bedside mix	Multi-dose in single vial
Vaccine Volume	0.5mL	0.5mL
Stability / Shelf Life	3 years at 2-8°C	3 years at 2-8°C
Special Populations: HIV+	No contraindication if on ART. Based on 2 years of safety data on >1,000 PLWH	Acceptable safety and efficacy, no contraindication
Special Populations: current or recent TB disease	Contraindication. No data available for TB on treatment. Very limited data available for people with incipient TB.	Acceptable safety profile based on post-licensure study
Special Populations	Safety established in adolescents 16 years and up	Safety & efficacy established in children >9 years

R&D Roadmap for tuberculosis vaccines

PDVAC meeting
17 June 2020

Frank Cobelens

Amsterdam Institute for Global Health and Development
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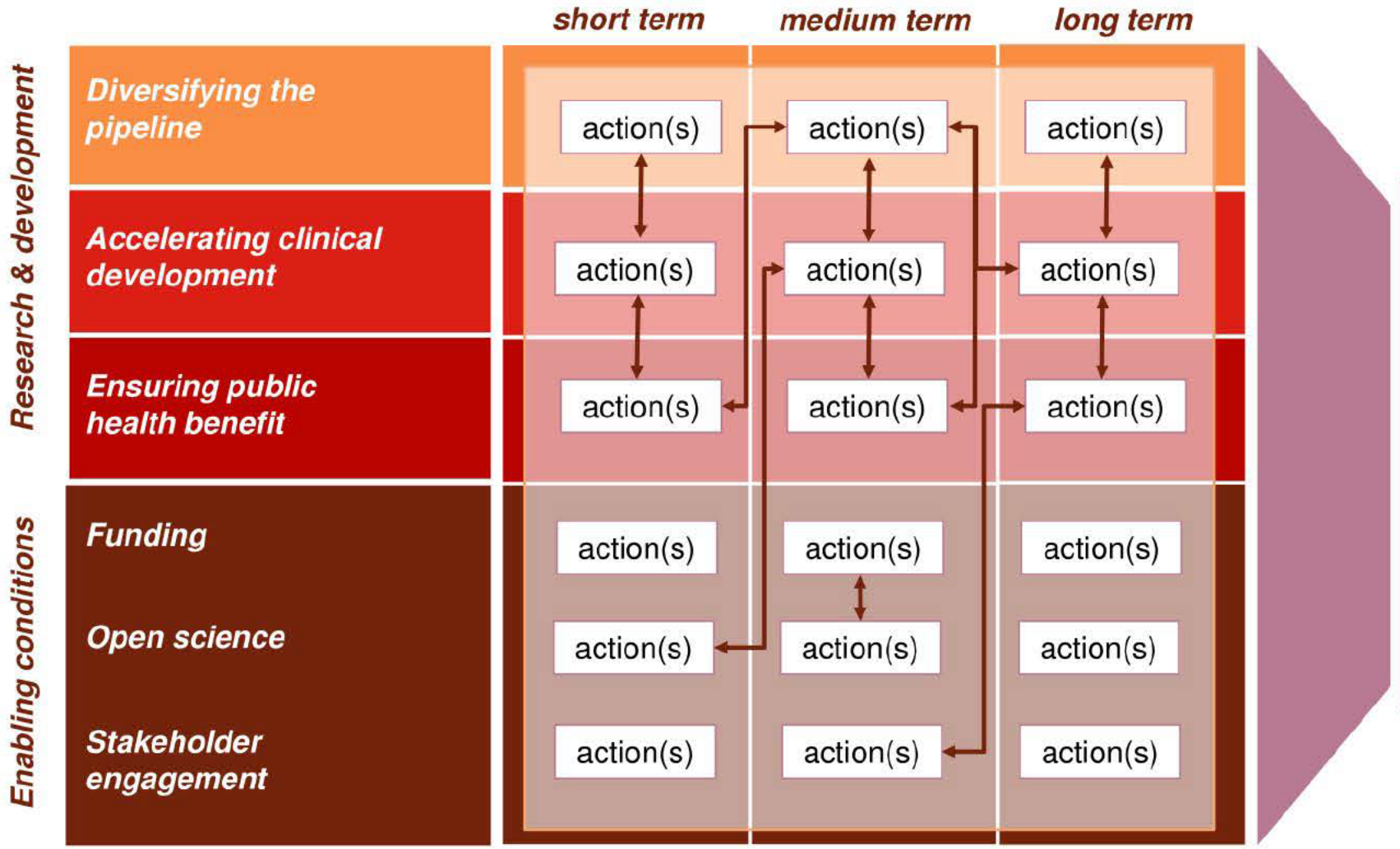
Purpose

European & Developing Countries Clinical Trials Partnership (EDCTP)
Clinical research to accelerate the development of new or improved drugs, vaccines, microbicides and diagnostics against poverty-related infectious diseases in sub-Saharan Africa

To develop a Global Roadmap for Research and Development for TB vaccines that:

- provides global stakeholders such as researchers, funders, industry, regulatory and policy decision makers with key actionable priorities that could help guide their actions.
- lists the short-term objectives and the long-term strategic objectives for global TB vaccine development.

Focus on developing and delivering affordable and effective vaccines for use in low- and middle-income countries.



Development goals (PPCs)

A safe, effective and affordable TB vaccine for adolescents and adults

An affordable TB vaccine for neonates and infants with improved safety and efficacy

A therapeutic vaccine to improve TB treatment outcomes

Process for roadmap development

Close collaboration with WHO to develop a Roadmap that has WHO's support

Roadmap development and consultation to follow WHO process:

- Consent workshop co-convened and co-organized with WHO (PDR & GTB)
- Review of draft AIGHD roadmap by PDVAC
- If draft roadmap is endorsed by PDVAC for co-authorship with WHO, draft will require public consultation in line with WHO processes
- Approval by relevant WHO bodies

Roadmap process

Stakeholders

Global policy bodies
National TB program managers/policy makers
National EPI managers/policy makers
Technical assistance agencies
Researchers involved in TB vaccine development
Modelers
Vaccine manufacturers
Regulators
Product Development Partnerships
Major research funders
Major donors of immunization and TB control
Advocacy & community representatives

Roadmap process

Oct-Dec 2019

Objectives

Get a comprehensive overview of the clinical development pipeline.
Elicit perspectives on the TB vaccine development goals
Define barriers to achieve those goals*
Define solutions to overcome these barriers*

**preclinical – clinical – post-licensure*

Stakeholders

Global policy bodies
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National EPI managers/policy makers
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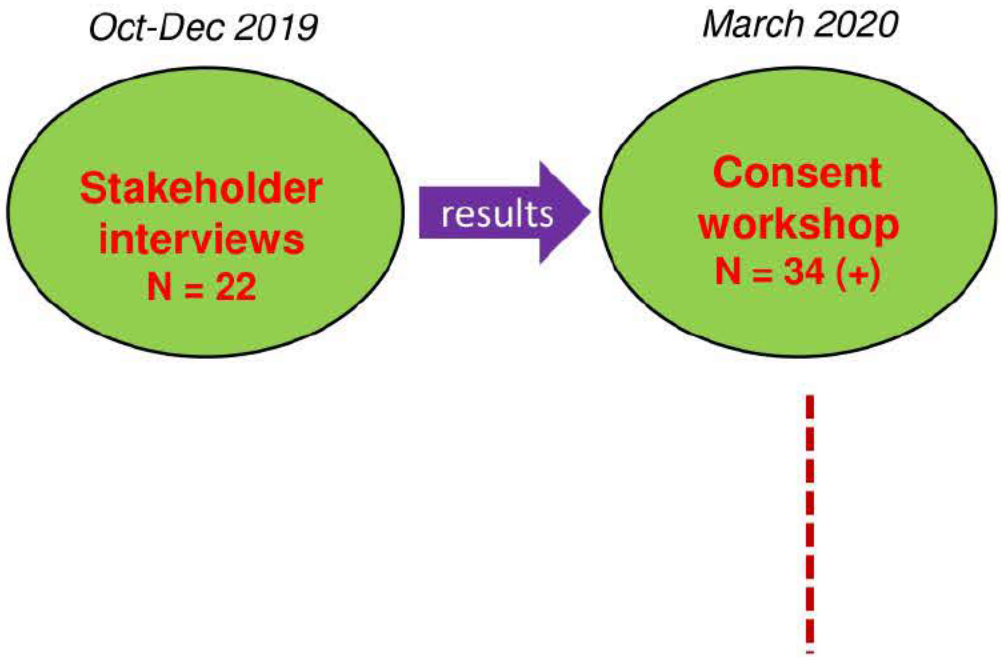
Roadmap process



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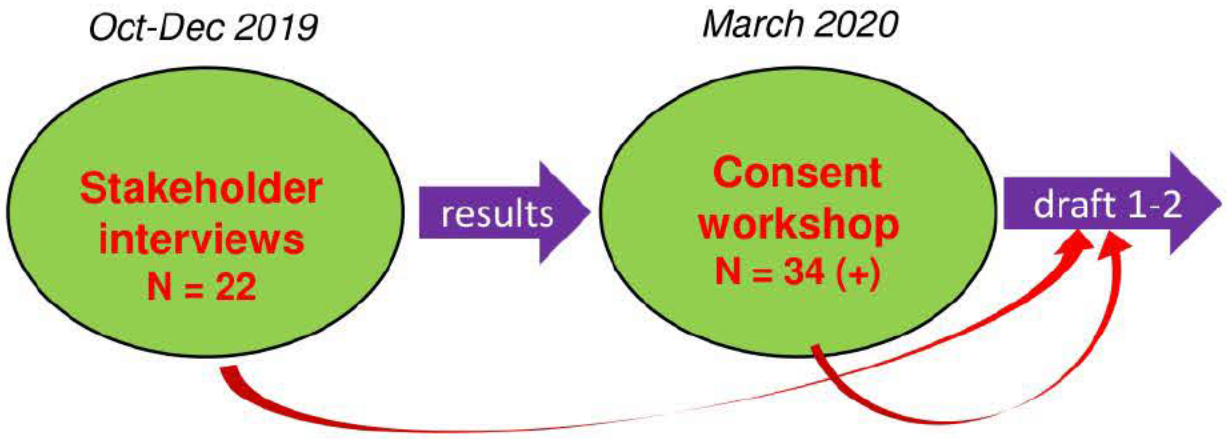
Researchers involved in TB vaccine development
Modelers
Vaccine manufacturers
Regulators
Product Development Partnerships
Major research funders
Major donors of immunization and TB control
Advocacy & community representatives

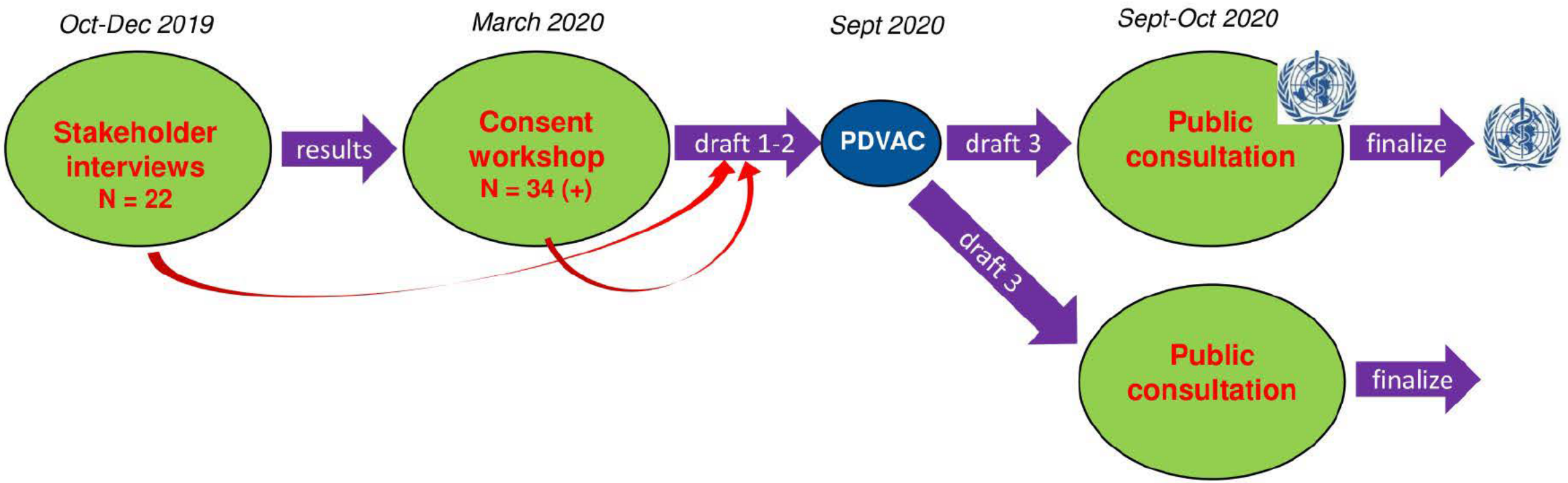
Objectives

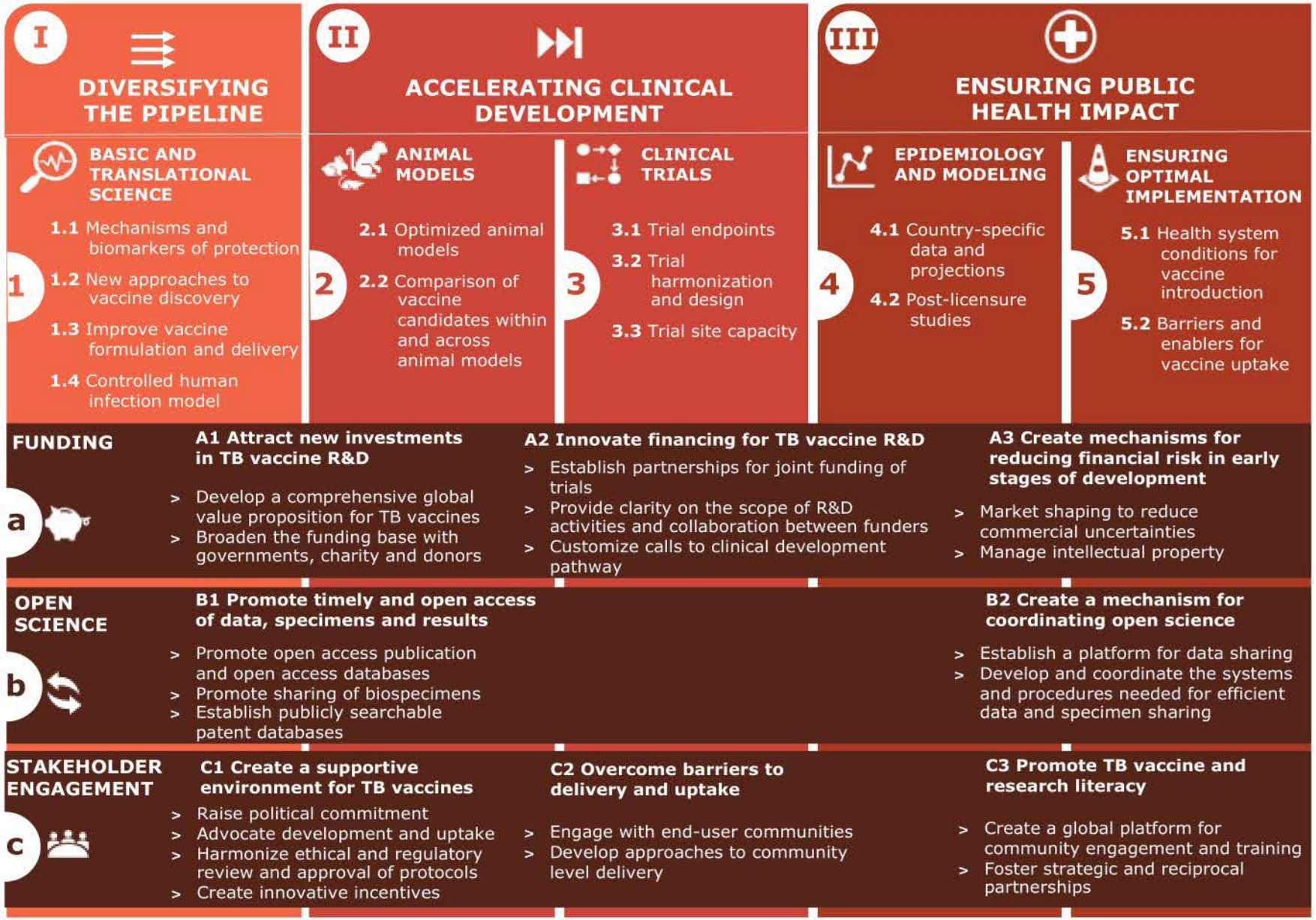
Clarify and specify the overall goals and key challenges of TB vaccine development
Define knowledge gaps and actions addressing the key challenges across the development pathway
Reach consensus about prioritization, interdependencies and timing of the actions
Define supportive conditions and next steps in the design of the TB R&D roadmap

Roadmap process



Roadmap process




I
DIVERSIFYING THE PIPELINE
II
ACCELERATING CLINICAL DEVELOPMENT
III
ENSURING PUBLIC HEALTH IMPACT
BASIC AND TRANSLATIONAL SCIENCE
1.1 Mechanisms and biomarkers of protection
1
1.2 New approaches to vaccine discovery
1.3 Improve vaccine formulation and delivery
1.4 Controlled human infection model
ANIMAL MODELS
2.1 Optimized animal models
2
2.2 Comparison of vaccine candidates within and across animal models
CLINICAL TRIALS
3.1 Trial endpoints
3
3.2 Trial harmonization and design
3.3 Trial site capacity
EPIDEMIOLOGY AND MODELING
4.1 Country-specific data and projections
4
4.2 Post-licensure studies
ENSURING OPTIMAL IMPLEMENTATION
5.1 Health system conditions for vaccine introduction
5
5.2 Barriers and enablers for vaccine uptake
FUNDING
a
A1 Attract new investments in TB vaccine R&D
> Develop a comprehensive global value proposition for TB vaccines
> Broaden the funding base with governments, charity and donors
A2 Innovate financing for TB vaccine R&D
> Establish partnerships for joint funding of trials
> Provide clarity on the scope of R&D activities and collaboration between funders
> Customize calls to clinical development pathway
A3 Create mechanisms for reducing financial risk in early stages of development
> Market shaping to reduce commercial uncertainties
> Manage intellectual property
OPEN SCIENCE
b
B1 Promote timely and open access of data, specimens and results
> Promote open access publication and open access databases
> Promote sharing of biospecimens
> Establish publicly searchable patent databases
B2 Create a mechanism for coordinating open science
> Establish a platform for data sharing
> Develop and coordinate the systems and procedures needed for efficient data and specimen sharing
STAKEHOLDER ENGAGEMENT
c
C1 Create a supportive environment for TB vaccines
> Raise political commitment
> Advocate development and uptake
> Harmonize ethical and regulatory review and approval of protocols
> Create innovative incentives
C2 Overcome barriers to delivery and uptake
> Engage with end-user communities
> Develop approaches to community level delivery
C3 Promote TB vaccine and research literacy
> Create a global platform for community engagement and training
> Foster strategic and reciprocal partnerships

Diversifying the pipeline –key barriers

- Relatively few candidates in preclinical and early clinical development
- Approach to vaccine development taken thus far is too narrow: emphasis on stimulating classical, CD4+ Th1 cells
- Only limited set of candidate TB antigens are currently considered: known Mtb virulence factors

Diversifying the pipeline – R&D actions

To further expand our knowledge of the human protective immune responses, identify biomarkers that correlate with protection and explore new approaches to TB vaccine discovery and vaccine delivery

1 BASIC AND TRANSLATIONAL SCIENCE

- **1.1** Mechanisms and biomarkers of protection
- **1.2** New approaches to vaccine discovery
- **1.3** Improve vaccine formulation and delivery
- **1.4** Controlled human infection model

- Conduct observational clinical studies combining pathogenesis and immunology
- Study the role of non-conventional, cellular immunity, antibody responses and trained innate immunity
- Identify biomarkers and biosignatures that correlate with vaccine-induced protection

- Develop new vaccine concepts that can induce alternative immune responses
- Study mucosal immune responses
- Deploy genome-wide strategies for antigen discovery

- Study the effects on vaccination outcomes of adjuvants, vaccine platforms and lineage of the Mtb challenge strain
- Explore new routes of vaccine administration
- Study how vaccines can direct immune responses to the lungs

- Develop a controlled human infection model for immunobiology studies

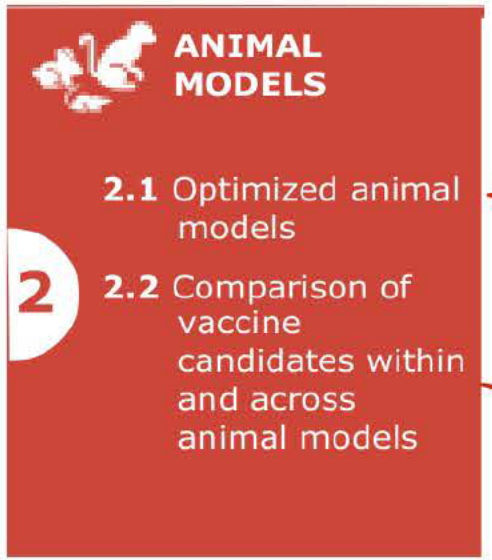
Accelerating clinical development –key barriers

- Lack of relevant, validated preclinical models that predict infection and disease in humans
  - limits effective stage gating/down-selection of candidates for clinical development

- Lack of evidence to support decisions to move a candidate forward through the clinical development pipeline
  - lack of agreed laboratory correlates of protection
  - necessitates large phase II/III trials of long duration with *prevention of disease* (PoD) as clinical efficacy endpoint
  - alternative efficacy endpoints for proof-of-principle: *prevention of infection* (PoI), *prevention of recurrence* (PoR)
    - but unknown to what extent PoI or PoR endpoints predict PoD

Accelerating clinical development (1)

To develop, optimize and use diverse "fit for purpose" animal models that can predict/replicate findings in humans



- Develop fit for purpose animal models
- Develop animal models to provide insight into the relation between *Prevention of Infection* and *Prevention of Disease*
- Develop immune compromised animal models that can predict/replicate findings in specific human target populations

- Standardize and harmonize animal models
- Perform head-to-head testing of candidate vaccines

Accelerating clinical development (2)

XYZ = *(partially) addressed in M72 & BCG revax clinical development program*

To develop, optimize and use diverse "fit for purpose" animal models that can predict/replicate findings in humans

CLINICAL TRIALS

3
- **3.1** Trial endpoints
- **3.2** Trial harmonization and design
- **3.3** Trial site capacity

- Define and develop standardized **PoD trial endpoints** that better capture the various TB disease states in diverse target populations
- Define and validate **correlates of protection** for TB disease
- Define and develop better **PoI trial endpoints**
- Quantify the clinical translation of PoI into PoD

- Harmonize clinical trial protocols
- Develop new models for TB vaccine trials with increased efficiency

- Make inventory of **clinical trial site capacity**
- Collect **epidemiological data in sites** considered for phase II/III trials
- Develop **vaccine trial sites**
- Study potential barriers to trial acceptance
- Promote community engagement in TB vaccine trials

Ensuring public health benefit –key barriers/needs

➢ Need to understand countries' likely demand for a new TB vaccine and associated considerations when added to their national immunization programmes (*value proposition*)

  ➢ Especially for vaccine to be used in adults and adolescents

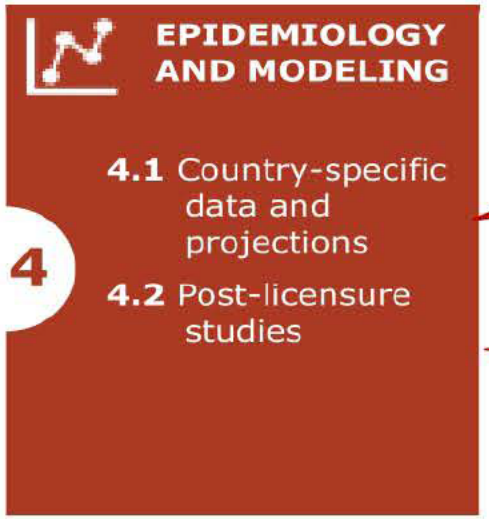
➢ Need for evidence on how to integrate vaccine implementation with ongoing TB prevention efforts and how to use the vaccine among vulnerable groups

  ➢ Need to understand most (cost-)effective use

➢ Need for estimating the national and global demand to stimulate manufacturers to enter into the market and prepare and scale-up vaccine production

Ensuring public health benefit (1)

To quantify key epidemiological and health economic metrics to support vaccine introduction, and evaluate vaccine effectiveness and impact post-licensure

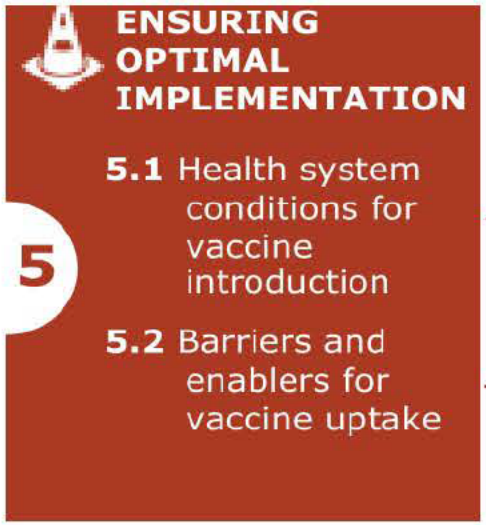


- Conduct in-depth country-specific value proposition analyses
- Collect epidemiological data at country and subnational level
- Modelling to define vaccine development investment cases and potential country-specific vaccine use cases

- Develop valid approaches for real-life vaccine scale-up studies
- Conduct post-licensure evaluations of vaccine effectiveness, impact and safety

Ensuring public health benefit (2)

To understand user preferences and implementation needs for new TB vaccines



- Define the generic public health system requirements to deliver a new TB vaccine
- Conduct pre-introduction assessments of country immunization programmes

- Assess drivers of acceptability and uptake of new TB vaccines in various settings

Key enabling conditions: funding

FUNDING

a 

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Key enabling conditions: open science

Key enabling conditions: stakeholder engagement

STAKEHOLDER ENGAGEMENT

C 

C1 Create a supportive environment for TB vaccines

- Raise political commitment
- Advocate development and uptake
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- Create a global platform for community engagement and training
- Foster strategic and reciprocal partnerships

This project is part of the EDCTP2 programme. The EDCTP programme is supported under Horizon 2020, the European Union's Framework Programme for Research and Innovation

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Johan Vekemans
Matteo Zignol

The EDCTP2 programme is supported by the European Union's Horizon 2020 research and innovation programme

PDVAC session on TB vaccines

Current and future evidence on TB vaccines from mathematical and economic modelling

(b) (6)

and many, many others

2020_09_03

Overview

Objectives

- Summarize overall modelling evidence
- Summarize v prelim M72/AS01 and BCG re-vx modelling evidence
- Summarize WHO-funded, Full Value Assessment of TB Vaccines project
- Summarize BMGF-funded, M72/AS01 and BCG revaccination specific modelling project

Outcomes

- PDVAC qus, and advice on what, if any, high priority follow-up work
- PDVAC qus, and advice on if and how could be more useful to global and country stakeholders

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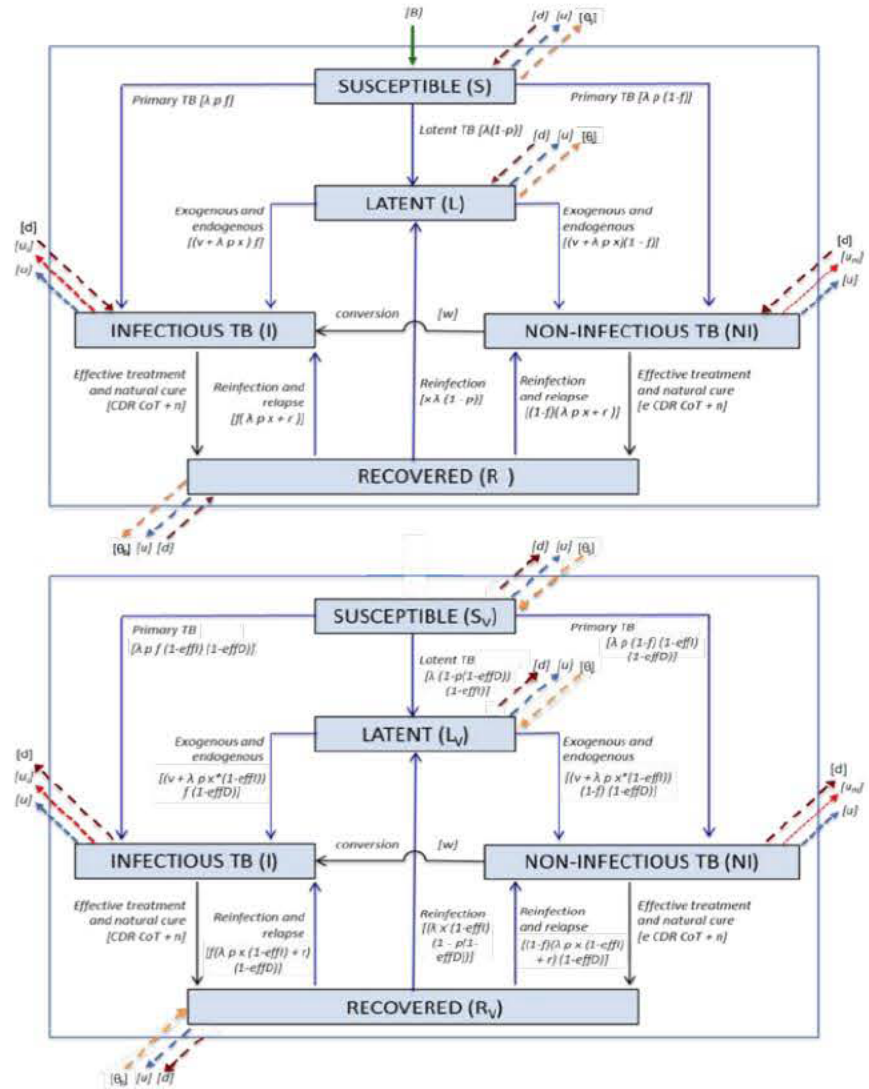
Informing strategic TB vaccine development

- Vaccines fit for purpose and maximise future population-level epidemiological impact
- Mathematical modelling as a logical framework
  - Project impact of potential vaccine characteristics and implementation strategies to guide TPP/PPCs
  - Based upon clinical trial data, estimate potential future epidemiological impact to guide decision making

In the context of a busy pipeline and new trial results – use mathematical modelling to inform strategic TB vaccine development



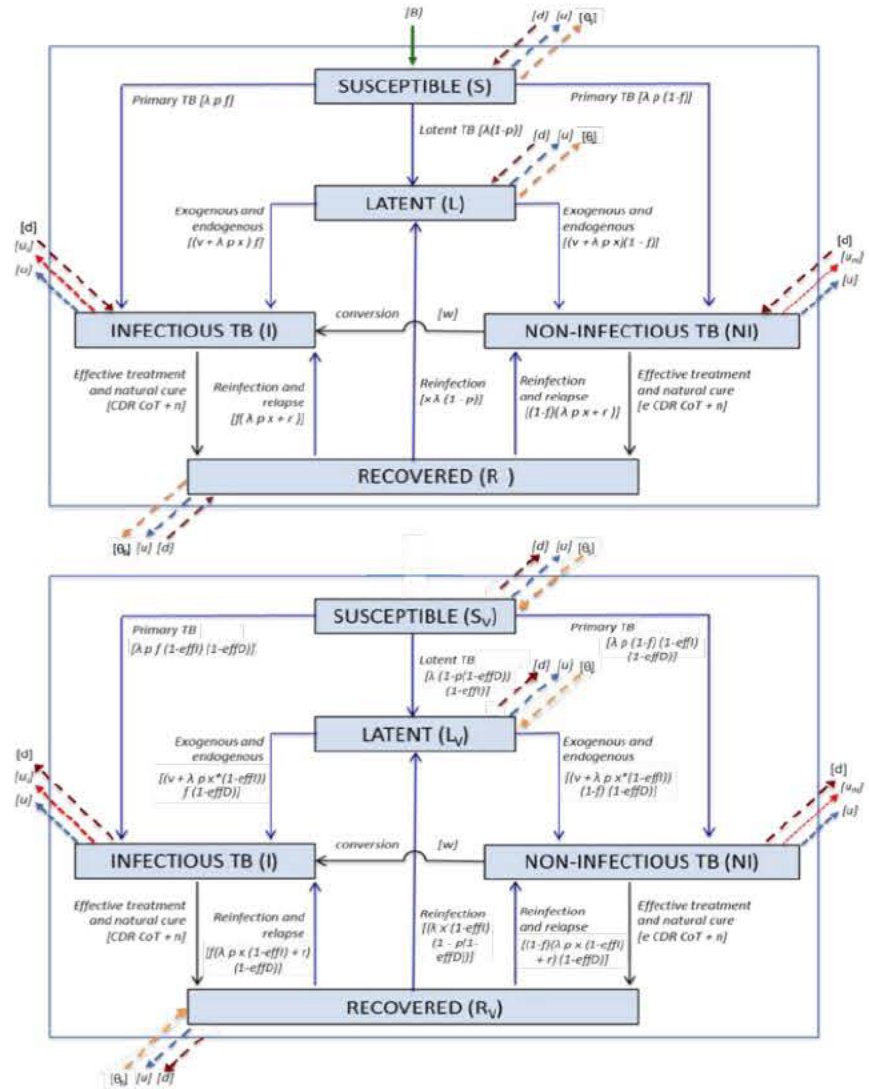
Informing strategic TB vaccine development

- Vaccines fit for purpose and maximise future population-level epidemiological impact
- Mathematical modelling as a logical framework
  - Project impact of potential vaccine characteristics and implementation strategies to guide TPP/PPCs
  - Based upon clinical trial data, estimate potential future epidemiological impact to guide decision making

Systematic review (Harris et al. 2016) summarising 23 studies

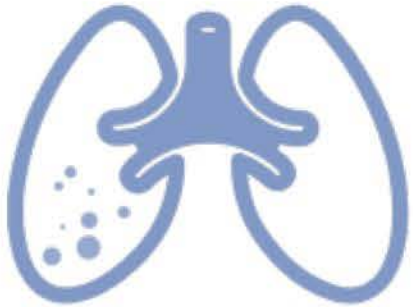
\+ 4 studies published since the review (Liu, Arregui, Harris, Renardy)

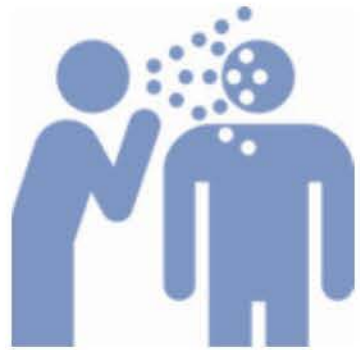
\+ 2 unpublished studies

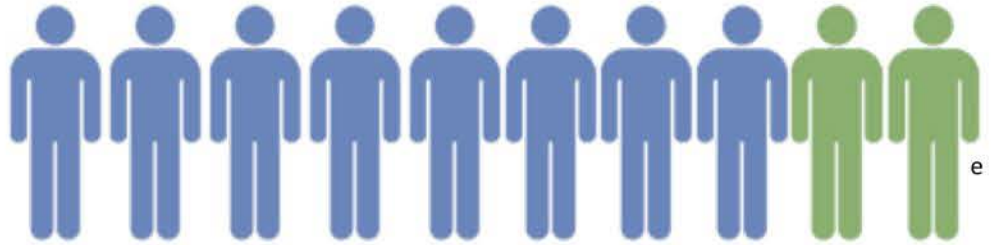


Vaccine characteristics

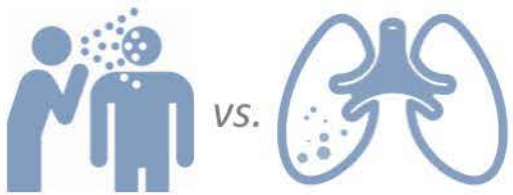
vs.







Summary of lit. and generic candidate modelling 1/3



Over 2025-50

Prevention of infection (POI) versus prevention of disease (POD)

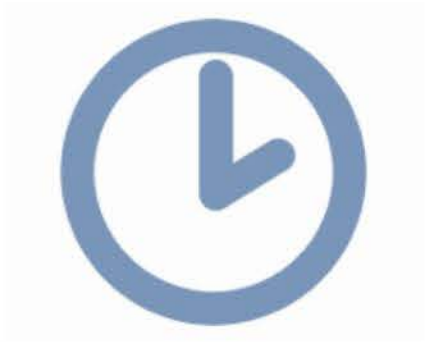
- Globally, **prevention of disease** vaccines would provide **faster and greater impact** than prevention of infection, but
- Impact of **prevention of infection vaccine increases in higher transmission settings,** eg India & SA

Pre- versus post-infection

- In China, South Africa and India, a vaccine efficacious for **prevention of disease** in **post-infection** populations would have **greatest impact**, but
- Vaccines efficacious for prevention **of infection or disease in pre-infection** populations, **had increasing impact** in **higher transmission settings** eg India & SA

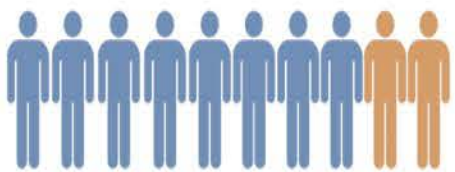
Harris 2016, 2019, in press, Shrestha 2016, Lui 2017, Arregui 2017, Shrestha 2017

Summary of lit. and generic candidate modelling 2/3



Over 2025-50

- Duration of protection
  - In LMICs, as little as **5 years protection may be cost effective** if targeted at adolescents and adults
  - With 10-yearly mass campaigns, and 50% VE, duration of protection around 5 years in China, 4 years in S Africa and 3 years in India could lead to **~25% reduction in TB incidence in 2050**



- Vaccine efficacy
  - In LMICs, as low as **20% VE could be cost effective** if delivered to adolescents/adults

Harris 2016, 2019, in press, Shrestha 2016, Lui 2017, Arregui 2017, Shrestha 2017

Summary of lit. and generic candidate modelling 3/3

Over 2025-50

- Age
  - In LMICs, **adolescent and adult** vaccination may deliver **greater and faster** impact than infant vaccination
  - To reduce TB in 0-4 year olds, **vaccination of adolescents/adults may be more effective than vaccinating neonates directly**
  - Vaccines suitable for latently infected **older adults** (>60 years) **may provide greater impact than adolescent vaccination** in ageing, reactivation driven epidemics, such as China

- HIV
  - Population-level impact in S Africa would be **higher** with a vaccine **safe and effective in HIV** positive populations.

Harris 2016, 2019, in press, Shrestha 2016, Lui 2017, Arregui 2017, Shrestha 2017

Implications for vaccine development 1/2

Recruitment populations

- If maximum population-level impact by 2050 is the goal, **development of vaccines for adolescents/adults should be prioritized**
  - China - inclusion of older adults in clinical trials (at least 60-64 years)
- **Post-infection** populations in all settings
- **Pre-infection** populations should also, or instead, be recruited in **higher transmission** settings (India & SA)
- Ideally, if feasible, trials should be powered to assess efficacy in both populations
- If vaccine safe, **HIV-positive** populations should be recruited

Implications for vaccine development 2/2

Endpoints

- In all settings, **disease** endpoints would be useful for demonstrating future impact
- However, in **higher transmission** settings (India & SA) **infection** endpoints could be used, especially as proof of concept
- Vaccine efficacy – assess feasibility of designing trials to **detect lower vaccine efficacies**

Study duration

- Studies would benefit from **extended follow up** to 5+ years (e.g. immuno subgroup)
  - But short duration vaccines may be impactful and cost-effective

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Outcomes

- PDVAC qus, and advice on what, if any, high priority follow-up work
- PDVAC qus, and advice on if and how could be more useful to global and country stakeholders

Summary of BCG revac and M72 '-like' impact modelling

- If efficacy signals are confirmed, both vaccines could deliver substantial population-level impact
- To maximise value proposition
  - For BCG revaccination
    - explore whether has prevention of disease efficacy
  - For M72/AS01E
    - explore duration of protection, or feasibility of mass campaigns
    - explore pre-infection efficacy, and prevention of infection

Vaccine	POI/POD*	Pre-/post-infection	Vaccine efficacy	Duration of protection**	HIV indication	Incidence rate reduction in 2050		
						China	South Africa	India
Assumed BCG revaccination			50%	10 years	Contraindicated	16% (13-[illegible]%)	22% (16-[illegible]%)	39% (32-[illegible]%)
						21% (17-[illegible]%)	32% (23-[illegible]%)	52% (44-[illegible]%)
Assumed M72/AS01E			[illegible]%	2 years	Indicated but assumed [illegible]% relative efficacy reduction	3% (2-[illegible]%)	4% (1-7[illegible])	7% (5-1[illegible]%)
				10 years (or more frequent mass vaccination)		37% (3[illegible]-[illegible]%)	34% (25-[illegible]%)	41% (32-[illegible]%)
						50% (47-[illegible]%)	59% (49-[illegible]%)	73% (68-[illegible]%)

* Assumed POI vaccine efficacy same, regardless of the likelihood of progression to disease upon infection

** Assuming routine vaccination of 9 year olds and 10 yearly mass campaigns of adults

Harris et al., in press, Science Trans Med

Summary of preliminary CE for M72/AS01E 1/2

VACCINE CHARACTERISTICS

POD

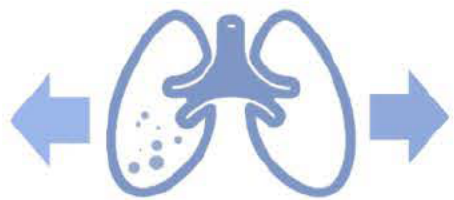
50% VE

15 years

POPULATION

South Africa
India

Safe and equally effective

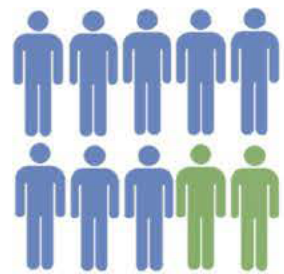


Post-infection OR pre&post-infection

VACCINE DEPLOYMENT

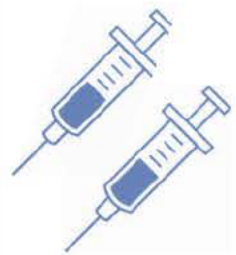
2025-2050

Routine for 10 or 15 year olds



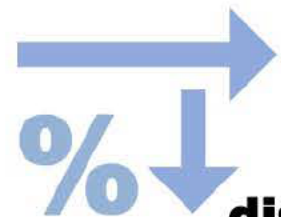
80% coverage

VACCINE COSTS



2 doses

$5/course (vaccine & delivery)



3% discounting

Harris et al unpublished

Summary of preliminary CE for M72/AS01E 2/2

- The incremental cost per DALY averted: (discounted 2025-50, incl vaccine and TB treatment costs)
  - In **South Africa**, ranged from
    - $24 (2- 66) for a pre- and post-infection vaccine delivered to 10 year olds, to
    - $316 (182 - 636) for a post infection vaccine delivered to 15 year olds
    - **All scenarios explored were cost effective** when compared to the latest (conservative) 'revealed' willingness to pay threshold of $547/life year saved [Meyer-Rath PLoS ONE 2017]
  - In **India**, ranged from
    - $143 (43-337) for a pre- and post-infection vaccine delivered to 10 year olds, to
    - $1,660 (718-4,246) for a post infection vaccine delivered to 15 year olds
    - **Using GDP per capita threshold of 1,939 (2017) in India, all scenarios are cost effective**
    - **However, a local preliminary analysis of opportunity costs** gave a lower bound for a WTP threshold of $223 (Ochalek, CHE working paper 2019) => **a post infection only vaccine delivered to 15 year olds may not be cost effective**
- **A M72-like vaccine could be cost effective in both settings, depending on WTP**

Overview

Objectives

- Summarize overall modelling evidence
- Summarize v prelim M72/AS01 and BCG re-vx modelling evidence
- **Summarize WHO-funded, Full Value Assessment of TB Vaccines project**
- Summarize BMGF-funded, M72/AS01 and BCG revaccination specific modelling project

Outcomes

- PDVAC qus, and advice on what, if any, high priority follow-up work
- PDVAC qus, and advice on if and how could be more useful to global and country stakeholders

Full value assessment of TB vaccines (WHO)

...

Full value assessment of TB vaccines in all LMICs and individually in BRICS

WHO

Method

- Data collation
- Epi & econ modelling (HS & societal)
- WHO PPCs (incl. M72/AS01 & BCG reVx)

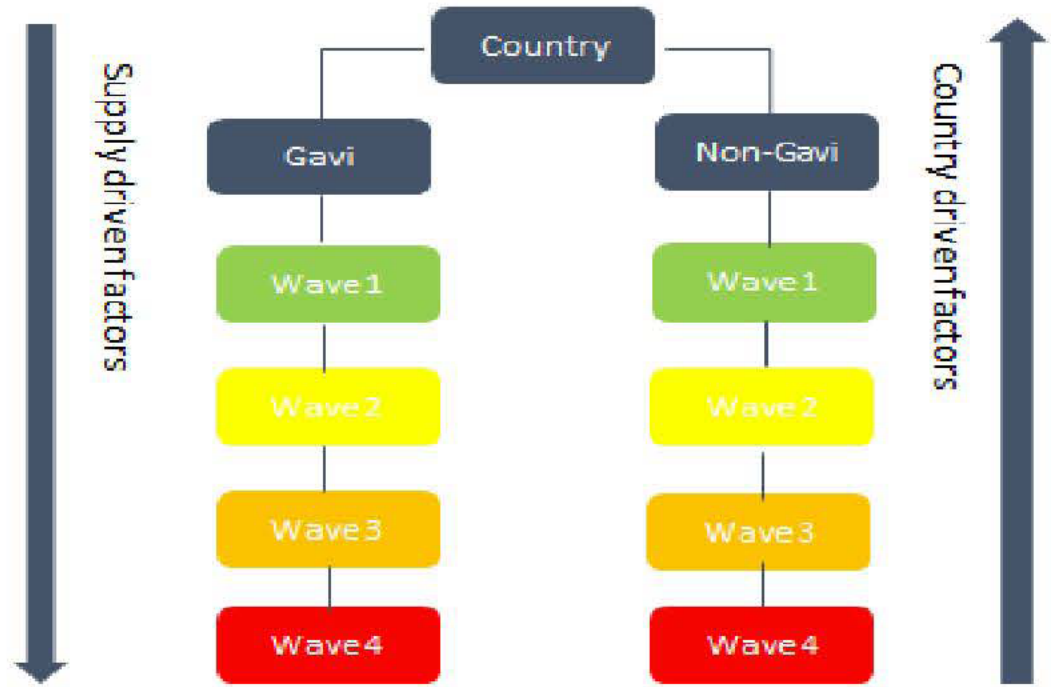
- Impact on
  - TB inci, morb & mort, by DS/DR/HIV & GAVI/ WHO reg
  - Costs, CE, budget impact
  - ROI, equity, GDP, AMR drug use

- Country and global decision makers
- Funders

	2021												2022											
	9	10	11	12	1	2	3	4	5	6	7	8	9	10	11	12	1	2	3	4	5	6	7	8	9	10	11
Full value assessment of TB vaccines (WHO)																											
M72 & BCG revax impact and CE (BMGF)																											
Introduction and implementation data collection																											

Introduction Timelines: Proposed Approach

- Countries will be archetyped according to Gavi vs non-Gavi status
- Countries will be grouped into Waves of introduction (1, 2, 3, 4)
- Criteria for grouping into Waves & for date of introduction will include:
  - *Supply driven factors:*
    - Supplier prioritization, Gavi & procurement agency criteria & processes
  - *Country driven factors:*
    - Demand, political will, health systems readiness, regulatory timelines



	2021																2022										
	9	10	11	12	1	2	3	4	5	6	7	8	9	10	11	12	1	2	3	4	5	6	7	8	9	10	11
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- PDVAC qus, and advice on if and how could be more useful to global and country stakeholders

Epi & econ impact of M72/AS01 and BCG reVx (BMGF)

...

Epi & econ impact of M72 and BCG reVx in South Africa & India

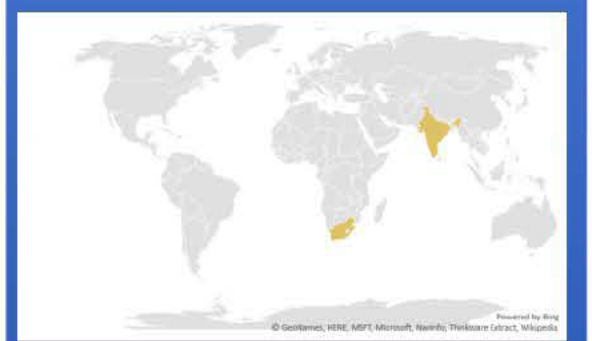
Decision Science Framework: Uncert/VOI in

1. Product characteristics
   - Dur, POD/I, PRI/PSI, VE by HIV and repeat
2. Intro policy and implementation
   - Product, rout/mass/repeat, HIV/ART
   - Timing BCG – quick SA vs >POI vs >POD
   - Timing M72 – quick SA vs >glob Ph3 POD
3. Health system performance
   - no change, policy, new tools
4. Value
   - HS vs societal/thresholds

BMGF

Method

- Data collation
- Epi & econ modelling M72 & BCG ReVx
- POI & POD; PRI & PSI



- Impact on
  - TB inci, morb & mort, by DS/DR/HIV
  - CE and budget impact
- India nat and sub national

- BMGF

	2021													2022											
	9	10	11	12	1	2	3	4	5	6	7	8	9	10	11	12	1	2	3	4	5	6	7	8	9	10	11
Full value assessment of TB vaccines (WHO)																											
M72 & BCG revax impact and CE (BMGF)																											
Introduction and implementation data collection																											

M72/AS01 & BCG reVx implementation strategy interviews in S Africa, India (and China)

Mixed methods

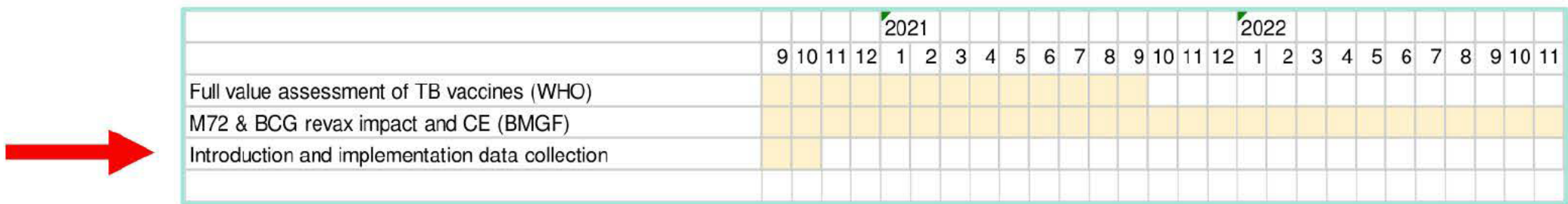
- quantitative and qualitative results
- quantitative indicators of implementation strategies
- qualitative: acceptability, challenges and solutions

Semi-structured interviews to investigate:

- implementation scenarios
- associated costs
- context-specific challenges to adolescent/adult TB vaccine implementation

Study population

- Interviewees are 8 decision makers/stakeholders per country



New Epi/Econ model for the TB Vaccine field

In discussion with both funders, decided to **create new future-proofed model**, rather than adapt old ones…

Scientific and technical benefits

- **Incorporate new natural history insights** in vaccine impact estimates, eg self clear
- Estimate impact of **combinations** of protection from **multiple vaccines and natural immunity**
  - Eg natural + BCG revx + M72
- Very **flexible**

Should be able to **address stakeholder questions for next 5-10 years…**

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Outcomes

- **PDVAC qus, and advice on what, if any, high priority follow-up work**
- **PDVAC qus, and advice on if and how could be more useful to global and country stakeholders**

Acknowledgements and Thanks! (incomplete)

Contributors/Advisors:

- WHO (Gitte Giersing, Johan Vekemans)
- IAVI (Derek Tait, Shelly Malhotra)
- BMGF (Willem Hanekom, Anne Kasmar, Geoff Garnett, Ann Ginsburg)
- TBVI (Bernard Fritzell, Nick Drager)
- India (Kieran Rade, Raguram Rao)
- China (Li Tao and Lixia Wang)
- South Africa (Mark Hatherill, Michele Tamaris)
- Aeras (Tom Evans, Vicky Cardenas, Danny Casimiro, Chen Chen, Sharon Chan)

Funders:

Questions for PDVAC

World Health Organization

- Are there critical activities that would benefit from PDR/PDVAC leadership and engagement, either related to M72/AS01 and BCG revaccination specifically, or enabling TB vaccine development more generally?
- Does PDVAC have recommendations on the draft TB vaccine roadmap?
- Does PDVAC support WHO co-authorship of the roadmap?
- Are there any recommendations for high priority follow up work to the WHO-funded Full Value Assessment of TB Vaccines project
- Are there suggestions with respect to how the BMGF-funded M72/AS01 and BCG revaccination modelling project could be more useful to global and country stakeholders

From: GIERSING, Birgitte
Sent: Wed, 2 Sep 2020 21:31:21 +0000
To: Graham, Barney (NIH/VRC) [E];Sinead Delany-Moretlwe;Bernard Fritzell;(SPmig) Shabir Madhi;Karron, Ruth;klaus.cichutek;Marian Wentworth;Papania, Mark (CDC/DDPHSIS/CGH/GID);Yshao;Jerome Kim;Peter Smith;Claudio Lanata (b) (6);dracravioto;Kaslow, David;Bekeredjian-Ding, Isabelle;Gagandeep Kang
Cc: SPARROW, Erin Grace;Pabillon-Green, Karen;FRIEDE, Martin Howell;Isabel Frost
Subject: Draft slide deck: PDVAC virtual session on TB
Attachments: Consolidated DRAFT PDVAC TB Sept 2020.pdf

Dear PDVAC members,
Please find attached the DRAFT slides for the meeting tomorrow. The modelling slides still need some tidying up, and I need to add my overview slides – final deck to follow in the morning.
Best,
Gitte

From: GIERSING, Birgitte
Sent: 02 September 2020 23:17
To: SPARROW, Erin Grace (b) (6); Graham, Barney (NIH/VRC) [E] (b) (6); Sinead Delany-Moretlwe (b) (6); Bernard Fritzell (b) (6); (SPmig) Shabir Madhi (b) (6); Karron, Ruth (b) (6); klaus.cichutek (b) (6); G Kang (b) (6); Marian Wentworth (b) (6); Papania, Mark (CDC/DDPHSIS/CGH/GID) (b) (6); Yshao (b) (6); Jerome Kim (b) (6); Peter Smith (b) (6); Claudio Lanata (b) (6) (b) (6); dracravioto (b) (6); Kaslow, David (b) (6); GRIFFIN, Geraldine Margaret (b) (6); Pabillon-Green, Karen (b) (6); Bekeredjian-Ding, Isabelle (b) (6); FRIEDE, Martin Howell (b) (6); (b) (6); (b) (6); Gagandeep Kang (b) (6); GEBRESELASSIE, Nebiat (b) (6); Frank Cobelens (b) (6); Alexander Schmidt (b) (6); Taryn Rogalski-Salter (b) (6); Ann Ginsberg (b) (6); Richard White (b) (6); (b) (6); Mark Hatherill (b) (6); Helinski, Michelle (b) (6); Deepali Patel (b) (6); FALZON, Dennis (b) (6); ZIGNOL, Matteo (b) (6); (b) (6); Isabel Frost (b) (6); Nicola Viebig (b) (6); (b) (6); (b) (6); (b) (6)
Subject: Logistics: PDVAC virtual session on TB

Dear all,

We're looking forward to the PDVAC session on TB vaccine development tomorrow. Please find the final agenda and list of participants attached.

We have a very full agenda, so **please read the following to help us manage the meeting effectively** by zoom (dial in details below):

- When entering the call, you will be in a waiting room until we admit you onto the call. Please dial in a couple of minutes early if possible to help us co-ordinate this.
- Apologies but there will not be the opportunity for everyone to introduce themselves. We plan to start promptly at 3pm Geneva, and will do one roll call. We will not be able to announce you if join the call after this initial roll call.
- Everyone will be muted upon entering the call. Please raise your hand or use the chat function if you'd like to speak outside of requests for comments/questions from the chair.
- The meeting will be recorded to assist with drafting the minutes.
- At the end of the meeting (5pm Geneva), all participants apart from the PDVAC committee will be asked to disconnect for the closed session.

All the best,
Gitte

-----Original Appointment-----
From: SPARROW, Erin Grace (b) (6)
Sent: 01 July 2020 12:03
To: SPARROW, Erin Grace; Graham, Barney (NIH/VRC) [E]; Sinead Delany-Moretlwe; Bernard Fritzell; (SPmig) Shabir Madhi; Karron, Ruth; klaus.cichutek; G Kang; Marian Wentworth; Papania, Mark (CDC/DDPHSIS/CGH/GID); Yshao; Jerome Kim; Peter Smith; Claudio Lanata; (b) (6) dracravioto; Kaslow, David; GIERSING, Birgitte; GRIFFIN, Geraldine Margaret; Pabillon-Green, Karen; Bekeredjian-Ding, Isabelle; FRIEDE, Martin Howell; (b) (6) (b) (6)
Cc: GEBRESELASSIE, Nebiat; Frank Cobelens; Alexander Schmidt; Taryn Rogalski-Salter; Ann Ginsberg; Richard White; (b) (6); Mark Hatherill; Helinski, Michelle; Deepali Patel; Gagandeep Kang; FALZON, Dennis; ZIGNOL, Matteo; (b) (6); Isabel Frost; Nicola Viebig; (b) (6); (b) (6); (b) (6)
Subject: Confirmed: PDVAC virtual session on TB
When: 03 September 2020 15:00-17:30 (UTC+01:00) Amsterdam, Berlin, Bern, Rome, Stockholm, Vienna.
Where:

Dear All,

Please find the zoom details for the PDVAC session on TB vaccines below and attached the agenda and list of participants. Please note that the final 30 minutes will be a closed discussion for PDVAC members only.

Topic: PDVAC virtual session 3 September - TB vaccines
Time: Sep 3, 2020 03:00 PM Zurich

Join Zoom Meeting
https://zoom.us/j (b) (6) ?pwd=czk0YlpDd2NjMW5ybm91QzdQb1RMUT09

Meeting ID: (b) (6)
Passcode: (b) (6)

Find your local number: https://zoom.us/u/acQreLzV6E

Thanks,
Erin

Questions for PDVAC

- Are there critical activities that would benefit from PDR/PDVAC leadership and engagement, either related to M72/AS01 and BCG revaccination specifically, or enabling TB vaccine development more generally?
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BILL & MELINDA GATES MEDICAL RESEARCH INSTITUTE

Update on Gates MRI TB Vaccine Development Activities

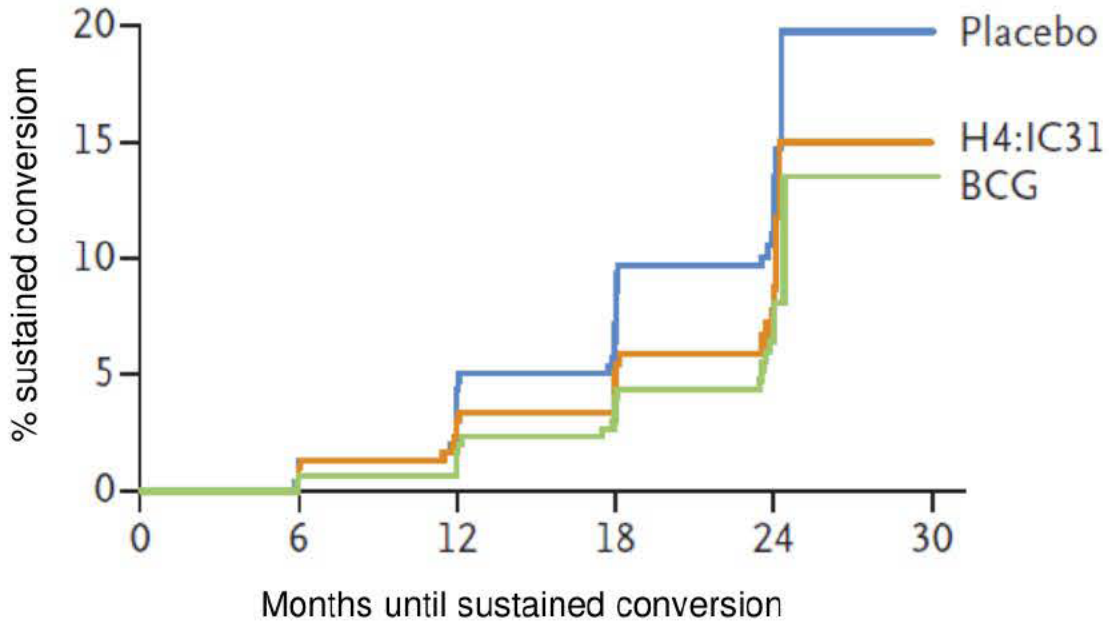
Alexander Schmidt, Taryn Rogalski-Salter,
Robin Mogg, Nicole Frahm & Marie Green

PDVAC, September 3, 2020

GATES MRI BCG REVACCINATION STUDY

AERAS C-040-404 STUDY

- N=990, 1:1:1, primary endpoint: initial QFT-conversion, secondary EP: sustained QFT-conversion
- BCG: 45% (95%CI 6.4-68.1%) vaccine efficacy for sustained QFT conversion



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Prevention of *M. tuberculosis* Infection with H4:IC31 Vaccine or BCG Revaccination

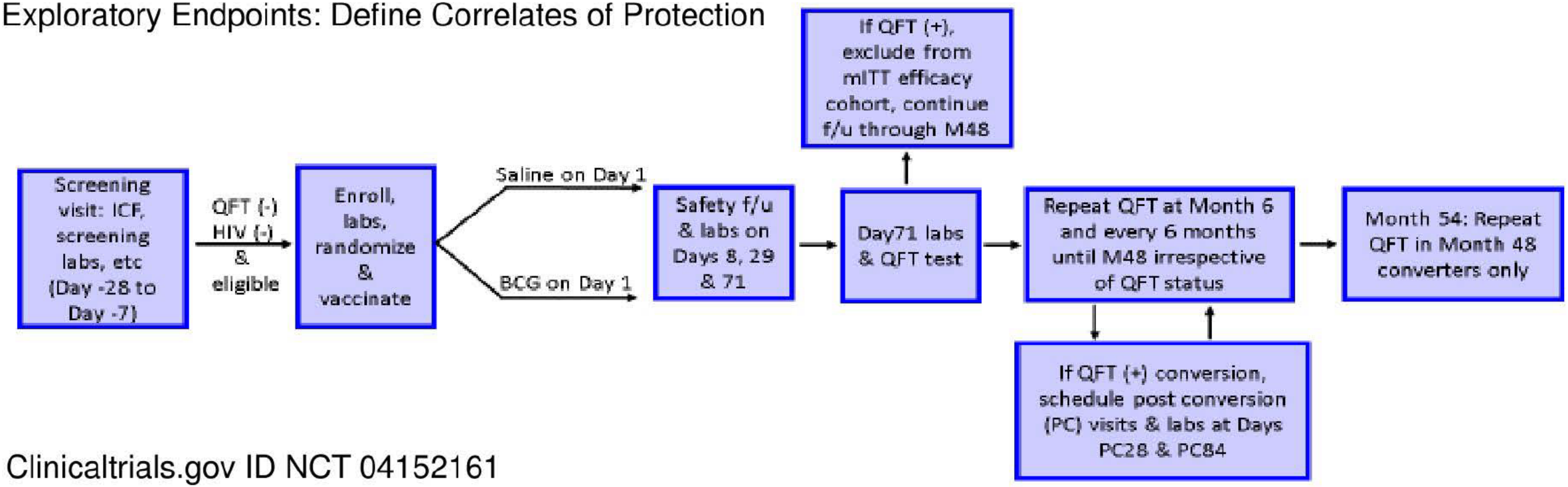
E. Nemes, H. Geldenhuys, V. Rozot, K.T. Rutkowski, F. Ratangee, N. Bilek, S. Mabwe, L. Makhethe, M. Erasmus, A. Toefy, H. Mulenga, W.A. Hanekom, S.G. Self, L.-G. Bekker, R. Ryall,* S. Gurunathan, C.A. DiazGranados, P. Andersen, I. Kromann, T. Evans, R.D. Ellis, B. Landry, D.A. Hokey, R. Hopkins, A.M. Ginsberg, T.J. Scriba, and M. Hatherill, for the C-040-404 Study Team†

DOI: 10.1056/NEJMoa1714021

GATES MRI BCG ReVax STUDY

Goal: generate data that can potentially support policy changes for BCG revaccination

- Randomized, placebo controlled, observer-blind, Phase 2b study with two arms (BCG vaccine and saline placebo)
- 1,800 QFT-negative participants 10-18 years of age are randomized 1:1 to receive a single intradermal injection
- Primary Endpoint: Sustained QFT conversion (initial conversion and IGRA positive 3 & 6 months thereafter)
- Exploratory Endpoints: Define Correlates of Protection



Clinicaltrials.gov ID NCT 04152161

alexander.schmidt@gatesmri.org

BCG ReVax STUDY STATUS

- Five sites in South Africa (SATVI, CAPRISA, Wits RHI, Desmond Tutu HRF, Be Part)
- First participant randomized November 6, 2019
- Screening and randomization paused due to COVID-19-related restrictions from March 19, 2020
- Enrolment resumed starting in July 2020 (site-by-site)
- Approx. 400 of 1,800 participants enrolled
- Enrolment completion anticipated for Q3 2021
- Primary endpoint analysis will occur when a total of 118 sustained *Mtb* infection events have occurred in the mITT efficacy population (anticipated in late 2023, or early 2024)

BCG Immune Correlates Program (CoP for POSI)
- using biospecimens from Aeras C-040-404 trial -

CELLULAR IMMUNITY

- Antigen-specific T cells and NK cells (McElrath)
  - Intracellular cytokine staining
- Donor-unrestricted T cells (DURTs, MAITs) (McElrath)
  - Tetramer staining
- scRNAseq (Shalek)

HUMORAL IMMUNITY

- Antibody titer, subclass and avidity (Tomaras)
  - Binding antibody multiplex assay
- Antibody function (Alter)
  - Systems serology
- Antibody-mediated mycobacterial growth inhibition (Alter)

INNATE / TRAINED IMMUNITY

- Whole blood composition (Nemes)
  - DLC-ICE
- scATACseq (Barreiro)
- EpiToF (Utz/Khatri)

OMICS ANALYSES

Bulk RNAseq (Scriba)

WHAT IS NEEDED TO ADVANCE BCG REVACCINATION?

Anticipated data availability:

- Candidate Correlate of Protection (CoP) data for prevention of sustained infection (POSI) (based on Aeras revaccination study biospecimens) in 2023.
  - / Candidate CoP to be confirmed with biospecimens from Gates MRI BCG ReVax study.
- Candidate CoP data for prevention of Disease (POD) (based on M72 Phase 2b trial) in 2023.
  - / To be confirmed with biospecimens from M72/AS01 Phase 3 study.
  - / Best case assumption is that we can identify a CoP for progression from sustained infection to disease.
- BCG ReVax primary endpoint data (sustained IGRA-conversion) in 2024

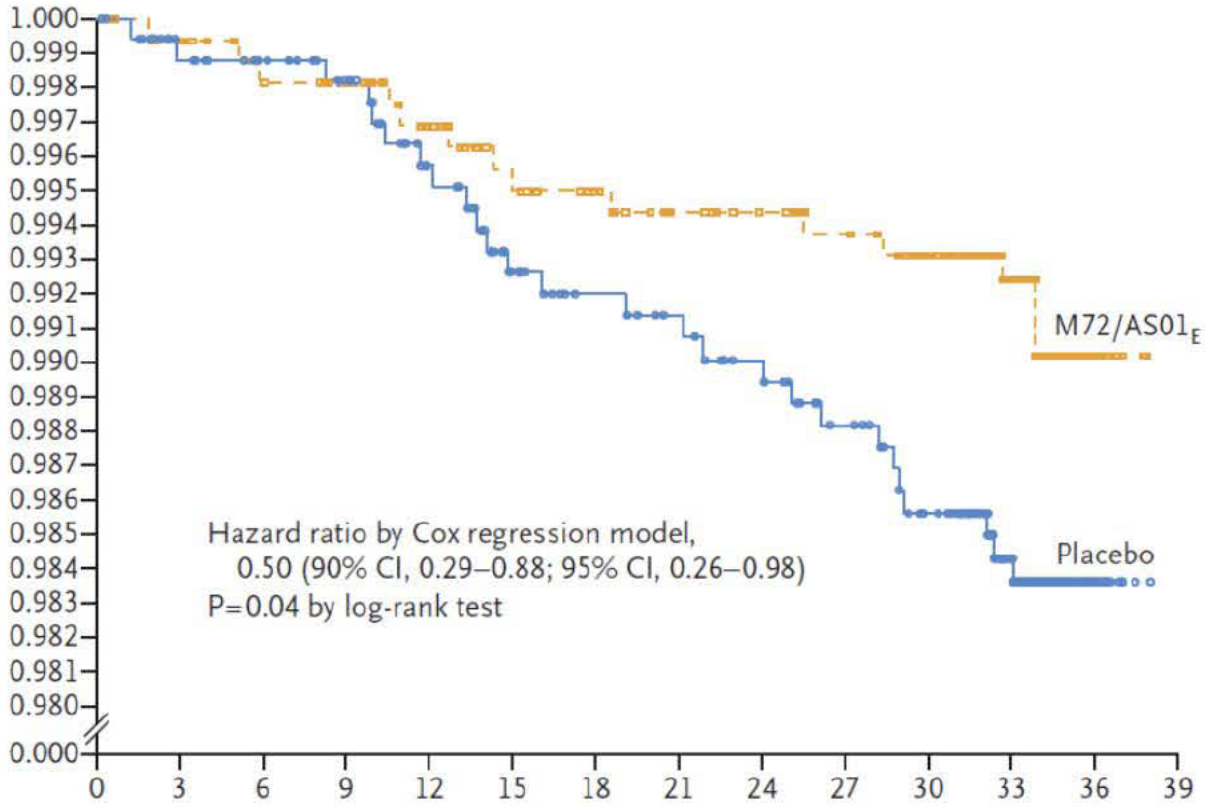
- Other BCG developers may replicate BCG ReVax study in a second geography
- POD clinical endpoint efficacy trial is unlikely to be conducted (too large, too expensive)

M72/AS01 VACCINE DEVELOPMENT

M72/AS01$_E$ & PREVENTION OF DISEASE

PHASE 2B TRIAL IN A QFT-POSITIVE POPULATION

- 49.7% (95% CI 2.1 to 74.2%) vaccine efficacy
- Acceptable safety profile



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Phase 2b Controlled Trial of M72/AS01$_E$ Vaccine to Prevent Tuberculosis

O. Van Der Meeren, M. Hatherill, V. Nduba, R.J. Wilkinson, M. Muyoyeta, E. Van Brakel, H.M. Ayles, G. Henostroza, F. Thienemann, T.J. Scriba, A. Diacon, G.L. Blatner, M.-A. Demoitié, M. Tameris, M. Malahleha, J.C. Innes, E. Hellström, N. Martinson, T. Singh, E.J. Akite, A. Khatoon Azam, A. Bollaerts, A.M. Ginsberg, T.G. Evans, P. Gillard, and D.R. Tait

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Final Analysis of a Trial of M72/AS01$_E$ Vaccine to Prevent Tuberculosis

D.R. Tait, M. Hatherill, O. Van Der Meeren, A.M. Ginsberg, E. Van Brakel, B. Salaun, T.J. Scriba, E.J. Akite, H.M. Ayles, A. Bollaerts, M.-A. Demoitié, A. Diacon, T.G. Evans, P. Gillard, E. Hellström, J.C. Innes, M. Lempicki, M. Malahleha, N. Martinson, D. Mesia Vela, M. Muyoyeta, V. Nduba, T.G. Pascal, M. Tameris, F. Thienemann, R.J. Wilkinson, and F. Roman

DOI: 10.1056/NEJMoa1803484 & DOI: 10.1056/NEJMoa1909953

M72/AS01$_E$ PRODUCT DEVELOPMENT

Generate data to support licensure of the vaccine and recommendations for effective use

- GSK licensed M72/AS01$_E$ to the Gates MRI, paving the way for continued vaccine development and potential use in LMICs
- GSK will ensure an efficient transfer of the asset technology
- Gates MRI will lead product development and sponsor future clinical trials
- GSK will provide AS01 adjuvant for the development program
- Gates MRI will actively reach out to and collaborate with the many partners and stakeholders committed to accelerating the end of the TB epidemic.

KEY TOPICS & QUESTIONS FOR M72

- Phase 3 study
  - Does M72/AS01E protect IGRA-positive individuals from disease (and for how long)?
  - Does M72/AS01E protect IGRA-negative individuals from infection (and/or disease)?
  - Primary endpoint, age range, IGRA status, participating countries, how to enrich for high risk?
- Data needed for first dossier in South Africa
  - Lower bound of 95% CI? Submission with interim data (95%CI LB>0?), followed by primary analysis data (95%CI LB>15%?)
- Delivery considerations
  - Target age groups (depending of VE in IGRA-negative individuals)
  - Delivery channels, payors?
- What needs to be included in the Phase 3 study design, and what implementation research is needed to support WHO policy recommendation, PQ and financing?

CRITICAL PATH

Clinical & Regulatory:

- Generate Safety & Immunogenicity data to support inclusion of PLHIV in Phase 3 VE trial
- Develop Phase 3 protocol jointly with stakeholders, SMEs & NRAs
- Select countries and prepare sites for Phase 3 VE trial
- Reach agreement on protocol design & initial registration package with health authorities
- Conduct Phase 3 vaccine efficacy study

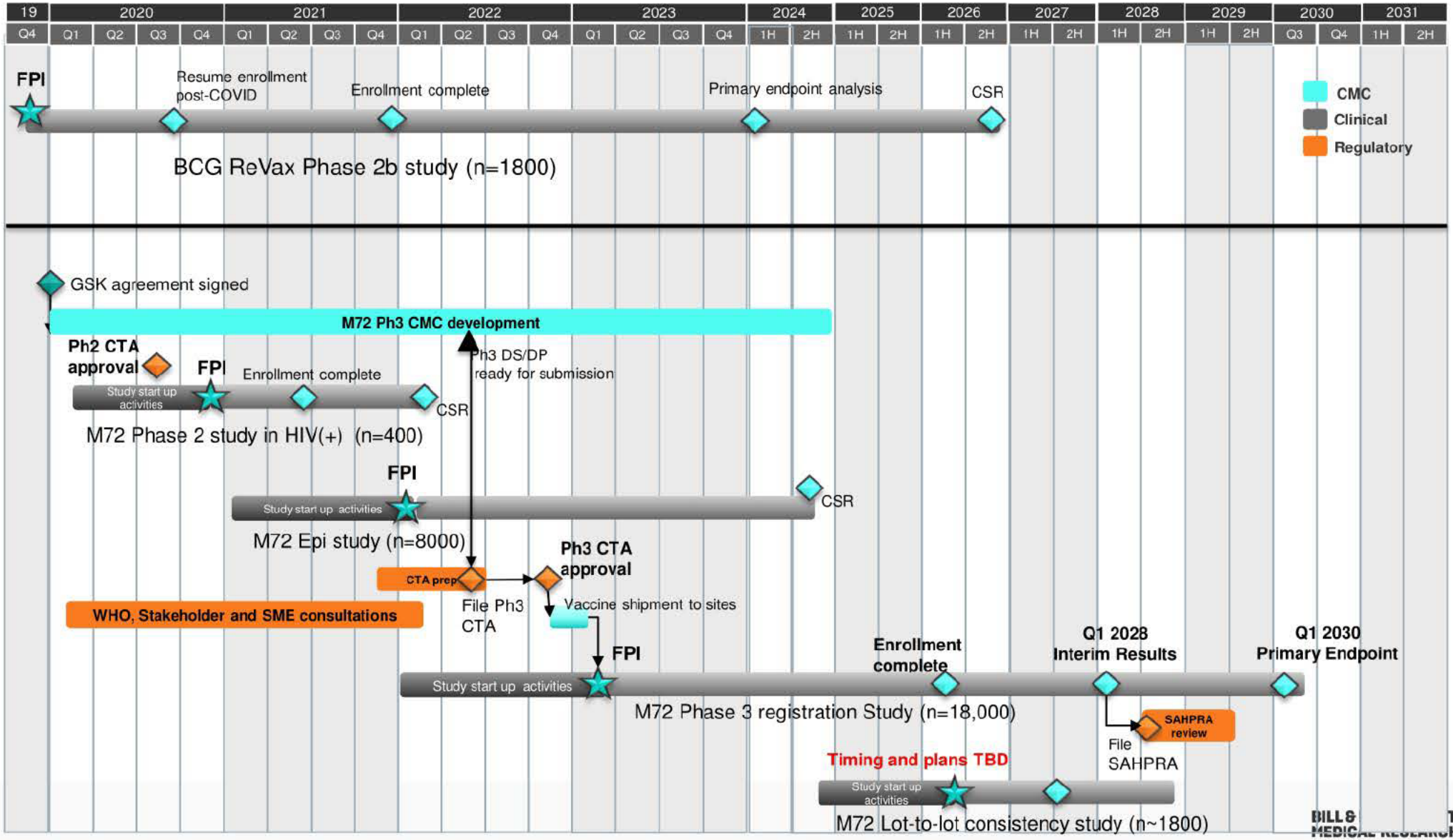
Technical Development:

- Develop M72 antigen manufacturing process to support Phase 3 and commercialization.
- Develop adjuvant manufacturing process to support Phase 3 and commercialization
- Manufacture new drug product & supply Phase 3
- Identify Commercial Manufacturer / Marketing Authorization Holder and transfer M72 manufacturing

INITIAL ASSUMPTIONS ON DEVELOPMENT TIMELINES

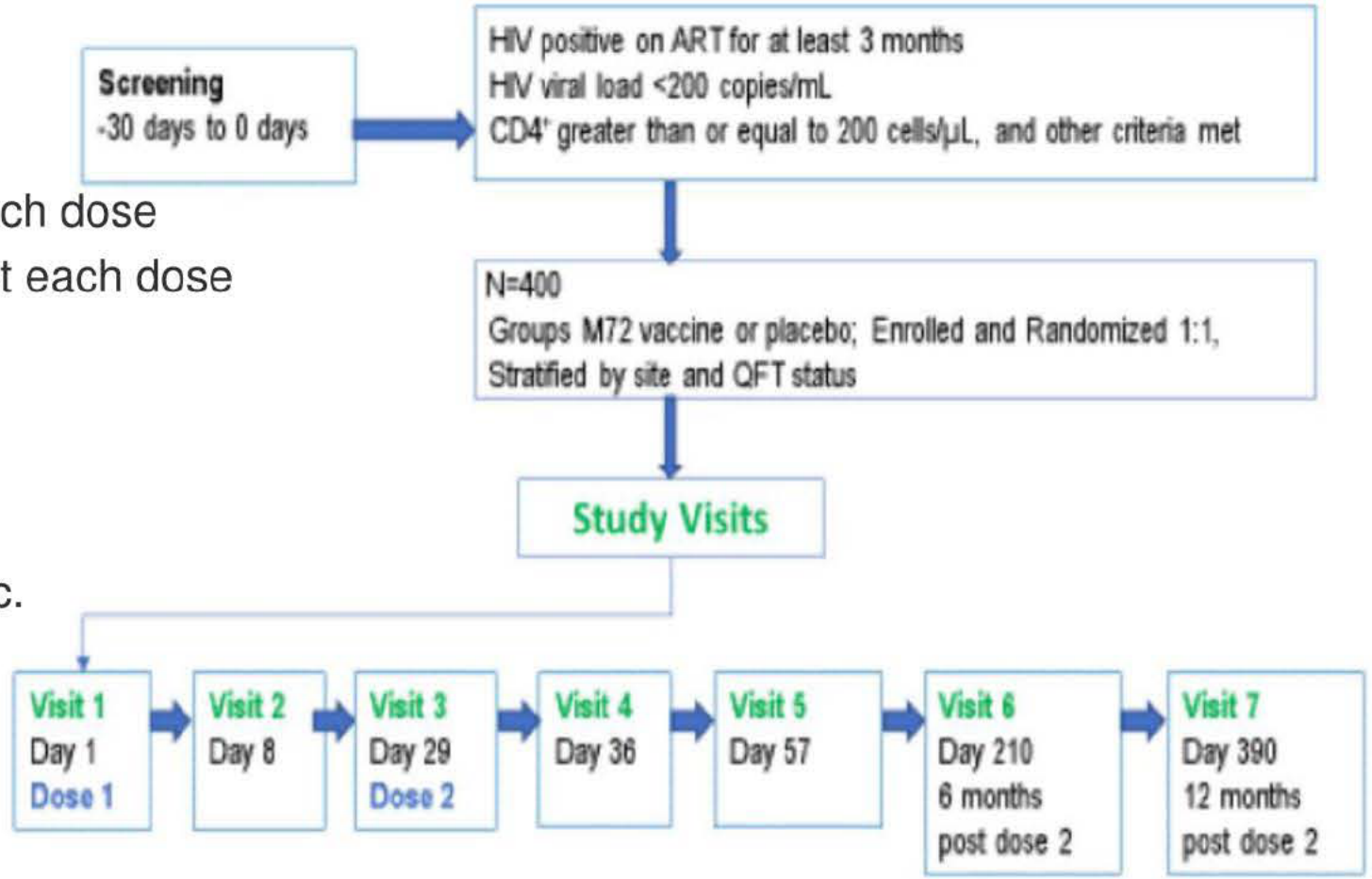
BCG ReVax

M72/AS01E



PHASE 2 STUDY IN PLHIV

- Observer-blind, 1:1 randomized study
- Primary objectives
  - Solicited AEs through 7 days post each dose
  - Unsolicited AEs through 28 days post each dose
  - All SAEs through end of study
- Secondary objectives:
  - M72-specific humoral and cellular immunogenicity
- Exploratory objectives: HIV RNA, CD4 etc.
- Study start anticipated for Nov 2020
- Sites in Durban, Cape Town, Johannesburg & Worcester
- SAHPRA approval received
- Awaiting IRB approvals
- Enrollment anticipated to start November 2020



EPI STUDY IN PREPARATION FOR PHASE 3

Scientific Objectives	Endpoints
Primary	
• To assess prevalence of LTBI	• Interferon gamma (IFNg) release assay positivity by age and by site
Secondary	
• To describe the incidence of TB	• Suspected TB cases by site, risk group, and overall • Lab-confirmed TB cases by site, risk group, & overall
Tertiary/Exploratory	
• To describe the association between IGRA IFNg concentration and progression to TB	• IGRA IFNg concentration at baseline & and risk of TB

EPI STUDY IN PREPARATION FOR PHASE 3

Operational goals:

- Build site capacity & train teams
- Establish operational feasibility for each site: QFT-positivity by age, quality of TB surveillance & study procedures
- Establish study cohorts; subset could be invited to participate in Phase 3 (e.g., IGRA-negatives & recent converters)

Design:

- Approx. 8,000 study participants, f/u 12 - 24 months; study to end at a given site once site is ready to start Phase 3 enrolment
- Approx. 50 sites
- IGRA status at baseline, follow-up every 2 months to identify suspected TB

PHASE 3 EFFICACY STUDY DESIGN FOR M72/AS01$_E$

- **Objectives:**
  - Unequivocally demonstrate VE for POD in QFT-positive participants
  - Support licensure for use irrespective of QFT status, i.e., include enough QFT-neg participants to establish safety, immunogenicity & initial assessment of VE in QFT-neg vaccinees. (Screening for QFT status in national programs is currently not feasible)
  - Support licensure including people living with HIV
- Trial simulations suggest that at least 14,000 subjects in very high incidence settings are needed to demonstrate VE in a randomized controlled trial (1:1 vs placebo)
- An interim analysis for VE could be explored to potentially accelerate submission of a first dossier

PHASE 3: KNOWLEDGE GAPS & CHALLENGES

- Significant uncertainty with regards to incidence of *Mtb* infection & TB disease
  - Highest possible TB incidence rate needed to increase probability of success
  - Clinical trials capacity needed in poor communities in LMICs
- Significant uncertainty with regards to true vaccine efficacy (VE)
  - Primary endpoint definition appears to have impact on VE and incidence rate in IGRA-positives
  - No data on VE in IGRA-negative populations
  - No data on VE in PLHIV
- How can we mitigate uncertainties?
  - Determine site-level QFT prevalence, build capacity, enrich for high incidence, event-triggered primary analysis, adaptive trial, IDMC oversight of unblinded data

PARAMETER ASSUMPTIONS FOR TRIAL SIMULATIONS

Trial Parameter	Value	Reference
Age range	16 – 30 year of age	
Proportion baseline QFT-pos	65%	
Incidence of Disease (D) in QFT-pos	0.4 – 0.6% per year	Van Der Meeren et al (2018), NEJM
True VE in QFT-pos	50 – 65%	Van Der Meeren et al (2018), NEJM
Participant follow-up time	5 years	Study defined
Accrual time	3 years	Assumed
Participant drop out rate	5% per year	
Incidence of Infection (INF) in QFT-neg	5% per year (i.e., sustained QFT-pos conversion)	Nemes et al (2018), NEJM
Incidence of D in QFT-neg	1.6% per year after sustained conversion (no disease among non-sustained converters)	Nemes et al (2017), American Journal of Respiratory and Critical Care Medicine
True VE in QFT-neg	VE(INF) = 25%; VE(D) = VE(INF)	No data

PHASE 3 DESIGN CONSIDERATIONS

How likely are we to succeed?

- Probability of success (i.e., study "power") based on (i) number of observed events; (ii) true VE; and (iii) lower bound of VE needed

Show 95% CI LB on VE >	# required events when true VE =								
	70%	65%	60%	55%	50%	45%	40%	35%	30%
0%	29	39	51	66	88	118	162	227	331
15%	39	54	74	104	150	222	347	585	1115
20%	44	62	88	127	191	300	508	975	2358

Equal randomization, Type I error = 1-sided 2.5%, 90% power

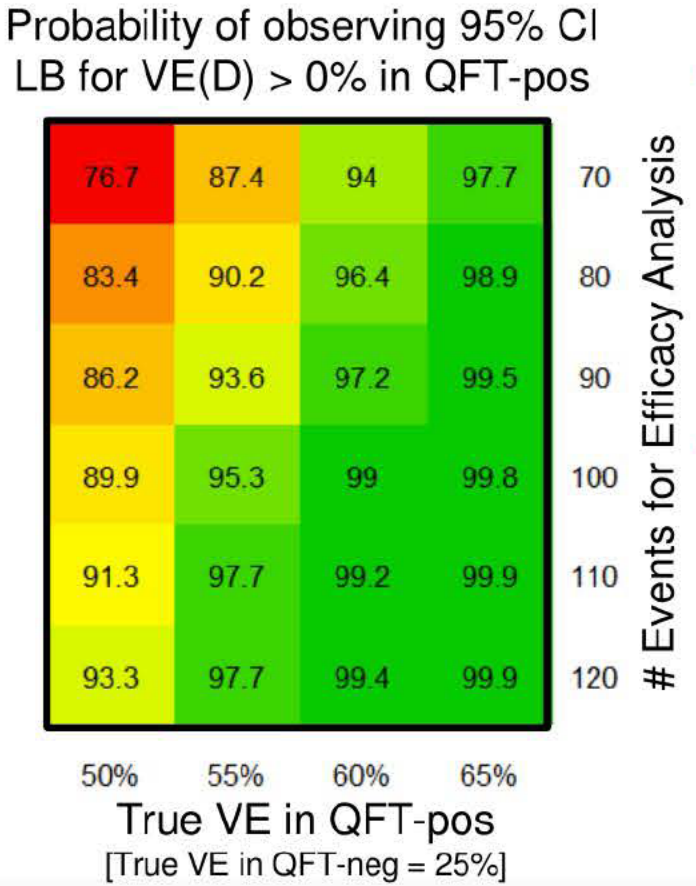
How long will it take to get the answer?

- Expected timing of analysis based on (i) sample size; (ii) underlying incidence; (iii) participant follow-up time; (iv) drop-out rate; and (v) study accrual rate

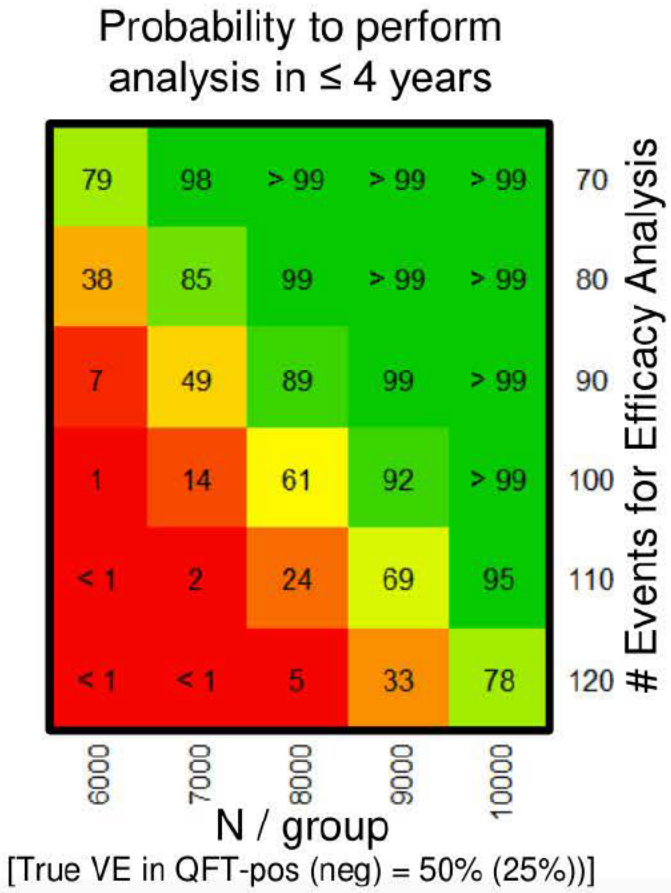
CLINICAL TRIAL SIMULATIONS INFORM PHASE 3 STUDY DESIGN

Point 1: # events needed to rigorously confirm vaccine efficacy against disease (VE(D)) depends on underlying true VE

Point 2: High probability to accrue # events needed within 4 years of study start with 7000 – 10000 / group

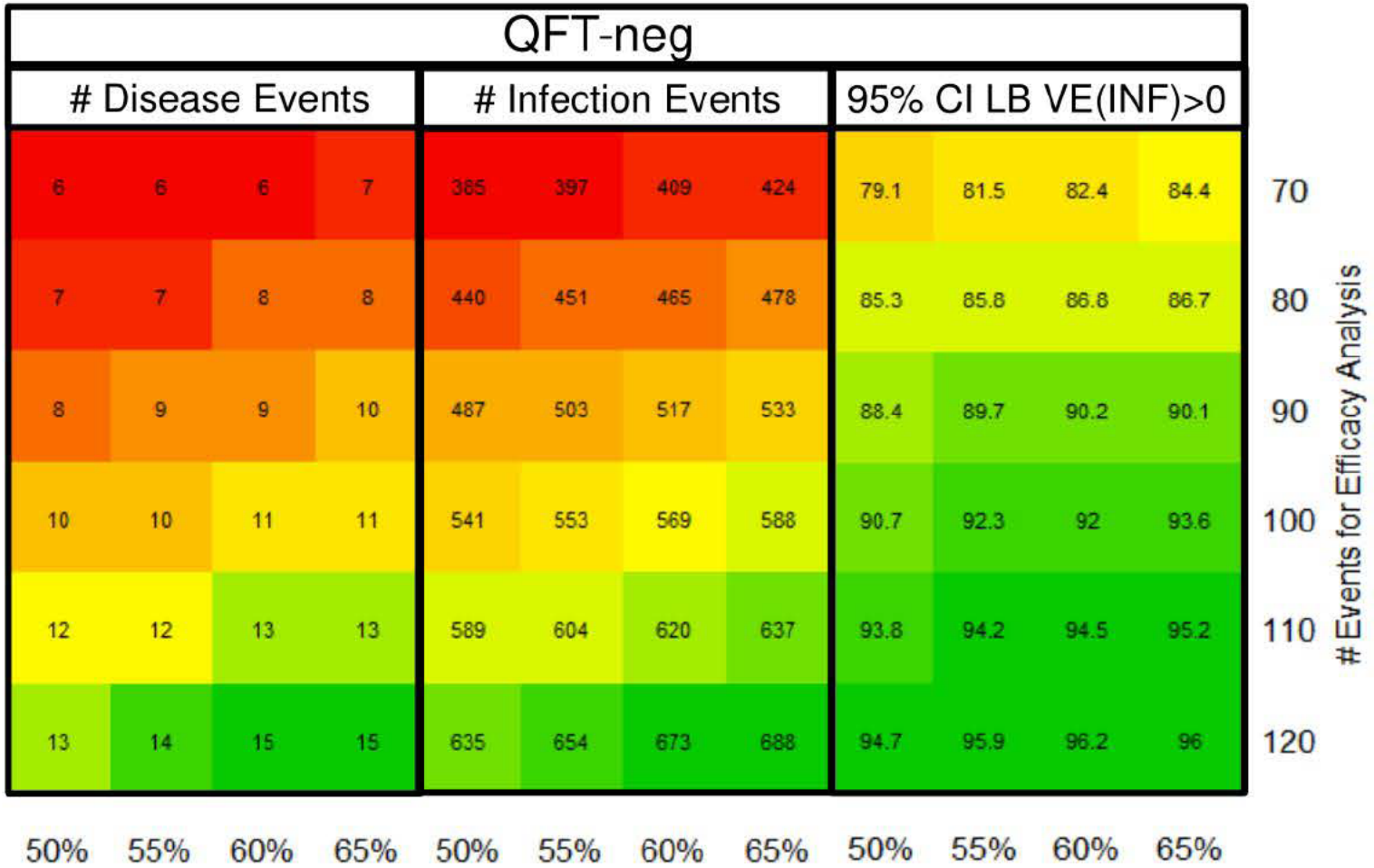


- Probability of observing 95% CI LB for VE(D) > 0% in "all-comers" comparable to QFT-pos
- Increasing LB of CI for VE(D) from 0 to e.g., 15% significantly increases the # events required for Phase 3 success



- Waiting an additional 6 months (e.g., to 4.5 years) increases probability to
- ≥ 80% for 100 events with N ≥ 7000 / group, 110 events with N ≥ 8000 / group, 120 events with ≥ 9000 / group

PHASE 3 TRIAL EXPECTATIONS: # OF EVENTS EXPECTED BY BASELINE QFT STATUS



Point 3: Limited power to assess VE(D) in QFT-neg participants due to low # of disease events expected

- Only ~10% of disease events expected to be from QFT-neg participants
- With 100 total disease events, expect over 500 infection events in QFT-neg participants
- With ≥ 90 - 100 total disease events, high probability to show 95% CI LB for VE(INF) > 0% [Assuming VE(INF) = 25% in QFT-neg]

M72/AS01$_E$ PHASE 3: NEXT STEPS

- Primary endpoint, case definition and trial design need thorough discussion with stakeholders, subject matter experts and LMIC national regulatory agencies
- TPT implementation & impact on trial design (inclusion of HHCs, IGRA-testing while on study) will need discussion
- Country selection prep has been initiated; epidemiology study to start late 2021 / early 2022
- Phase 3 study start anticipated in early 2023

WRAP-UP / CALL TO ACTION

- Gates MRI remains committed to accelerating the end of tuberculosis
- Developing effective vaccines is a cornerstone of this plan
  - / BCG REVAX
    - Results expected 2024
  - / M72/ASO1E
    - Efficacy study start expected in Q2 2023, interim VE data anticipated in 2028
    - Urgent need to define trial design & endpoints, trial population, participating countries & sites, and to prepare for recommendation should Phase 3 data be supportive
    - WHO participation in defining trial design is critical to the success of the program
    - Can PDVAC members participate in Phase 3 design & endpoint definition (SAB Q1 2021)?
    - Can PDVAC co-ordinate workstreams/stakeholders within WHO?
    - Is it possible to receive SAGE input prior to finalization of Phase 3 protocol? (Q2 2021)?

THANK YOU

	Draft Product Profile at First Registration	Draft Target Product Profile (life-cycle target)
Indication	Active immunization to prevent pulmonary TB disease	Active immunization to prevent pulmonary TB disease
Target Population	16-35 years of age: no restrictions	9 years of age and above; no restrictions
POD VE in QFT+ (LB)	50% (0%) at first submission 50% (15%) for recommendation	70%(25%)
POD VE in QFT- (LB)	0	50%
Duration of Protection	At least 3 years (median follow-up)	At least 10 years
Regimen	2 doses (10 µg) 4 weeks apart	2 doses (10 µg) 1 to 12 months apart
Indirect Protection	No data	Established
Safety	Acceptable safety profile	Acceptable safety profile
Presentation/formulation	Single dose vial for antigen and adjuvant respectively, needles not provided, bedside mix	Multi-dose in single vial
Vaccine Volume	0.5mL	0.5mL
Stability / Shelf Life	3 years at 2-8°C	3 years at 2-8°C
Special Populations: HIV+	No contraindication if on ART. Based on 2 years of safety data on >1,000 PLWH	Acceptable safety and efficacy, no contraindication
Special Populations: current or recent TB disease	Contraindication. No data available for TB on treatment. Very limited data available for people with incipient TB.	Acceptable safety profile based on post-licensure study
Special Populations	Safety established in adolescents 16 years and up	Safety & efficacy established in children >9 years

R&D Roadmap for tuberculosis vaccines

PDVAC meeting
17 June 2020

Frank Cobelens

Amsterdam Institute for Global Health and Development
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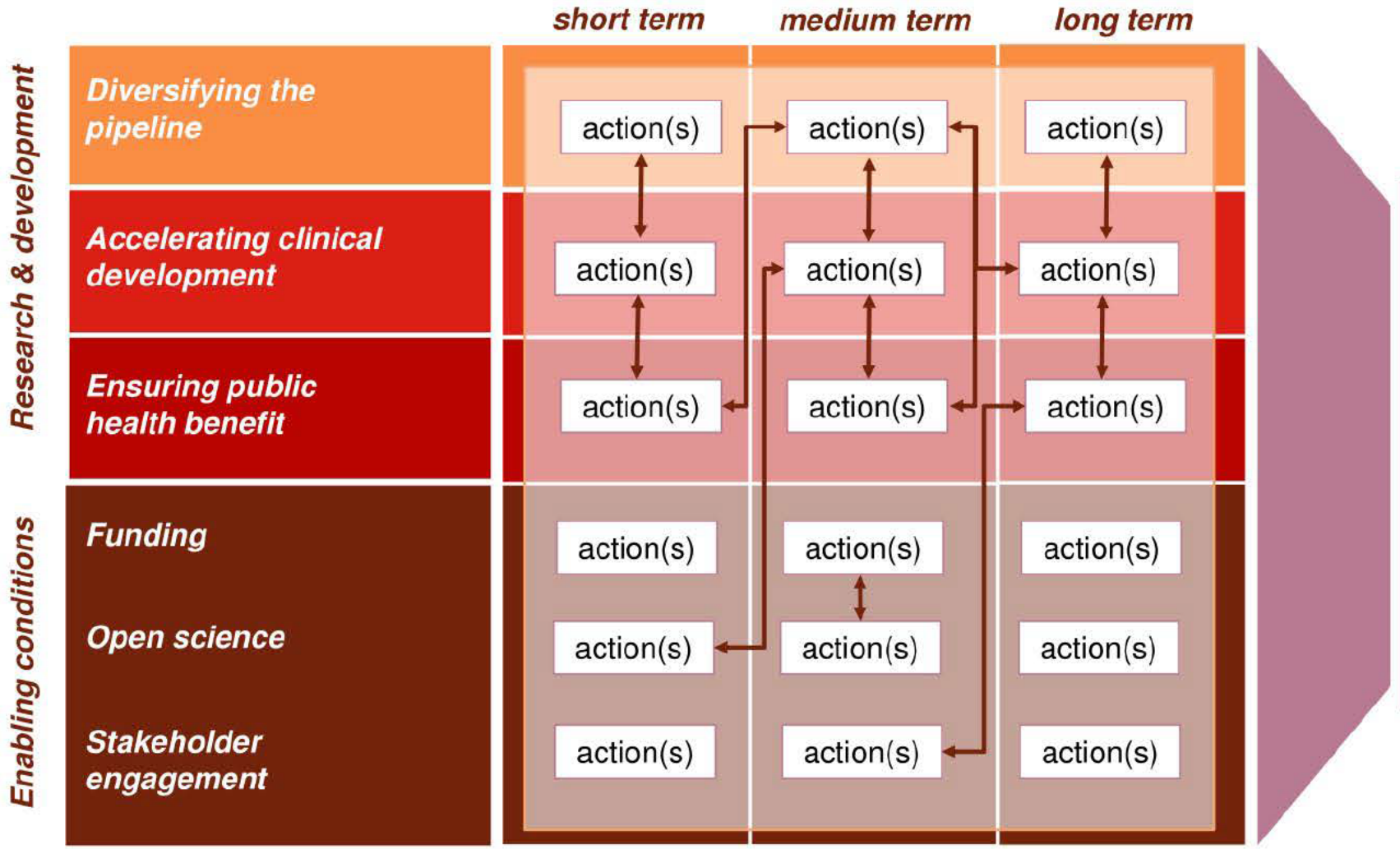
Purpose

European & Developing Countries Clinical Trials Partnership (EDCTP)
Clinical research to accelerate the development of new or improved drugs, vaccines, microbicides and diagnostics against poverty-related infectious diseases in sub-Saharan Africa

To develop a Global Roadmap for Research and Development for TB vaccines that:

- provides global stakeholders such as researchers, funders, industry, regulatory and policy decision makers with key actionable priorities that could help guide their actions.
- lists the short-term objectives and the long-term strategic objectives for global TB vaccine development.

Focus on developing and delivering affordable and effective vaccines for use in low- and middle-income countries.



Development goals (PPCs)

A safe, effective and affordable TB vaccine for adolescents and adults

An affordable TB vaccine for neonates and infants with improved safety and efficacy

A therapeutic vaccine to improve TB treatment outcomes

Process for roadmap development

Close collaboration with WHO to develop a Roadmap that has WHO's support

Roadmap development and consultation to follow WHO process:

- Consent workshop co-convened and co-organized with WHO (PDR & GTB)
- Review of draft AIGHD roadmap by PDVAC
- If draft roadmap is endorsed by PDVAC for co-authorship with WHO, draft will require public consultation in line with WHO processes
- Approval by relevant WHO bodies

Roadmap process

Stakeholders

Global policy bodies
National TB program managers/policy makers
National EPI managers/policy makers
Technical assistance agencies
Researchers involved in TB vaccine development
Modelers
Vaccine manufacturers
Regulators
Product Development Partnerships
Major research funders
Major donors of immunization and TB control
Advocacy & community representatives

Roadmap process

Oct-Dec 2019

Objectives

Get a comprehensive overview of the clinical development pipeline.
Elicit perspectives on the TB vaccine development goals
Define barriers to achieve those goals*
Define solutions to overcome these barriers*

**preclinical – clinical – post-licensure*

Stakeholders

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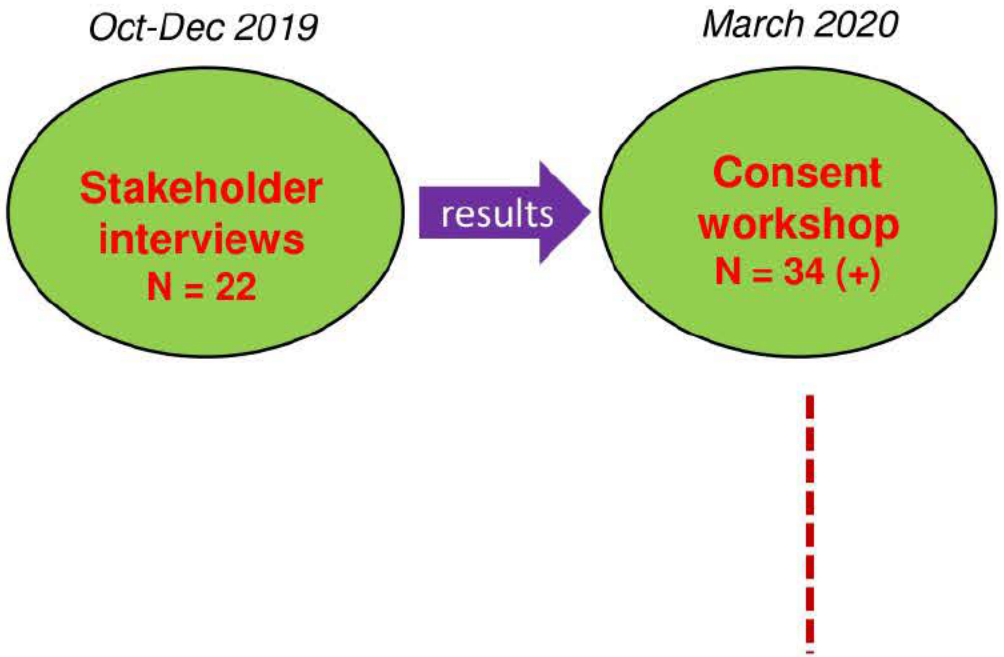
Roadmap process



Stakeholders

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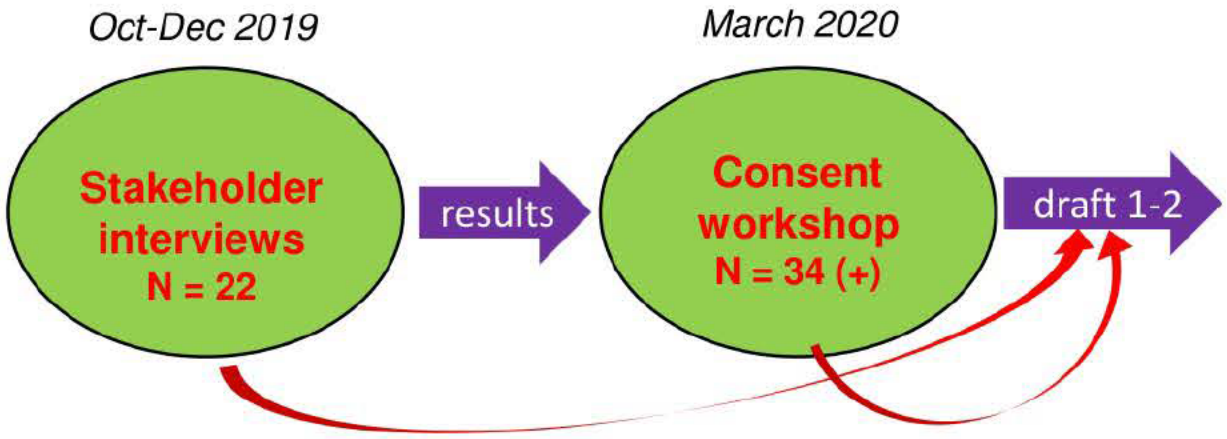
Researchers involved in TB vaccine development
Modelers
Vaccine manufacturers
Regulators
Product Development Partnerships
Major research funders
Major donors of immunization and TB control
Advocacy & community representatives

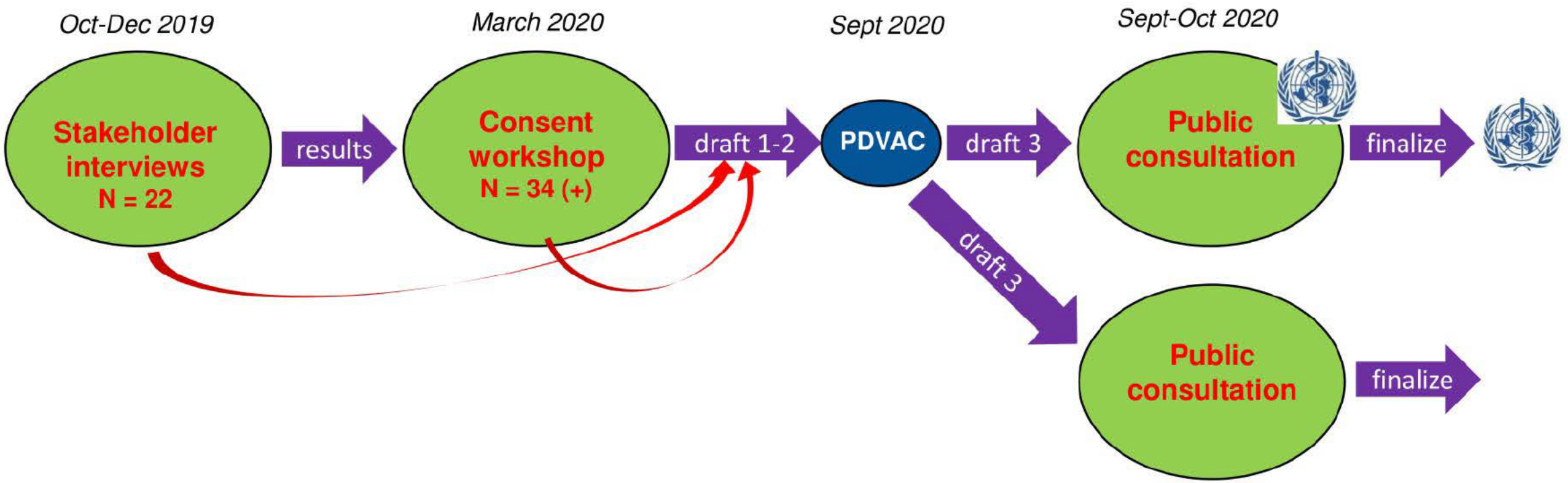
Objectives

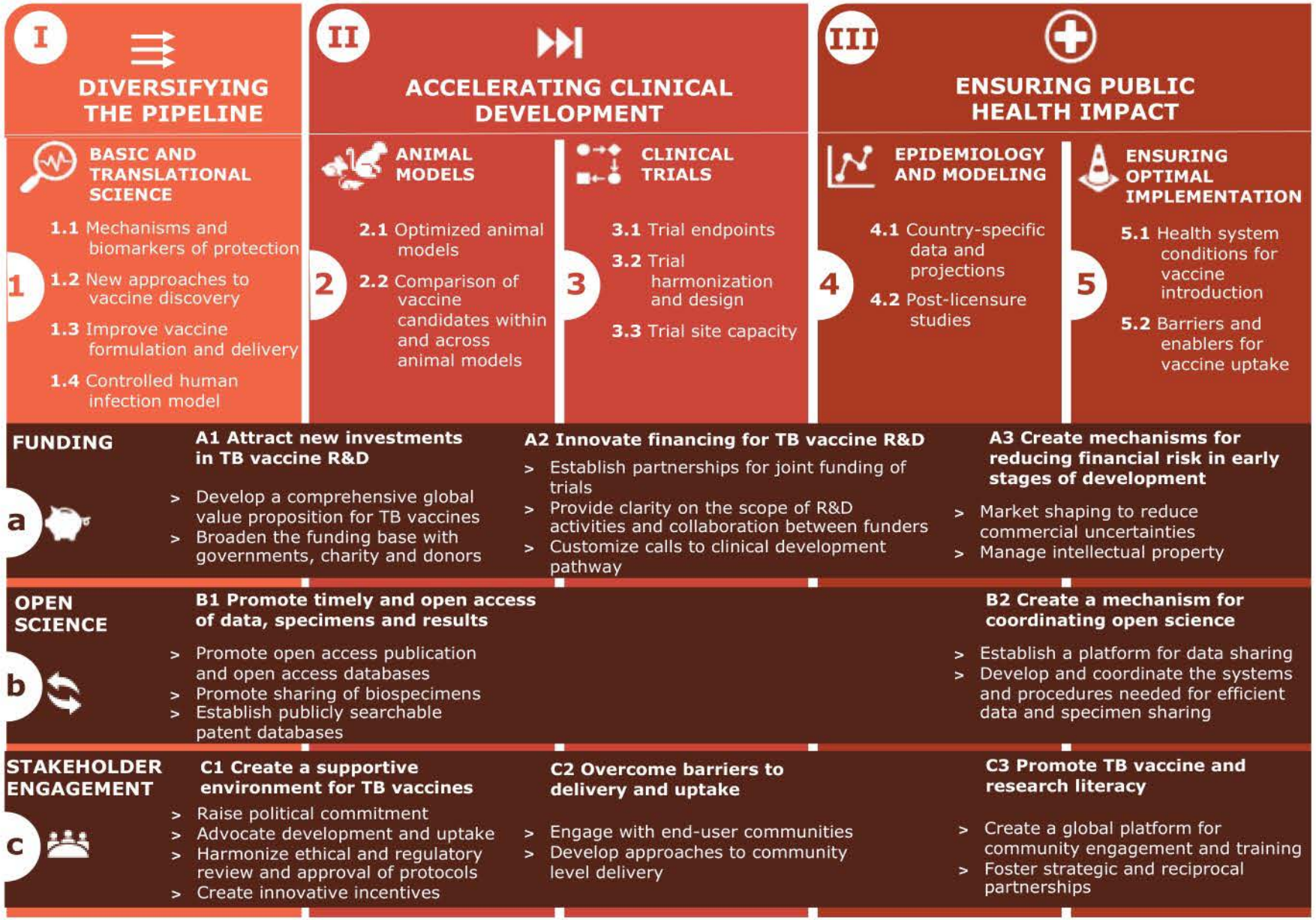
Clarify and specify the overall goals and key challenges of TB vaccine development
Define knowledge gaps and actions addressing the key challenges across the development pathway
Reach consensus about prioritization, interdependencies and timing of the actions
Define supportive conditions and next steps in the design of the TB R&D roadmap

Roadmap process



Roadmap process




I
DIVERSIFYING THE PIPELINE
II
ACCELERATING CLINICAL DEVELOPMENT
III
ENSURING PUBLIC HEALTH IMPACT
BASIC AND TRANSLATIONAL SCIENCE
1.1 Mechanisms and biomarkers of protection
1
1.2 New approaches to vaccine discovery
1.3 Improve vaccine formulation and delivery
1.4 Controlled human infection model
ANIMAL MODELS
2.1 Optimized animal models
2
2.2 Comparison of vaccine candidates within and across animal models
CLINICAL TRIALS
3.1 Trial endpoints
3
3.2 Trial harmonization and design
3.3 Trial site capacity
EPIDEMIOLOGY AND MODELING
4.1 Country-specific data and projections
4
4.2 Post-licensure studies
ENSURING OPTIMAL IMPLEMENTATION
5.1 Health system conditions for vaccine introduction
5
5.2 Barriers and enablers for vaccine uptake
FUNDING
a
A1 Attract new investments in TB vaccine R&D
> Develop a comprehensive global value proposition for TB vaccines
> Broaden the funding base with governments, charity and donors
A2 Innovate financing for TB vaccine R&D
> Establish partnerships for joint funding of trials
> Provide clarity on the scope of R&D activities and collaboration between funders
> Customize calls to clinical development pathway
A3 Create mechanisms for reducing financial risk in early stages of development
> Market shaping to reduce commercial uncertainties
> Manage intellectual property
OPEN SCIENCE
b
B1 Promote timely and open access of data, specimens and results
> Promote open access publication and open access databases
> Promote sharing of biospecimens
> Establish publicly searchable patent databases
B2 Create a mechanism for coordinating open science
> Establish a platform for data sharing
> Develop and coordinate the systems and procedures needed for efficient data and specimen sharing
STAKEHOLDER ENGAGEMENT
c
C1 Create a supportive environment for TB vaccines
> Raise political commitment
> Advocate development and uptake
> Harmonize ethical and regulatory review and approval of protocols
> Create innovative incentives
C2 Overcome barriers to delivery and uptake
> Engage with end-user communities
> Develop approaches to community level delivery
C3 Promote TB vaccine and research literacy
> Create a global platform for community engagement and training
> Foster strategic and reciprocal partnerships

Diversifying the pipeline –key barriers

- Relatively few candidates in preclinical and early clinical development
- Approach to vaccine development taken thus far is too narrow: emphasis on stimulating classical, CD4+ Th1 cells
- Only limited set of candidate TB antigens are currently considered: known Mtb virulence factors

Diversifying the pipeline – R&D actions

To further expand our knowledge of the human protective immune responses, identify biomarkers that correlate with protection and explore new approaches to TB vaccine discovery and vaccine delivery

1 BASIC AND TRANSLATIONAL SCIENCE

- **1.1** Mechanisms and biomarkers of protection
- **1.2** New approaches to vaccine discovery
- **1.3** Improve vaccine formulation and delivery
- **1.4** Controlled human infection model

- Conduct observational clinical studies combining pathogenesis and immunology
- Study the role of non-conventional, cellular immunity, antibody responses and trained innate immunity
- Identify biomarkers and biosignatures that correlate with vaccine-induced protection

- Develop new vaccine concepts that can induce alternative immune responses
- Study mucosal immune responses
- Deploy genome-wide strategies for antigen discovery

- Study the effects on vaccination outcomes of adjuvants, vaccine platforms and lineage of the Mtb challenge strain
- Explore new routes of vaccine administration
- Study how vaccines can direct immune responses to the lungs

- Develop a controlled human infection model for immunobiology studies

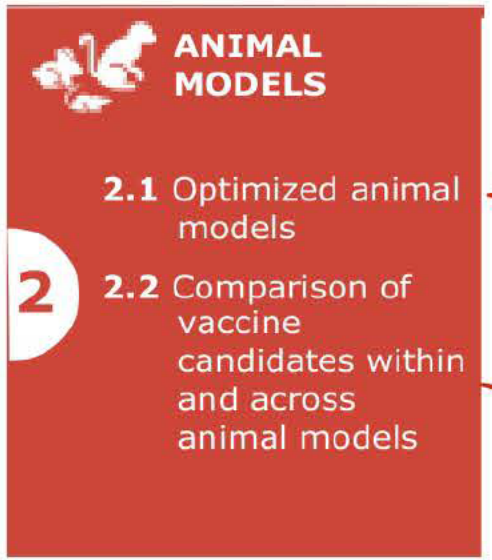
Accelerating clinical development –key barriers

- Lack of relevant, validated preclinical models that predict infection and disease in humans
  - limits effective stage gating/down-selection of candidates for clinical development

- Lack of evidence to support decisions to move a candidate forward through the clinical development pipeline
  - lack of agreed laboratory correlates of protection
  - necessitates large phase II/III trials of long duration with *prevention of disease* (PoD) as clinical efficacy endpoint
  - alternative efficacy endpoints for proof-of-principle: *prevention of infection* (PoI), *prevention of recurrence* (PoR)
    - but unknown to what extent PoI or PoR endpoints predict PoD

Accelerating clinical development (1)

To develop, optimize and use diverse "fit for purpose" animal models that can predict/replicate findings in humans



- Develop fit for purpose animal models
- Develop animal models to provide insight into the relation between *Prevention of Infection* and *Prevention of Disease*
- Develop immune compromised animal models that can predict/replicate findings in specific human target populations

- Standardize and harmonize animal models
- Perform head-to-head testing of candidate vaccines

Accelerating clinical development (2)

XYZ = *(partially) addressed in M72 & BCG revax clinical development program*

To develop, optimize and use diverse "fit for purpose" animal models that can predict/replicate findings in humans

CLINICAL TRIALS

3
- **3.1** Trial endpoints
- **3.2** Trial harmonization and design
- **3.3** Trial site capacity

- Define and develop standardized **PoD trial endpoints** that better capture the various TB disease states in diverse target populations
- Define and validate **correlates of protection** for TB disease
- Define and develop better **PoI trial endpoints**
- Quantify the clinical translation of PoI into PoD

- Harmonize clinical trial protocols
- Develop new models for TB vaccine trials with increased efficiency

- Make inventory of **clinical trial site capacity**
- Collect **epidemiological data in sites** considered for phase II/III trials
- Develop **vaccine trial sites**
- Study potential barriers to trial acceptance
- Promote community engagement in TB vaccine trials

Ensuring public health benefit –key barriers/needs

➢ Need to understand countries' likely demand for a new TB vaccine and associated considerations when added to their national immunization programmes (*value proposition*)

  ➢ Especially for vaccine to be used in adults and adolescents

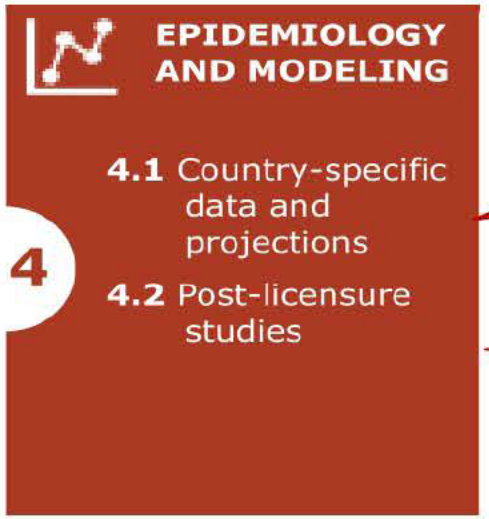
➢ Need for evidence on how to integrate vaccine implementation with ongoing TB prevention efforts and how to use the vaccine among vulnerable groups

  ➢ Need to understand most (cost-)effective use

➢ Need for estimating the national and global demand to stimulate manufacturers to enter into the market and prepare and scale-up vaccine production

Ensuring public health benefit (1)

To quantify key epidemiological and health economic metrics to support vaccine introduction, and evaluate vaccine effectiveness and impact post-licensure

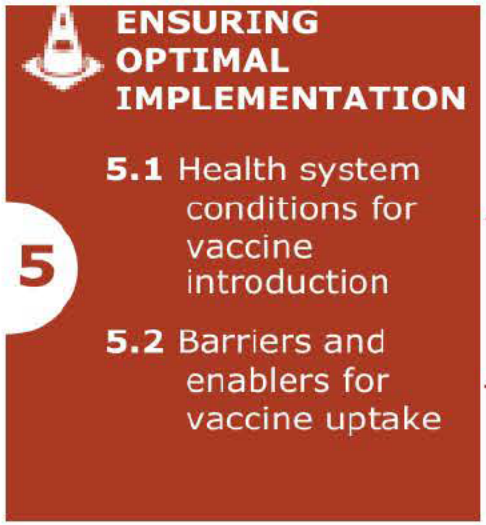


- Conduct in-depth country-specific value proposition analyses
- Collect epidemiological data at country and subnational level
- Modelling to define vaccine development investment cases and potential country-specific vaccine use cases

- Develop valid approaches for real-life vaccine scale-up studies
- Conduct post-licensure evaluations of vaccine effectiveness, impact and safety

Ensuring public health benefit (2)

To understand user preferences and implementation needs for new TB vaccines



- Define the generic public health system requirements to deliver a new TB vaccine
- Conduct pre-introduction assessments of country immunization programmes

- Assess drivers of acceptability and uptake of new TB vaccines in various settings

Key enabling conditions: funding

FUNDING

a 

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Key enabling conditions: open science

Key enabling conditions: stakeholder engagement

STAKEHOLDER ENGAGEMENT

C 

C1 Create a supportive environment for TB vaccines

- Raise political commitment
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This project is part of the EDCTP2 programme. The EDCTP programme is supported under Horizon 2020, the European Union's Framework Programme for Research and Innovation

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Matteo Zignol

The EDCTP2 programme is supported by the European Union's Horizon 2020 research and innovation programme

PDVAC session on TB vaccines

Upcoming evidence from mathematical and economic modelling

(b) (6)

and many, many others

2020_09_03

Overview

Objectives

- Summarize overall modelling evidence
- Summarize v prelim M72/AS01 and BCG re-vx modelling evidence
- Summarize WHO-funded, Full Value Assessment of TB Vaccines project
- Summarize BMGF-funded, M72/AS01 and BCG revaccination specific modelling project

Outcomes

- PDVAC qus, and advice on what, if any, high priority follow-up work
- PDVAC qus, and advice on if and how could be more useful to global and country stakeholders

Overview

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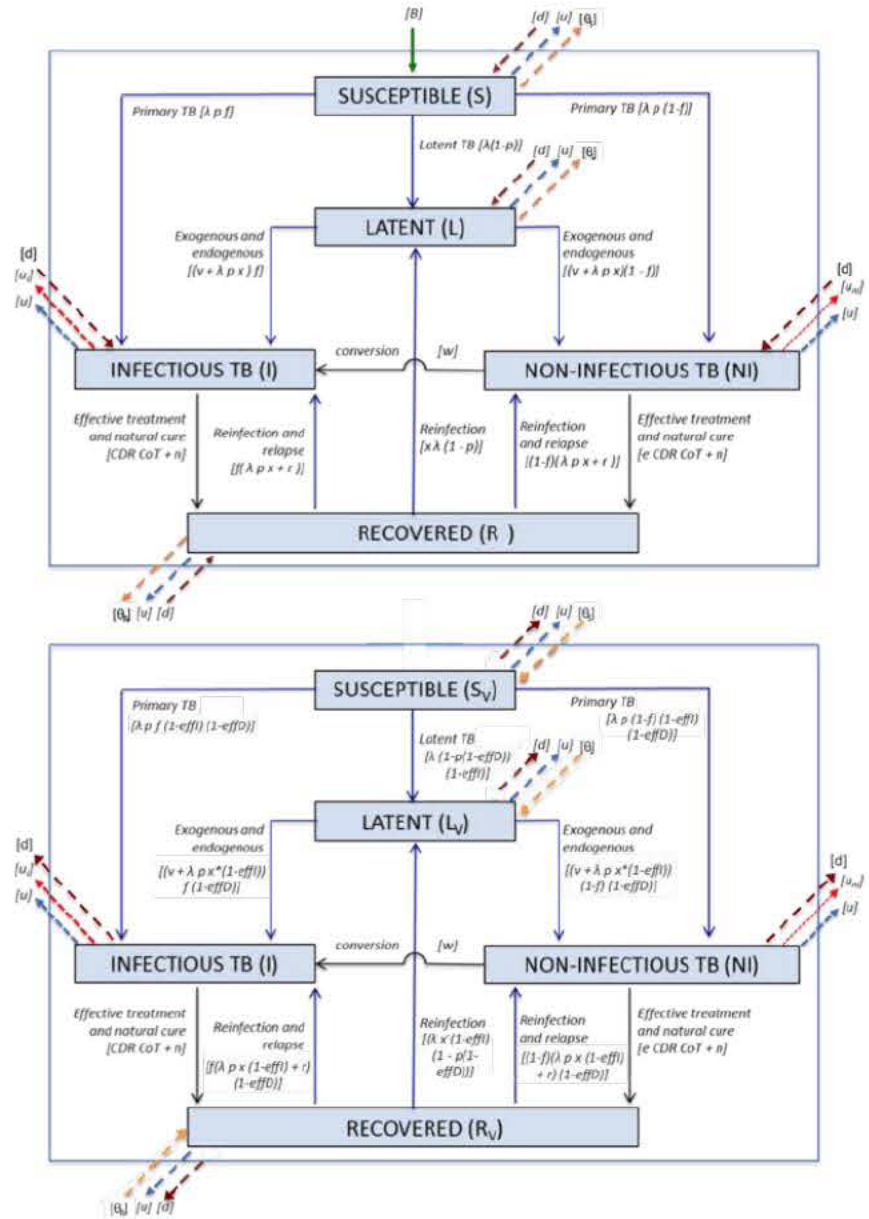
Informing strategic TB vaccine development

- Vaccines fit for purpose and maximise future population-level epidemiological impact
- Mathematical modelling as a logical framework
  - Project impact of potential vaccine characteristics and implementation strategies to guide TPP/PPCs
  - Based upon clinical trial data, estimate potential future epidemiological impact to guide decision making

In the context of a busy pipeline and new trial results – explore how mathematical modelling can continue to inform strategic TB vaccine development



Informing strategic TB vaccine development

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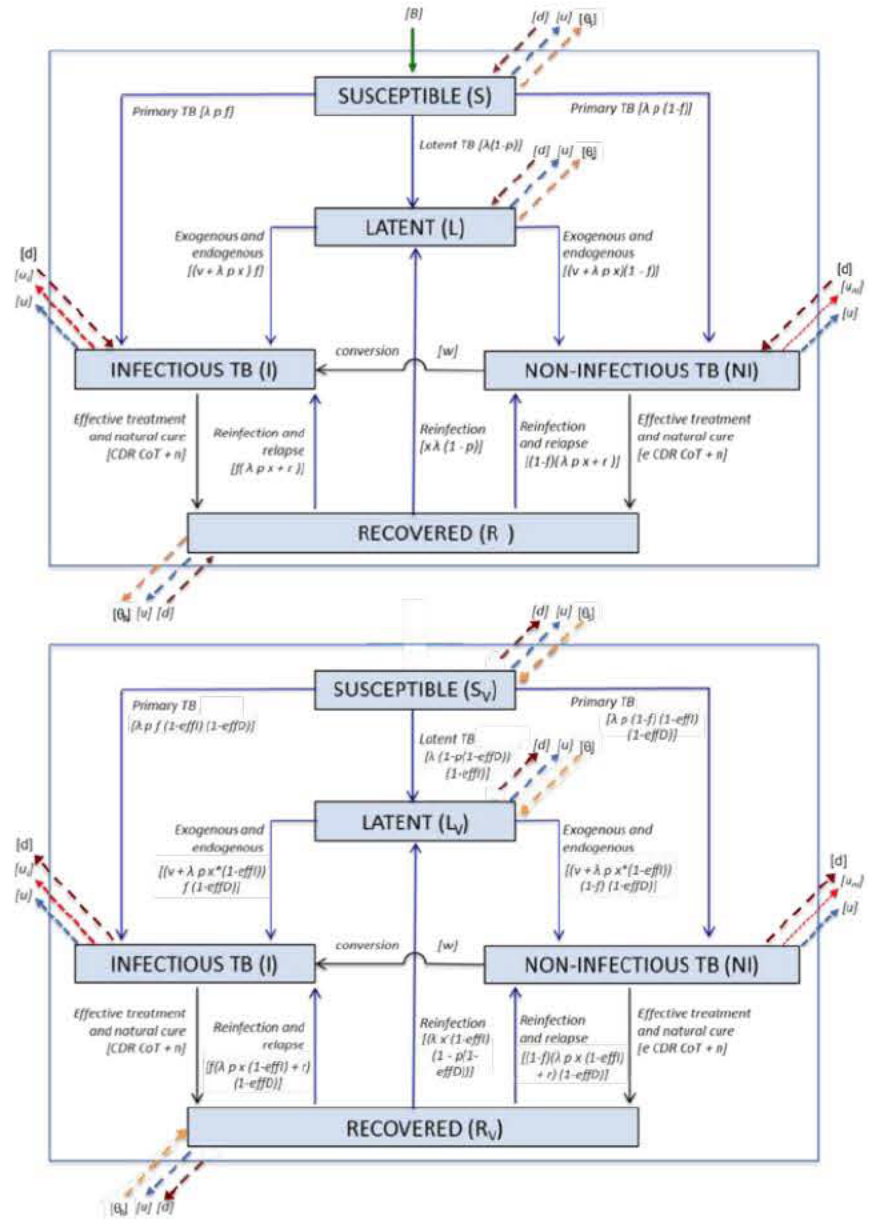
- Mathematical modelling as a logical framework
  - Project impact of potential vaccine characteristics and implementation strategies to guide TPP/PPCs
  - Based upon clinical trial data, estimate potential future epidemiological impact to guide decision making

Systematic review (Harris et al. 2016) summarising 23 studies

+ 4 studies published since the review (Liu, Arregui, Harris, Renardy)

+ 2 unpublished studies



POI /POD

Pre-/post

Duration

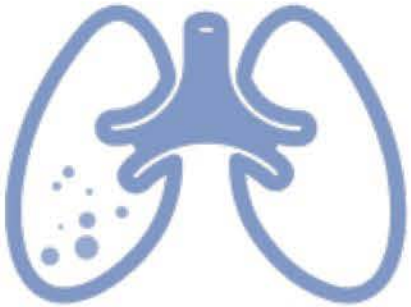
Efficacy

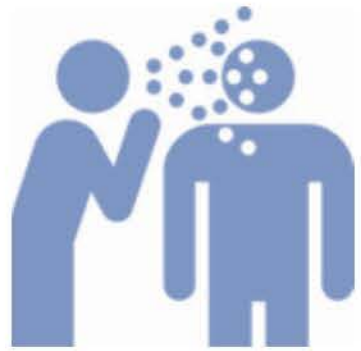
Age

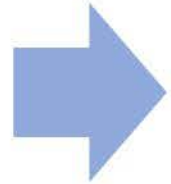
HIV

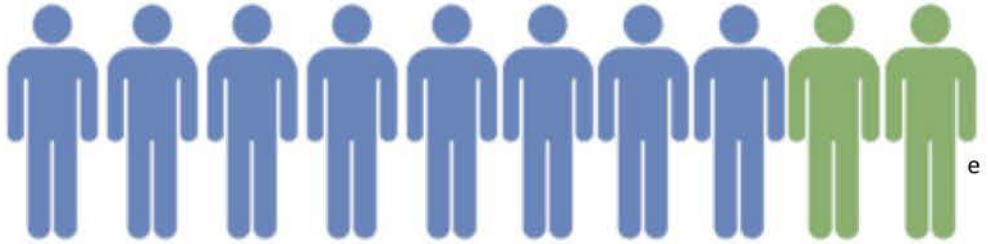
So what?

vs.

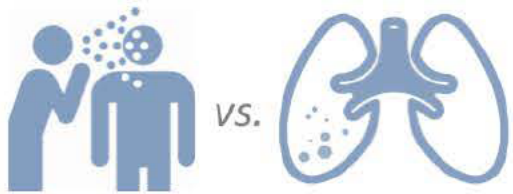








Summary of lit and generic candidate modelling 1/3



Over 2025-50

Prevention of infection (POI) versus prevention of disease (POD)

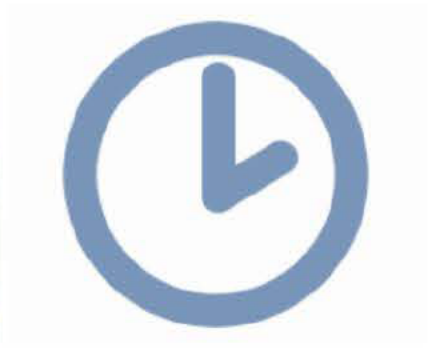
- Globally, **prevention of disease** vaccines would provide **faster and greater impact** than prevention of infection, but
- Impact of **prevention of infection vaccine increases in higher transmission settings,** eg India & SA

Pre- versus post-infection

- In China, South Africa and India, a vaccine efficacious for **prevention of disease** in **post-infection** populations would have **greatest impact**, but
- Vaccines efficacious for prevention **of infection or disease in pre-infection** populations, **had increasing impact** in **higher transmission settings** eg India & SA

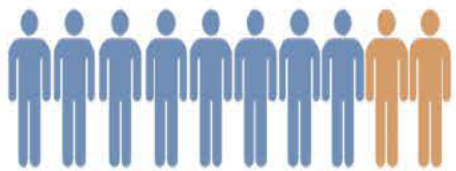
Harris 2016 & 2019, Shrestha 2016, Lui 2017, Arregui 2017, Shrestha 2017, Harris, in prep

Summary of lit and generic candidate modelling 2/3



Over 2025-50

- Duration of protection
  - In LMICs, as little as **5 years protection may be cost effective** if targeted at adolescents and adults
  - With 10-yearly mass campaigns, and 50% VE, duration of protection around 5 years in China, 4 years in S Africa and 3 years in India could lead to ~**25% reduction in TB incidence in 2050**



- Vaccine efficacy
  - In LMICs, as low as **20% VE could be cost effective** if delivered to adolescents/adults

Harris 2016 & 2019, Shrestha 2016, Lui 2017, Arregui 2017, Shrestha 2017, Harris, in prep

Summary of lit and generic candidate modelling 3/3

Over 2025-50

- Age
  - In LMICs, **adolescent and adult** vaccination may deliver **greater and faster** impact than infant vaccination
  - To reduce TB in 0-4 year olds, **vaccination of adolescents/adults may be more effective than vaccinating neonates directly**
  - Vaccines suitable for latently infected **older adults** (>60 years) **may provide greater impact than adolescent vaccination** in ageing, reactivation driven epidemics, such as China

- HIV
  - Population-level impact in S Africa would be **higher** with a vaccine **safe and effective in HIV** positive populations.

Harris 2016 & 2019, Shrestha 2016, Lui 2017, Arregui 2017, Shrestha 2017, Harris, in prep

Implications for vaccine development 1/2

Recruitment populations

- If maximum population-level impact by 2050 is the goal, **development of vaccines for adolescents/adults should be prioritized**
  - China - inclusion of older adults in clinical trials (at least 60-64 years)
- **Post-infection** populations in all settings
- **Pre-infection** populations should also, or instead, be recruited in **higher transmission** settings (India & SA)
- Ideally, if feasible, trials should be powered to assess efficacy in both populations
- If vaccine safe, **HIV-positive** populations should be recruited

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Implications for vaccine development 2/2

Endpoints

- In all settings, **disease** endpoints would be useful for demonstrating future impact
- However, in **higher transmission** settings (India & SA) **infection** endpoints could be used, especially as proof of concept
- Vaccine efficacy – assess feasibility of designing trials to **detect lower vaccine efficacies**

Study duration

- Studies would benefit from **extended follow up** to 5+ years (e.g. immuno subgroup)
  - But short duration vaccines may be impactful and cost-effective

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Summary of BCG revac and M72 '-like' impact modelling

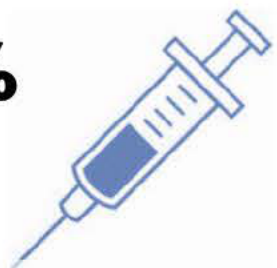
- If efficacy signals are confirmed, both vaccines could deliver substantial population-level impact
- To maximise impact
  - For BCG revaccination
    - explore whether has prevention of disease efficacy
  - For M72/AS01E
    - explore duration of protection, or feasibility of mass campaigns
    - explore pre-infection efficacy, and prevention of infection

Very preliminary potential cost effectiveness estimates for M72/AS01E

VACCINE CHARACTERISTICS

POD

50% VE



15 years

POPULATION

South Africa
India

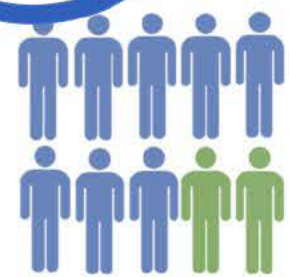
Safe and equally effective

Post-infection or pre&post-infection

VACCINE DEPLOYMENT

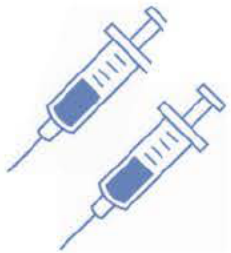
2025-2050

Routine for 10 or 15 year olds



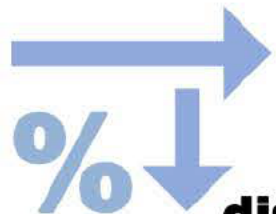
80% coverage

VACCINE COSTS



2 doses

$5/course
(vaccine & delivery)



3%
discounting

Harris et al unpublished

Summary 1/2

- An M72-like vaccine with 50% efficacy, 15 years duration of protection, and 80% coverage, could avert a substantial number of DALYs
- The incremental cost per DALY averted: (discounted 2025-50, incl vaccine and TB treatment costs)
  - In South Africa, ranged from
    - $24 (2- 66) for a pre- and post-infection vaccine delivered to 10 year olds, to
    - $316 (182 - 636) for a post infection vaccine delivered to 15 year olds
    - **All scenarios explored were cost effective** when compared to the latest (conservative) 'revealed' willingness to pay threshold of $547/life year saved [Meyer-Rath PLoS ONE 2017]
  - In India, ranged from
    - $143 (43-337) for a pre- and post-infection vaccine delivered to 10 year olds, to
    - $1,660 (718-4,246) for a post infection vaccine delivered to 15 year olds
    - **Using GDP per capita threshold of 1,939 (2017) in India, all scenarios are cost effective**
    - **However, a local preliminary analysis of opportunity costs** gave a lower bound for a WTP threshold of $223 (Ochalek, CHE working paper 2019) => **a post infection only vaccine delivered to 15 year olds may not be cost effective**

Summary 2/2

- Total # DALYs averted, and total vaccine costs, were higher in India, due to the much greater population size in India, than South Africa
- TB treatment cost savings were the main cost benefits, with minimal additional cost savings from diagnostics
- Total vaccination costs were substantially lower in South Africa, and treatment/diagnostic costs averted were relatively high, leading to a lower cost per DALY averted in South Africa, even when accounting for the additional costs incurred by the HIV programme for ART
- A M72-like vaccine could be cost effective in both settings, depending on WTP

Overview

Objectives

- Summarize overall modelling evidence
- Summarize v prelim M72/AS01 and BCG re-vx modelling evidence
- **Summarize WHO-funded, Full Value Assessment of TB Vaccines project**
- Summarize BMGF-funded, M72/AS01 and BCG revaccination specific modelling project

Outcomes

- PDVAC qus, and advice on what, if any, high priority follow-up work
- PDVAC qus, and advice on if and how could be more useful to global and country stakeholders

Full value assessment of TB vaccines

Full value assessment of TB vaccines in all LMICs and BRICS

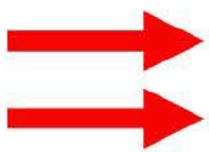
WHO

Method

- Data collation
- Trans & econ modelling (HS & societal)
- WHO PPCs (incl M72/AS01 & BCG reVx)

- Impact on
  - TB inci, morb & mort, by DS/DR/HIV
  - Costs, CE, budget impact
  - ROI, equity, GDP, AMR drug use

- Country and global decision makers
- Funders



	2021												2022											
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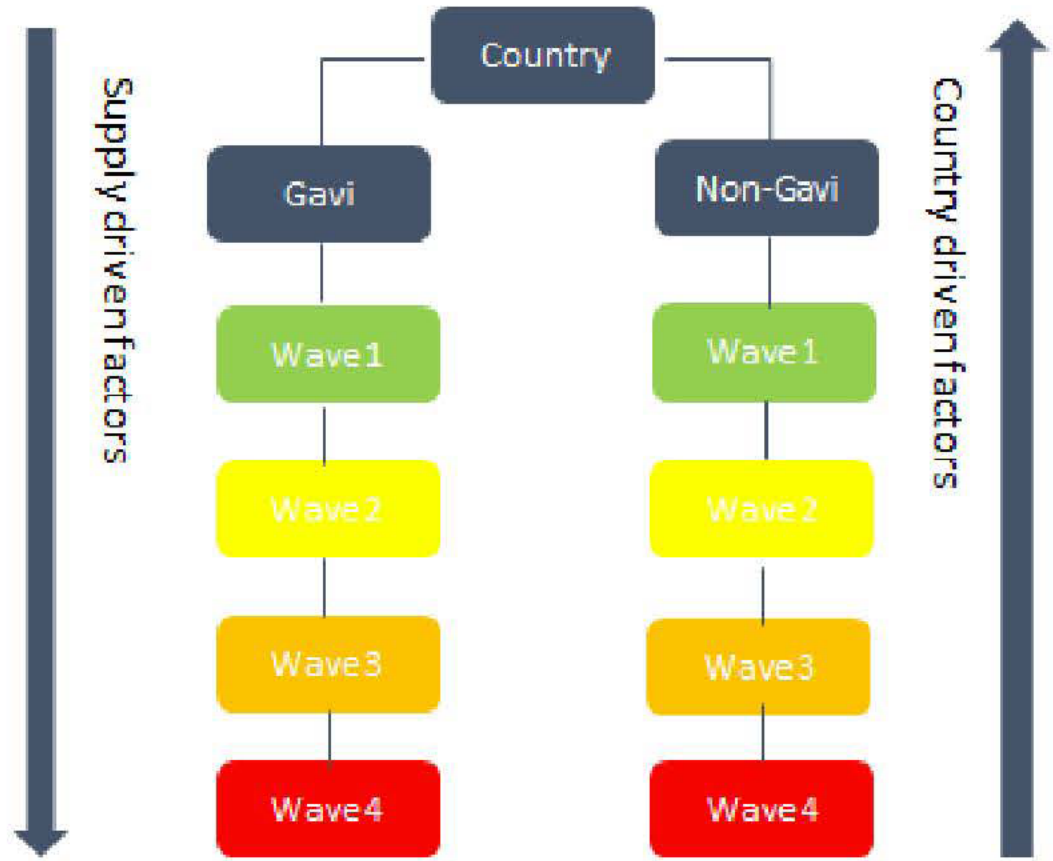
Full value assessment of TB vaccines (WHO)																											
M72 & BCG revax impact and CE (BMGF)																											
Introduction and implementation data collection																											

Introduction Timelines: Proposed Approach

- Countries will be archetyped according to Gavi vs non-Gavi status
- Countries will be grouped into Waves of introduction (1, 2, 3, 4)
- Criteria for grouping into Waves & for date of introduction will include:
  - *Supply driven factors:*
    - Supplier prioritization, Gavi & procurement agency criteria & processes
  - *Country driven factors:*
    - Demand, political will, health systems readiness, regulatory timelines



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- PDVAC qus, and advice on what, if any, high priority follow-up work
- PDVAC qus, and advice on if and how could be more useful to global and country stakeholders

Epi & econ impact of M72/AS01 and BCG reVx

Epi & econ impact of M72 and BCG reVx in South Africa & India

Decision Science Framework: Uncert in

- Product chars
- Intro policy and implementation
- Health system performance
- Value

BMGF

Method

- Data collation
- Trans & econ modelling (HS & societal)
- M72 & BCG ReVx

- Impact on
  - TB inci, morb & mort, by DS/DR/HIV
  - CE and budget impact
- India nat and sub national

- BMGF

	2021													2022											
	9	10	11	12	1	2	3	4	5	6	7	8	9	10	11	12	1	2	3	4	5	6	7	8	9	10	11
Full value assessment of TB vaccines (WHO)																											
M72 & BCG revax impact and CE (BMGF)																											
Introduction and implementation data collection																											

M72/AS01 & BCG reVx implementation strategy interviews in S Africa, India (and China)

Mixed methods	Semi-structured interviews to investigate:	Study population
• quantitative and qualitative results • quantitative indicators of implementation strategies • qualitative: acceptability, challenges and solutions	• implementation scenarios • associated costs • context-specific challenges to adolescent/adult TB vaccine implementation	• Interviewees are 8 decision makers/stakeholders per country 

New math. model for the TB Vaccine field

So in discussion with funders, decided to create new model, rather than adapt old ones...

Scientific benefits

- Incorporate new natural history insights in vaccine impact estimates, eg self clear
- Estimate impact of combinations of protection from multiple vaccines and natural immunity
  - Eg natural + BCG revx + M72

Technical/user benefits

- The model is a multi-purpose **tool** for infectious disease dynamics
- The user defines the model
  - age groups
  - Infection natural history and transmission
  - Dependencies by HIV, RISK, SES and TB Vaccine
  - Mixing, eg due to age and SES
- Simple and fast due to matrix operations

Overview

Objectives

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Outcomes

- **PDVAC qus, and advice on what, if any, high priority follow-up work**
- **PDVAC qus, and advice on if and how could be more useful to global and country stakeholders**

Acknowledgements and Thanks!

Contributors/Advisors:

- WHO (Gitte Giersing, Johan Vekemans)
- IAVI (Derek Tait, Shelly Malhotra)
- BMGF (Willem Hanekom, Anne Kasmar, Geoff Garnett, Ann Ginsburg)
- TBVI (Bernard Fritzell, Nick Drager)
- India (Kieran Rade, Raguram Rao)
- China (Li Tao and Lixia Wang)
- South Africa (Mark Hatherill, Michele Tamaris)
- Aeras (Tom Evans, Vicky Cardenas, Danny Casimiro, Chen Chen, Sharon Chan)

Funders:

From: GIERSING, Birgitte
Sent: Tue, 1 Sep 2020 09:05:39 +0000
To: Gagandeep Kang;Graham, Barney (NIH/VRC) [E];Sinead Delany-Moretlwe;Bernard Fritzell;(SPmig) Shabir Madhi;Karron, Ruth;klaus.cichutek;Marian Wentworth;Papania, Mark (CDC/DDPHSIS/CGH/GID);Yshao;Jerome Kim;Peter Smith;Claudio Lanata; (b) (6) ;dracravioto;Kaslow, David;Bekeredjian-Ding, Isabelle
Cc: FRIEDE, Martin Howell;SPARROW, Erin Grace;Pabillon-Green, Karen
Subject: PLEASE READ ahead of TB PDVAC meeting: Consolidated comments/position on the AIGHD TB vaccine roadmap
Attachments: TB Vaccine Roadmap draft for PDVAC consolidated responses 31 Aug 2020 anon.docx, Gates MRI TBV PDVAC 20200903.pdf

Dear PDVAC members,

Thank you to those who provided comments on the draft TB vaccine roadmap developed by AIGHD. Attached is a consolidated list of comments received (anonymised), and the **main elements are summarised below**. In addition to your review, I sent the draft to two country level stakeholders who attended the original stakeholder consultation in March, but had not provided any input to the current draft. These were:

- Dr. Xia Yin Yin, Dept. of High Risk & Vulnerable Population, National Center for TB Control and Prevention, China CDC (comments in yellow highlight)
- Denise Arakaki, Ministry of Health, National Tuberculosis Control Program, Brasilia, Brazil (comments in green highlight)

As you know, one of the outcomes from the meeting on Thursday is a decision on whether to co-publish this document. Four PDVAC members, and I reviewed the draft roadmap. 3/4 reviewers, including me, do not feel that this draft is appropriately focused for WHO co-publication, and will require significant re-shaping. During the upcoming PDVAC meeting, we are also seeking to identify the priority/critical needs for PDR/PDVAC engagement in TB vaccine development going forward. As you know, Johan is no longer with us, so we have a human resource 'crunch' in this area, as well as very limited funding for consultants or activities for at least the next 12 months. So we'll need to consider the effort needed to 'revamp' this roadmap alongside other priority activities. If we decide not to co-author, it would be helpful to discuss ways that WHO can support the roadmap objectives but perhaps focus on some of the elements that we feel are not strongly enough positioned in the roadmap.

We have a full session on Thursday, as always! I hope this summary facilitates decision in the closed session. I am also attaching Alex Schmidt's slides on M72 and BMG revax as these are now final. Frank and Richard's on the roadmap and model to follow.

All the best,
Gitte

***

There are many comments for clarification/re-pointing/expansion, and proposed edits, but major content gaps include:

(b) (4)

Birgitte Giersing, PhD
Team Lead Vaccine Platforms & Prioritization(a.i.)
Vaccine Product and Delivery Research (PDR)
Dept of Immunization, Vaccines and Biologicals (IVB) | **World Health Organization** (**WHO**)
(o) M135 (t) (b) (6) (m) (b) (6) (e) (b) (6)

(b) (4)

GLOBAL ROADMAP FOR RESEARCH AND DEVELOPMENT FOR TUBERCULOSIS VACCINES

(branding and organizational style to be included)

List of abbreviations

AVAREF	African Vaccine Regulatory Forum
BCG	Bacillus Calmette–Guérin
CD4+	T-lymphocytes expressing the Cluster of Differentiation 4 receptor
CD8+	T-lymphocytes expressing the Cluster of Differentiation 8 receptor
CEPI	Coalition for Epidemic Preparedness Innovations
CHIM	Controlled human infection model
CoP	Correlate of protection
CTVD	Collaboration for TB Vaccine Discovery
EDCTP	European Developing Countries Clinical Trials partnership
GFATM	Global Fund to fight AIDS, Tuberculosis and Malaria
GTBVP	Global TB Vaccine Platform
HPV	Human Papilloma Virus
IAVI	International AIDS Vaccine Initiative
IFN-γ	Interferon-gamma
IGRA	Interferon-gamma release assay
MAIT cells	Mucosal associated invariant T lymphocytes
Mtb	*Mycobacterium tuberculosis*
NGO	Non-governmental organization
NITAG	National Immunization Technical Advisory Group
PEPFAR	President's Emergency Plan for AIDS Relief
PLWH	People living with HIV/AIDS
PoD	Prevention of disease
PoI	Prevention of infection
PoR	Prevention of recurrence
R&D	Research and development
TB	Ttuberculosis
TBVI	Ttuberculosis Vaccine Initiative
Th1 cells	T-helper lymphocytes, type 1
Th17 cells	T-helper lymphocytes, type 17
WHO	World Health Organization

Executive summary

=> to be included

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1. PURPOSE, PROCESS AND SCOPE

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Scope of the Roadmap

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[redacted]

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2. Roadmap action lines

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II Theme 2: Accelerating clinical development

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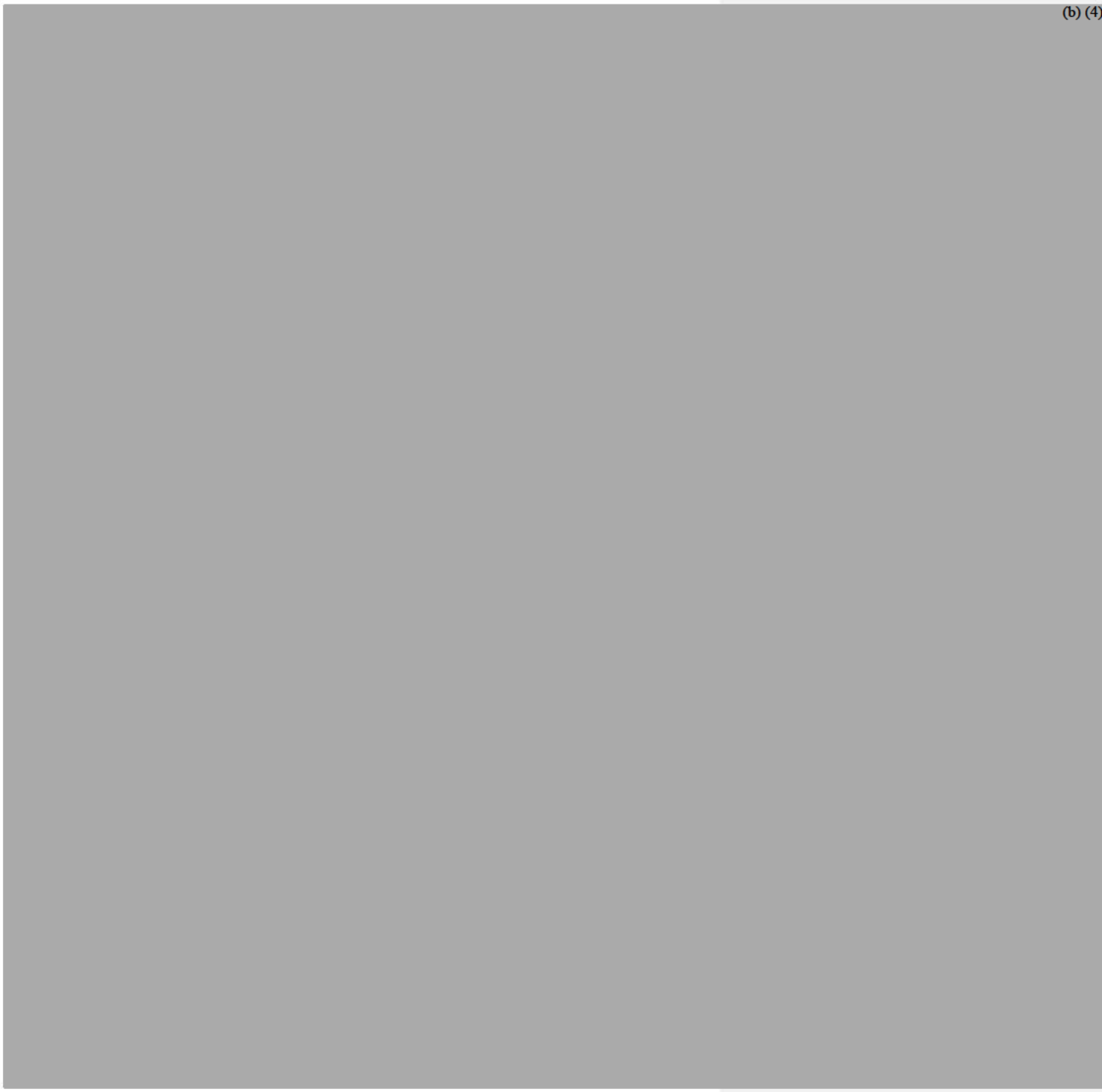

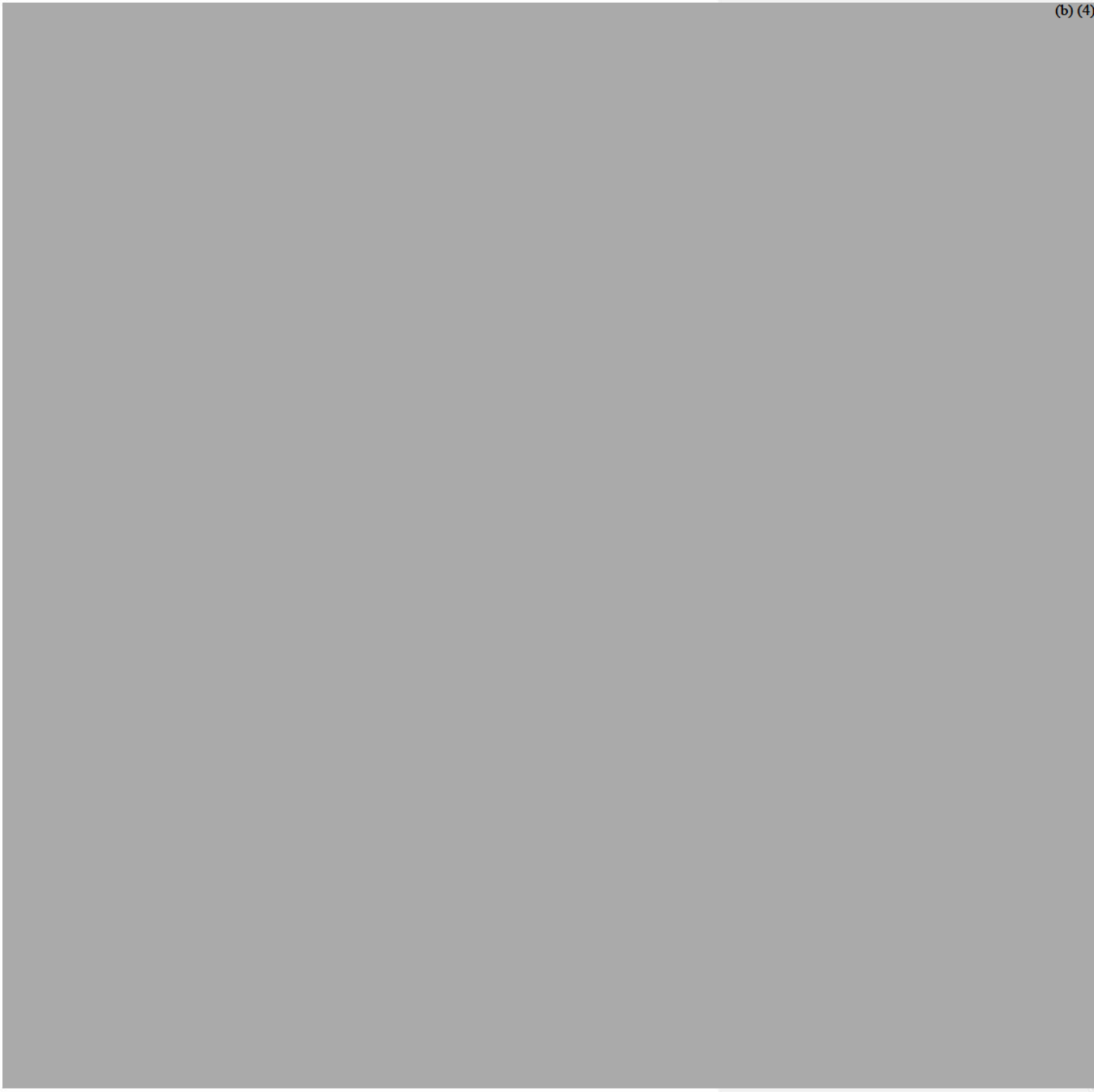
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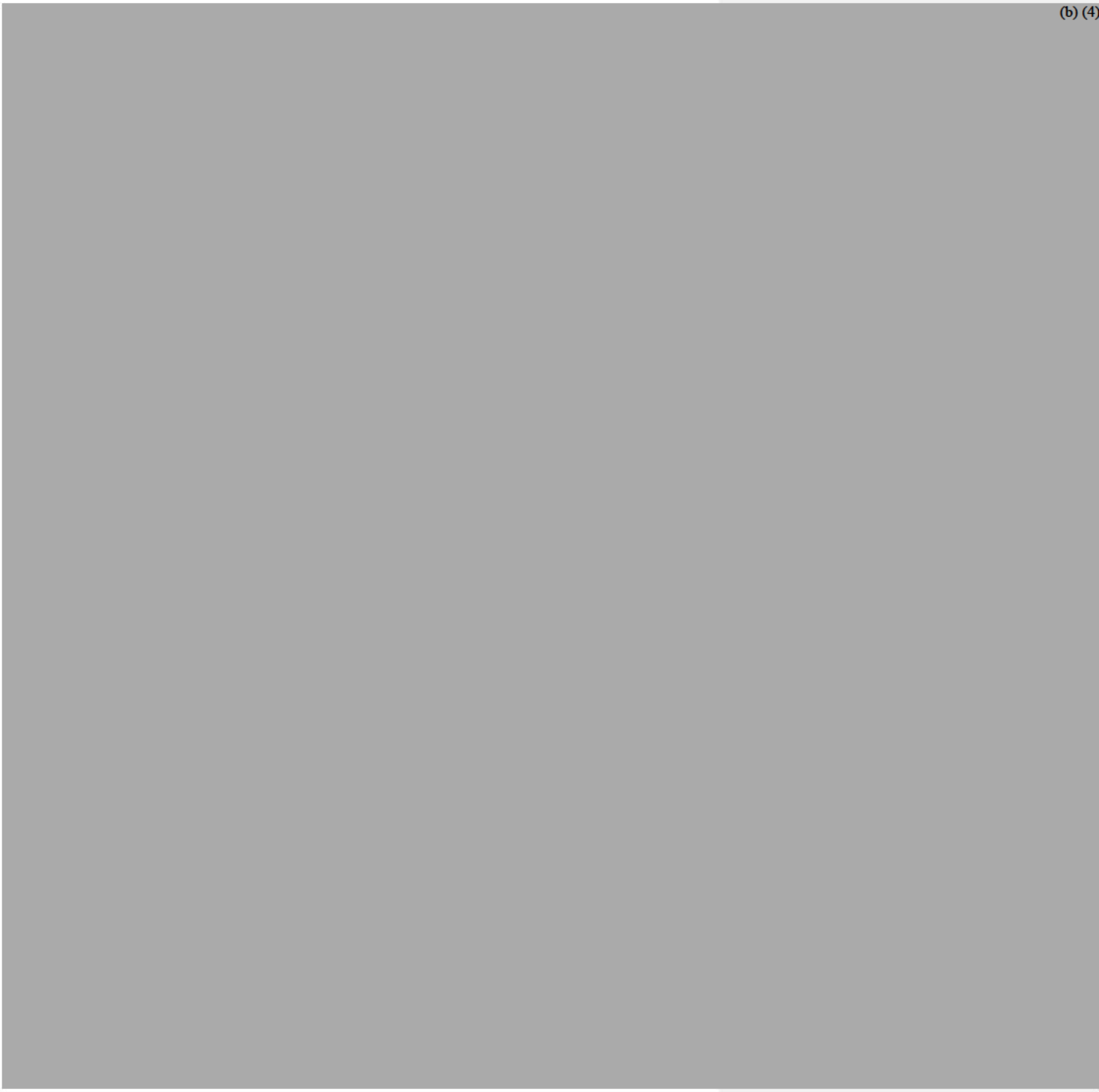
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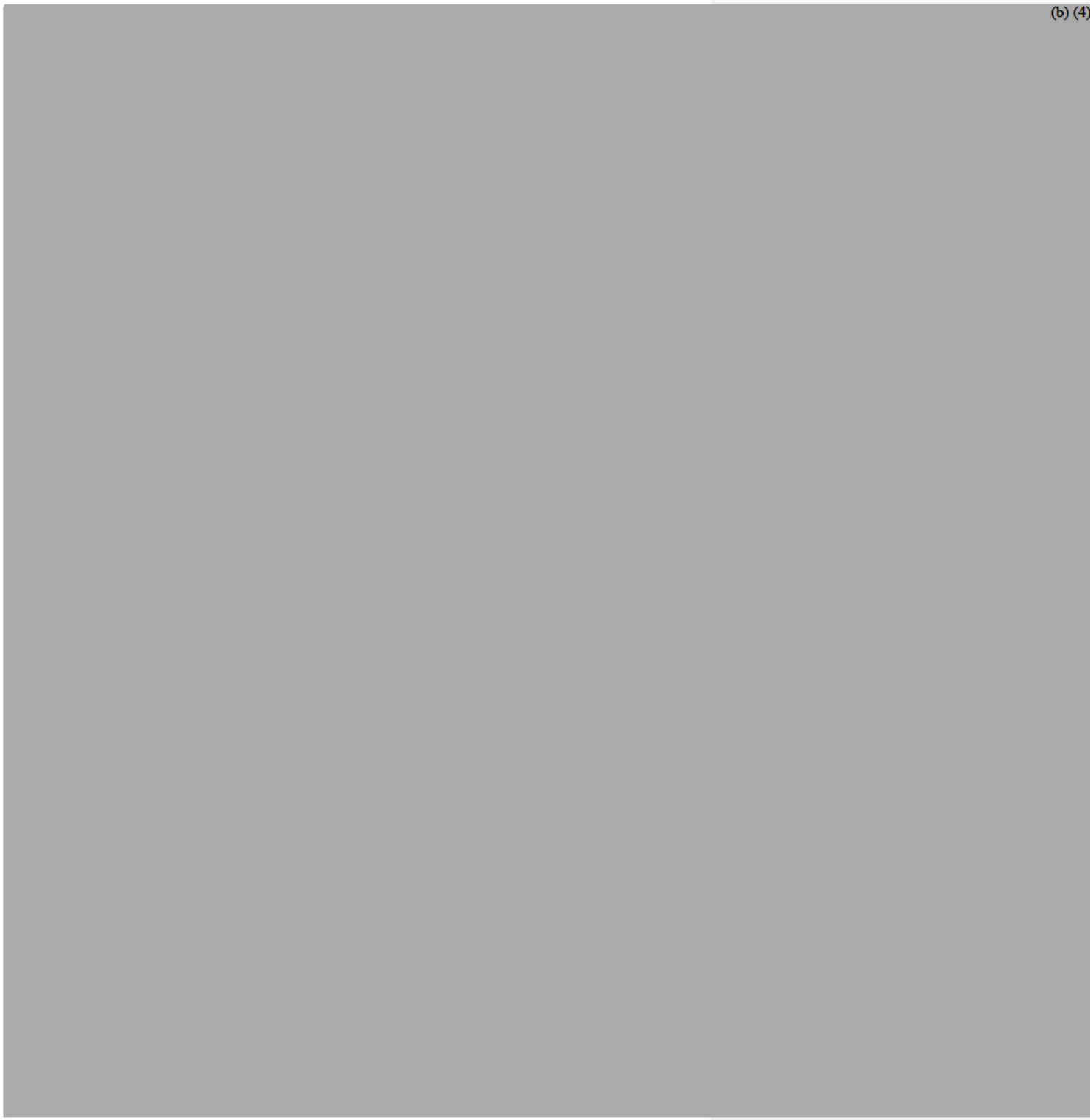
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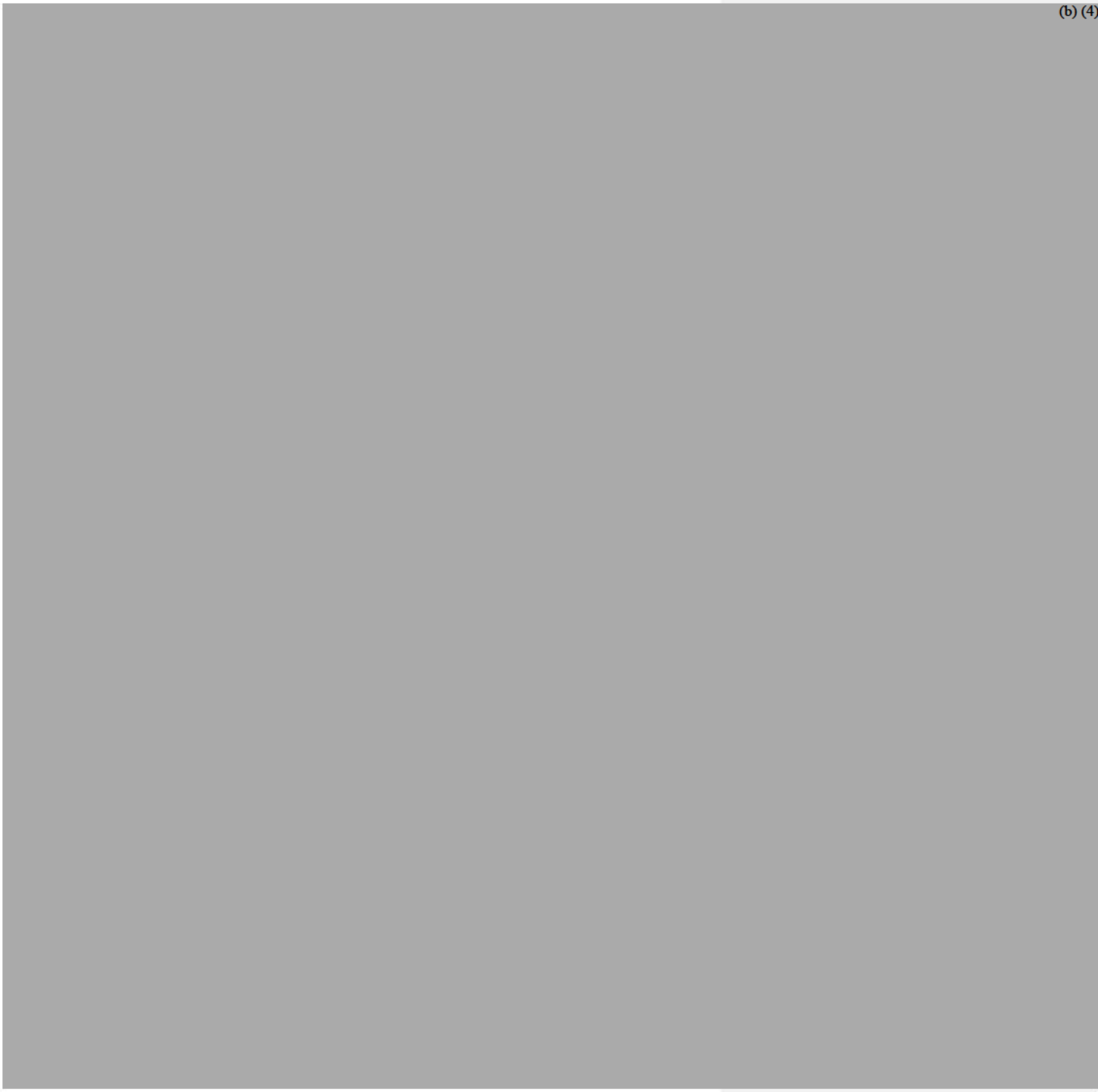
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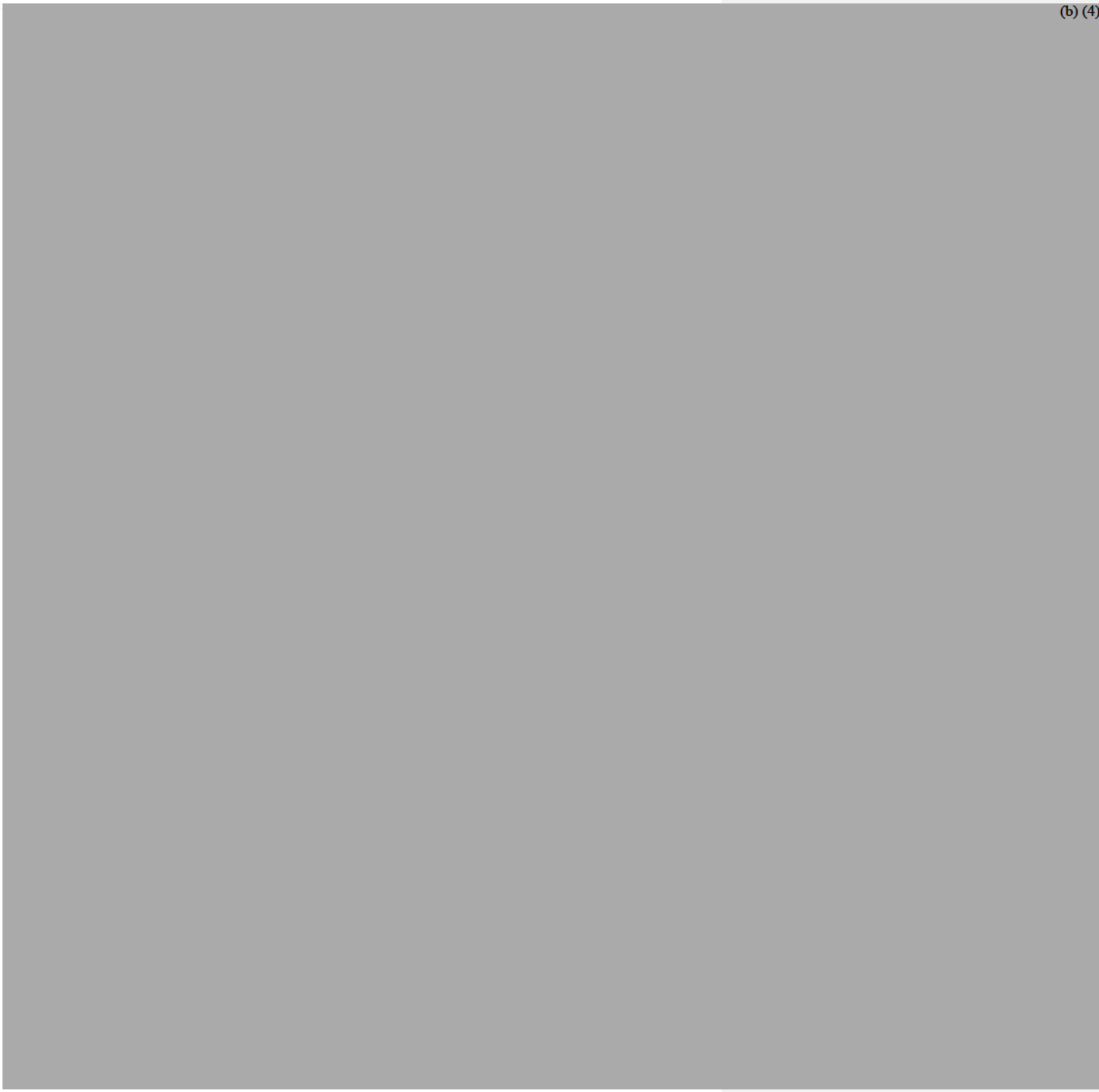
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BILL & MELINDA GATES MEDICAL RESEARCH INSTITUTE

Update on Gates MRI TB Vaccine Development Activities

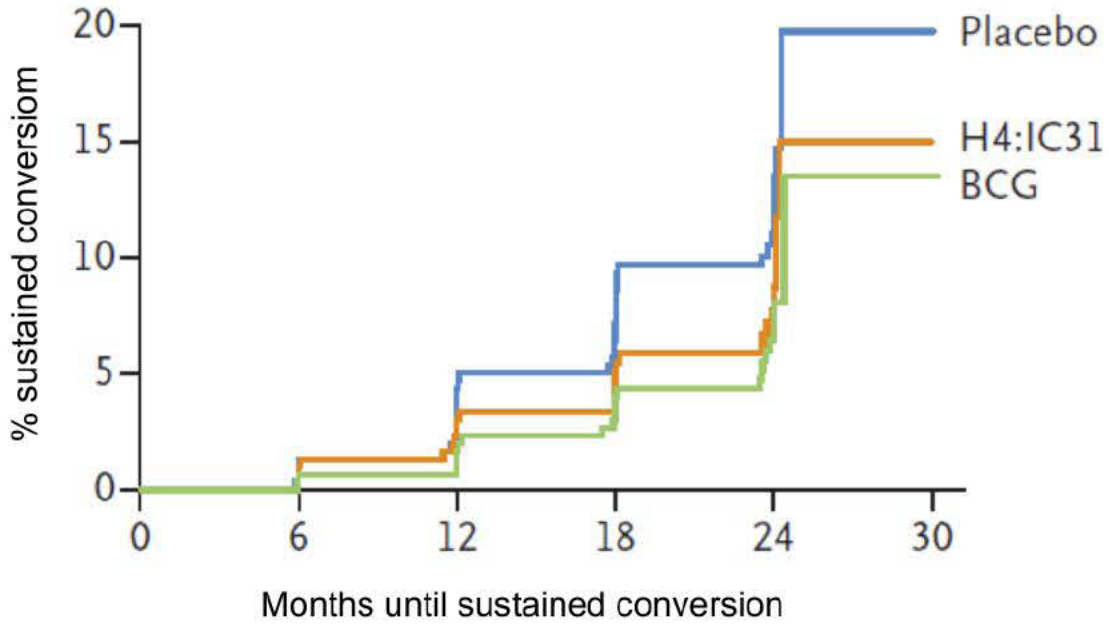
Alexander Schmidt, Taryn Rogalski-Salter,
Robin Mogg, Nicole Frahm & Marie Green

PDVAC, September 3, 2020

GATES MRI BCG REVACCINATION STUDY

AERAS C-040-404 STUDY

- N=990, 1:1:1, primary endpoint: initial QFT-conversion, secondary EP: sustained QFT-conversion
- BCG: 45% (95%CI 6.4-68.1%) vaccine efficacy for sustained QFT conversion



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Prevention of *M. tuberculosis* Infection with H4:IC31 Vaccine or BCG Revaccination

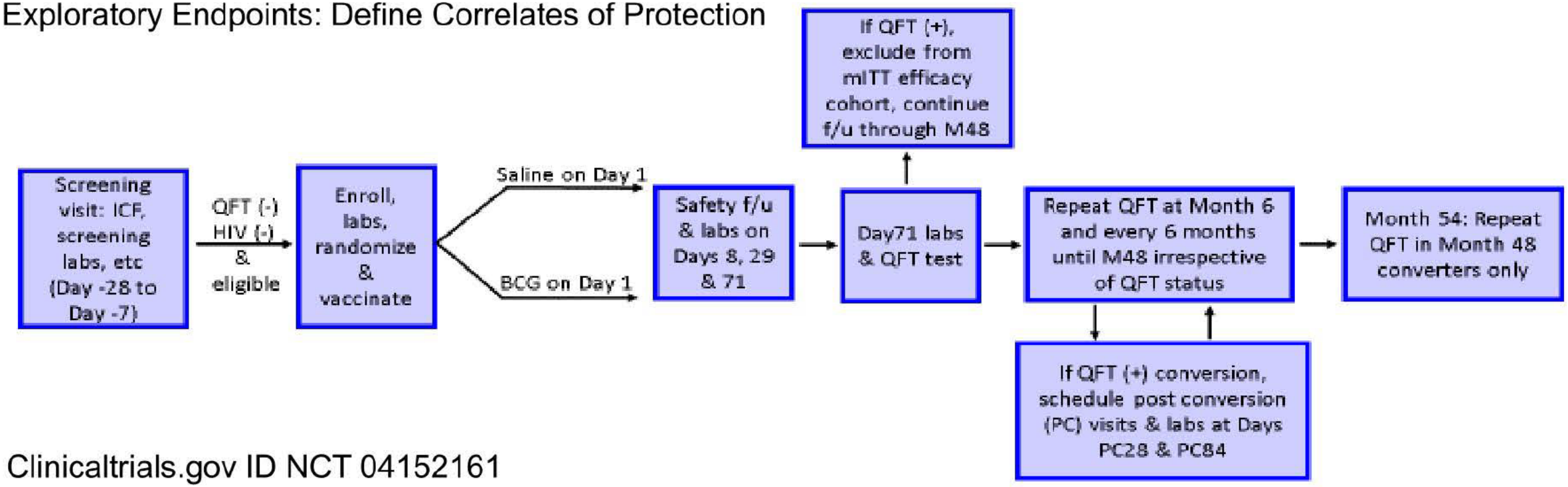
E. Nemes, H. Geldenhuys, V. Rozot, K.T. Rutkowski, F. Ratangee, N. Bilek, S. Mabwe, L. Makhethe, M. Erasmus, A. Toefy, H. Mulenga, W.A. Hanekom, S.G. Self, L.-G. Bekker, R. Ryall,* S. Gurunathan, C.A. DiazGranados, P. Andersen, I. Kromann, T. Evans, R.D. Ellis, B. Landry, D.A. Hokey, R. Hopkins, A.M. Ginsberg, T.J. Scriba, and M. Hatherill, for the C-040-404 Study Team†

DOI: 10.1056/NEJMoa1714021

GATES MRI BCG ReVax STUDY

Goal: generate data that can potentially support policy changes for BCG revaccination

- Randomized, placebo controlled, observer-blind, Phase 2b study with two arms (BCG vaccine and saline placebo)
- 1,800 QFT-negative participants 10-18 years of age are randomized 1:1 to receive a single intradermal injection
- Primary Endpoint: Sustained QFT conversion (initial conversion and IGRA positive 3 & 6 months thereafter)
- Exploratory Endpoints: Define Correlates of Protection



Clinicaltrials.gov ID NCT 04152161

alexander.schmidt@gatesmri.org

BCG ReVax STUDY STATUS

- Five sites in South Africa (SATVI, CAPRISA, Wits RHI, Desmond Tutu HRF, Be Part)
- First participant randomized November 6, 2019
- Screening and randomization paused due to COVID-19-related restrictions from March 19, 2020
- Enrolment resumed starting in July 2020 (site-by-site)
- Approx. 400 of 1,800 participants enrolled
- Enrolment completion anticipated for Q3 2021
- Primary endpoint analysis will occur when a total of 118 sustained *Mtb* infection events have occurred in the mITT efficacy population (anticipated in late 2023, or early 2024)

BCG Immune Correlates Program (CoP for POSI)
- using biospecimens from Aeras C-040-404 trial -

CELLULAR IMMUNITY

- Antigen-specific T cells and NK cells (McElrath)
  - Intracellular cytokine staining
- Donor-unrestricted T cells (DURTs, MAITs) (McElrath)
  - Tetramer staining
- scRNAseq (Shalek)

HUMORAL IMMUNITY

- Antibody titer, subclass and avidity (Tomaras)
  - Binding antibody multiplex assay
- Antibody function (Alter)
  - Systems serology
- Antibody-mediated mycobacterial growth inhibition (Alter)

INNATE / TRAINED IMMUNITY

- Whole blood composition (Nemes)
  - DLC-ICE
- scATACseq (Barreiro)
- EpiToF (Utz/Khatri)

OMICS ANALYSES

Bulk RNAseq (Scriba)

WHAT IS NEEDED TO ADVANCE BCG REVACCINATION?

Anticipated data availability:

- Candidate Correlate of Protection (CoP) data for prevention of sustained infection (POSI) (based on Aeras revaccination study biospecimens) in 2023.
  - / Candidate CoP to be confirmed with biospecimens from Gates MRI BCG ReVax study.
- Candidate CoP data for prevention of Disease (POD) (based on M72 Phase 2b trial) in 2023.
  - / To be confirmed with biospecimens from M72/AS01 Phase 3 study.
  - / Best case assumption is that we can identify a CoP for progression from sustained infection to disease.
- BCG ReVax primary endpoint data (sustained IGRA-conversion) in 2024

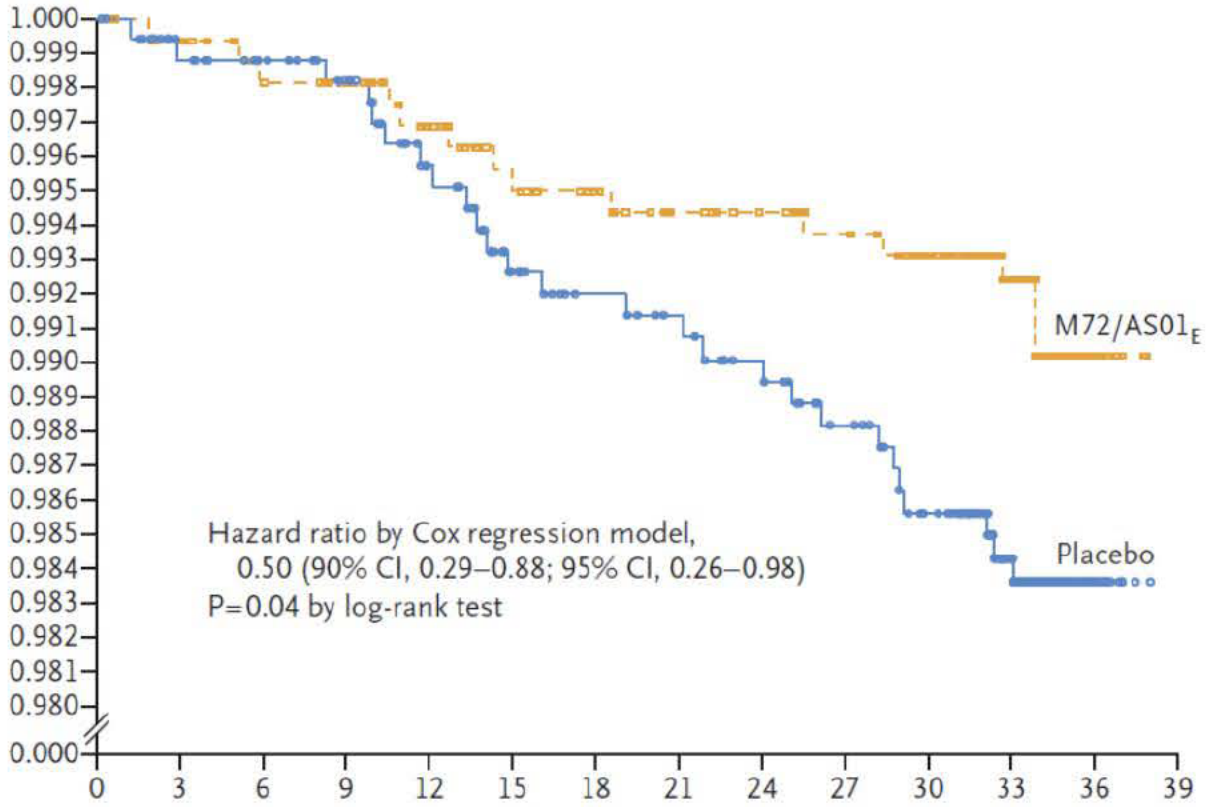
- Other BCG developers may replicate BCG ReVax study in a second geography
- POD clinical endpoint efficacy trial is unlikely to be conducted (too large, too expensive)

M72/AS01 VACCINE DEVELOPMENT

M72/AS01$_E$ & PREVENTION OF DISEASE

PHASE 2B TRIAL IN A QFT-POSITIVE POPULATION

- 49.7% (95% CI 2.1 to 74.2%) vaccine efficacy
- Acceptable safety profile



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Phase 2b Controlled Trial of M72/AS01$_E$ Vaccine to Prevent Tuberculosis

O. Van Der Meeren, M. Hatherill, V. Nduba, R.J. Wilkinson, M. Muyoyeta, E. Van Brakel, H.M. Ayles, G. Henostroza, F. Thienemann, T.J. Scriba, A. Diacon, G.L. Blatner, M.-A. Demoitié, M. Tameris, M. Malahleha, J.C. Innes, E. Hellström, N. Martinson, T. Singh, E.J. Akite, A. Khatoon Azam, A. Bollaerts, A.M. Ginsberg, T.G. Evans, P. Gillard, and D.R. Tait

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Final Analysis of a Trial of M72/AS01$_E$ Vaccine to Prevent Tuberculosis

D.R. Tait, M. Hatherill, O. Van Der Meeren, A.M. Ginsberg, E. Van Brakel, B. Salaun, T.J. Scriba, E.J. Akite, H.M. Ayles, A. Bollaerts, M.-A. Demoitié, A. Diacon, T.G. Evans, P. Gillard, E. Hellström, J.C. Innes, M. Lempicki, M. Malahleha, N. Martinson, D. Mesia Vela, M. Muyoyeta, V. Nduba, T.G. Pascal, M. Tameris, F. Thienemann, R.J. Wilkinson, and F. Roman

DOI: 10.1056/NEJMoa1803484 & DOI: 10.1056/NEJMoa1909953

M72/AS01$_E$ PRODUCT DEVELOPMENT

Generate data to support licensure of the vaccine and recommendations for effective use

- GSK licensed M72/AS01$_E$ to the Gates MRI, paving the way for continued vaccine development and potential use in LMICs
- GSK will ensure an efficient transfer of the asset technology
- Gates MRI will lead product development and sponsor future clinical trials
- GSK will provide AS01 adjuvant for the development program
- Gates MRI will actively reach out to and collaborate with the many partners and stakeholders committed to accelerating the end of the TB epidemic.

KEY TOPICS & QUESTIONS FOR M72

- Phase 3 study
  - Does M72/AS01E protect IGRA-positive individuals from disease (and for how long)?
  - Does M72/AS01E protect IGRA-negative individuals from infection (and/or disease)?
  - Primary endpoint, age range, IGRA status, participating countries, how to enrich for high risk?
- Data needed for first dossier in South Africa
  - Lower bound of 95% CI? Submission with interim data (95%CI LB>0?), followed by primary analysis data (95%CI LB>15%?)
- Delivery considerations
  - Target age groups (depending of VE in IGRA-negative individuals)
  - Delivery channels, payors?
- What needs to be included in the Phase 3 study design, and what implementation research is needed to support WHO policy recommendation, PQ and financing?

CRITICAL PATH

Clinical & Regulatory:

- Generate Safety & Immunogenicity data to support inclusion of PLHIV in Phase 3 VE trial
- Develop Phase 3 protocol jointly with stakeholders, SMEs & NRAs
- Select countries and prepare sites for Phase 3 VE trial
- Reach agreement on protocol design & initial registration package with health authorities
- Conduct Phase 3 vaccine efficacy study

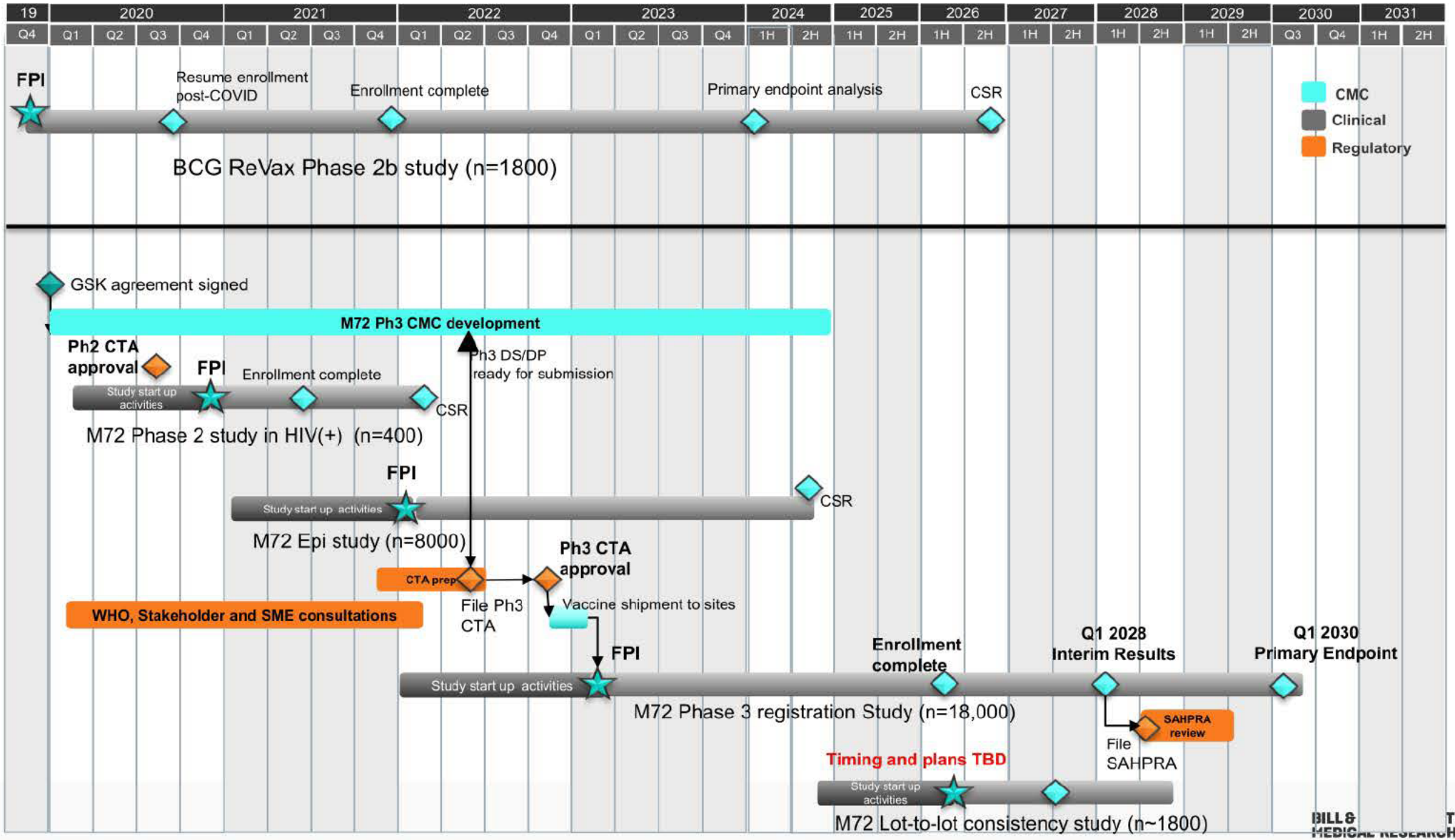
Technical Development:

- Develop M72 antigen manufacturing process to support Phase 3 and commercialization.
- Develop adjuvant manufacturing process to support Phase 3 and commercialization
- Manufacture new drug product & supply Phase 3
- Identify Commercial Manufacturer / Marketing Authorization Holder and transfer M72 manufacturing

INITIAL ASSUMPTIONS ON DEVELOPMENT TIMELINES

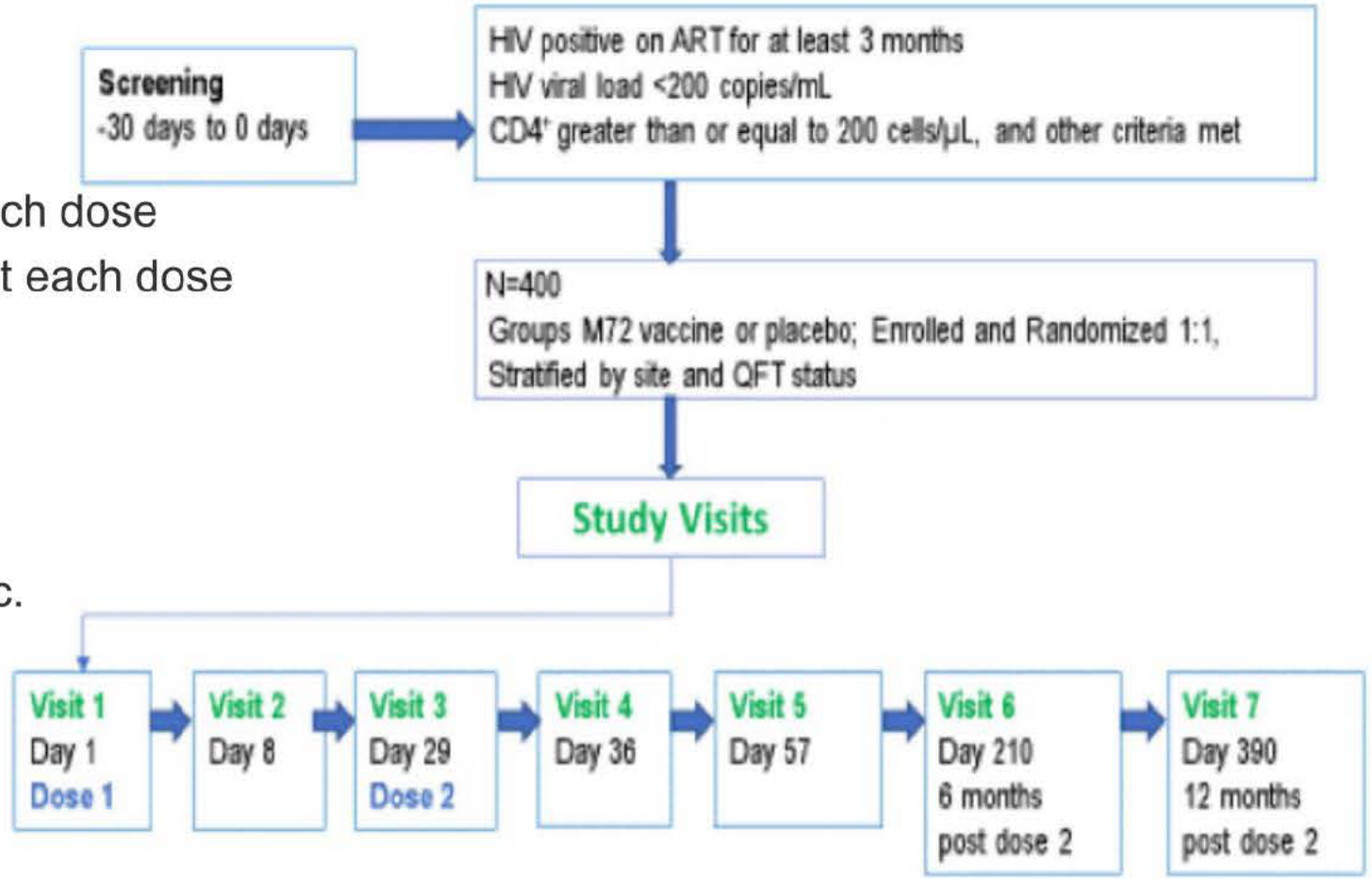
BCG ReVax

M72/AS01E



PHASE 2 STUDY IN PLHIV

- Observer-blind, 1:1 randomized study
- Primary objectives
  - Solicited AEs through 7 days post each dose
  - Unsolicited AEs through 28 days post each dose
  - All SAEs through end of study
- Secondary objectives:
  - M72-specific humoral and cellular immunogenicity
- Exploratory objectives: HIV RNA, CD4 etc.
- Study start anticipated for Nov 2020
- Sites in Durban, Cape Town, Johannesburg & Worcester
- SAHPRA approval received
- Awaiting IRB approvals
- Enrollment anticipated to start November 2020



EPI STUDY IN PREPARATION FOR PHASE 3

Scientific Objectives	Endpoints
Primary	
• To assess prevalence of LTBI	• Interferon gamma (IFNg) release assay positivity by age and by site
Secondary	
• To describe the incidence of TB	• Suspected TB cases by site, risk group, and overall • Lab-confirmed TB cases by site, risk group, & overall
Tertiary/Exploratory	
• To describe the association between IGRA IFNg concentration and progression to TB	• IGRA IFNg concentration at baseline & and risk of TB

EPI STUDY IN PREPARATION FOR PHASE 3

Operational goals:

- Build site capacity & train teams
- Establish operational feasibility for each site: QFT-positivity by age, quality of TB surveillance & study procedures
- Establish study cohorts; subset could be invited to participate in Phase 3 (e.g., IGRA-negatives & recent converters)

Design:

- Approx. 8,000 study participants, f/u 12 - 24 months; study to end at a given site once site is ready to start Phase 3 enrolment
- Approx. 50 sites
- IGRA status at baseline, follow-up every 2 months to identify suspected TB

PHASE 3 EFFICACY STUDY DESIGN FOR M72/AS01$_E$

- **Objectives:**
  - Unequivocally demonstrate VE for POD in QFT-positive participants
  - Support licensure for use irrespective of QFT status, i.e., include enough QFT-neg participants to establish safety, immunogenicity & initial assessment of VE in QFT-neg vaccinees. (Screening for QFT status in national programs is currently not feasible)
  - Support licensure including people living with HIV
- Trial simulations suggest that at least 14,000 subjects in very high incidence settings are needed to demonstrate VE in a randomized controlled trial (1:1 vs placebo)
- An interim analysis for VE could be explored to potentially accelerate submission of a first dossier

PHASE 3: KNOWLEDGE GAPS & CHALLENGES

- Significant uncertainty with regards to incidence of *Mtb* infection & TB disease
  - Highest possible TB incidence rate needed to increase probability of success
  - Clinical trials capacity needed in poor communities in LMICs
- Significant uncertainty with regards to true vaccine efficacy (VE)
  - Primary endpoint definition appears to have impact on VE and incidence rate in IGRA-positives
  - No data on VE in IGRA-negative populations
  - No data on VE in PLHIV
- How can we mitigate uncertainties?
  - Determine site-level QFT prevalence, build capacity, enrich for high incidence, event-triggered primary analysis, adaptive trial, IDMC oversight of unblinded data

PARAMETER ASSUMPTIONS FOR TRIAL SIMULATIONS

Trial Parameter	Value	Reference
Age range	16 – 30 year of age	
Proportion baseline QFT-pos	65%	
Incidence of Disease (D) in QFT-pos	0.4 – 0.6% per year	Van Der Meeren et al (2018), NEJM
True VE in QFT-pos	50 – 65%	Van Der Meeren et al (2018), NEJM
Participant follow-up time	5 years	Study defined
Accrual time	3 years	Assumed
Participant drop out rate	5% per year	
Incidence of Infection (INF) in QFT-neg	5% per year (i.e., sustained QFT-pos conversion)	Nemes et al (2018), NEJM
Incidence of D in QFT-neg	1.6% per year after sustained conversion (no disease among non-sustained converters)	Nemes et al (2017), American Journal of Respiratory and Critical Care Medicine
True VE in QFT-neg	VE(INF) = 25%; VE(D) = VE(INF)	No data

PHASE 3 DESIGN CONSIDERATIONS

How likely are we to succeed?

- Probability of success (i.e., study "power") based on (i) number of observed events; (ii) true VE; and (iii) lower bound of VE needed

Show 95% CI LB on VE >	# required events when true VE =								
	70%	65%	60%	55%	50%	45%	40%	35%	30%
0%	29	39	51	66	88	118	162	227	331
15%	39	54	74	104	150	222	347	585	1115
20%	44	62	88	127	191	300	508	975	2358

Equal randomization, Type I error = 1-sided 2.5%, 90% power

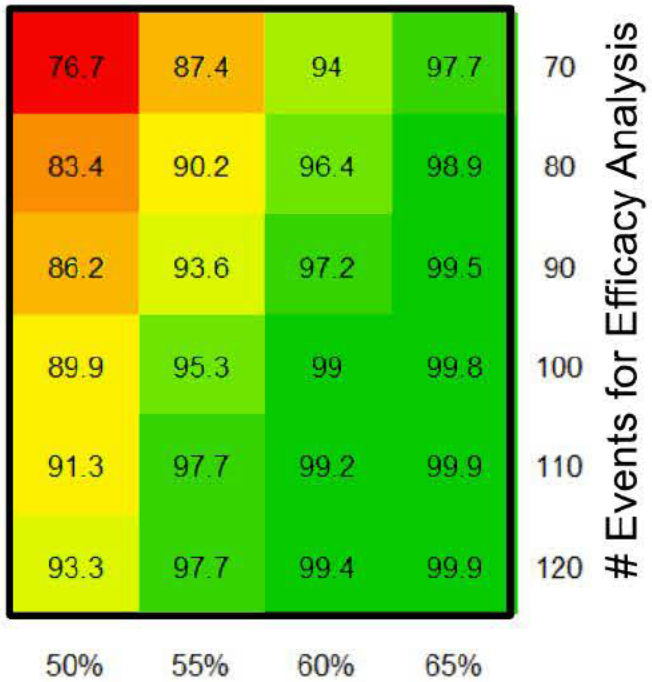
How long will it take to get the answer?

- Expected timing of analysis based on (i) sample size; (ii) underlying incidence; (iii) participant follow-up time; (iv) drop-out rate; and (v) study accrual rate

CLINICAL TRIAL SIMULATIONS INFORM PHASE 3 STUDY DESIGN

Point 1: # events needed to rigorously confirm vaccine efficacy against disease (VE(D)) depends on underlying true VE

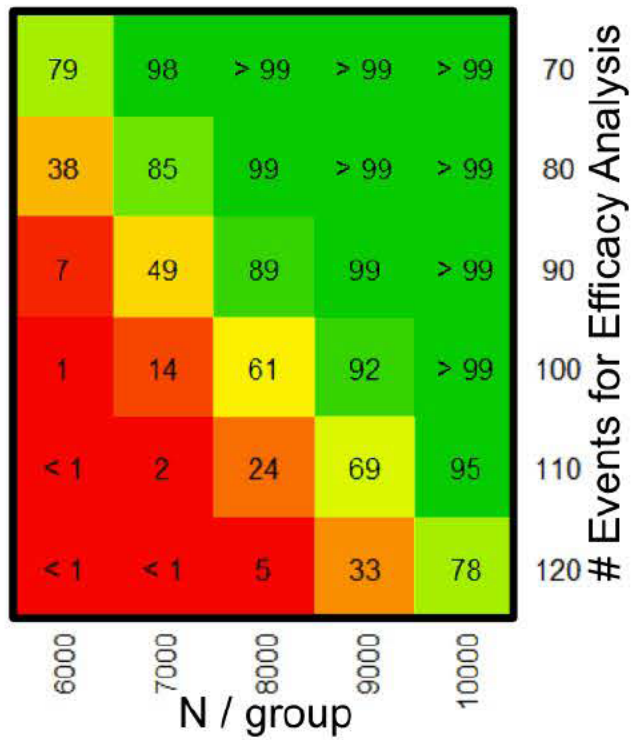
Probability of observing 95% CI LB for VE(D) > 0% in QFT-pos



- Probability of observing 95% CI LB for VE(D) > 0% in "all-comers" comparable to QFT-pos
- Increasing LB of CI for VE(D) from 0 to e.g., 15% significantly increases the # events required for Phase 3 success

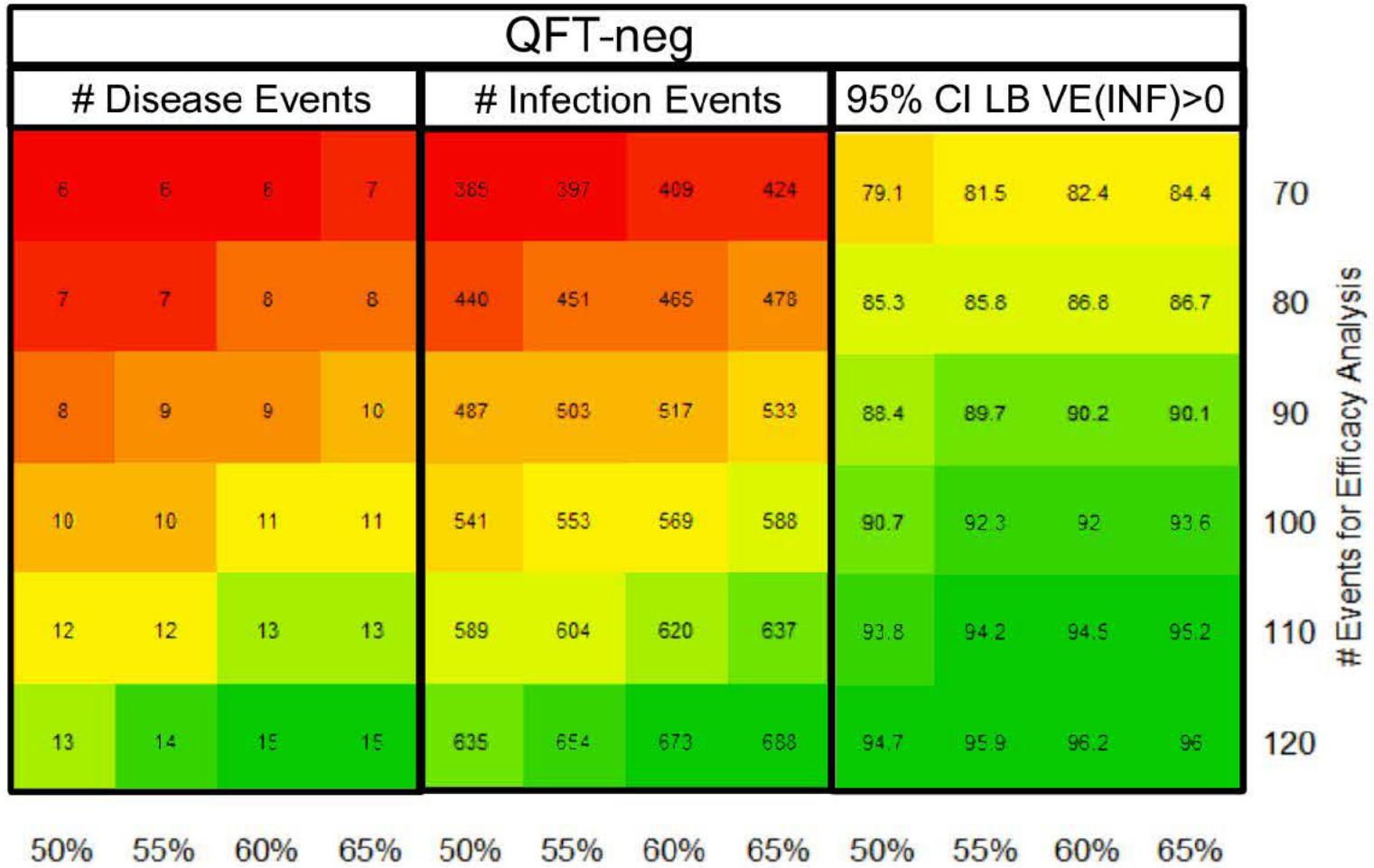
Point 2: High probability to accrue # events needed within 4 years of study start with 7000 – 10000 / group

Probability to perform analysis in ≤ 4 years



- Waiting an additional 6 months (e.g., to 4.5 years) increases probability to
- ≥ 80% for 100 events with N ≥ 7000 / group, 110 events with N ≥ 8000 / group, 120 events with ≥ 9000 / group

PHASE 3 TRIAL EXPECTATIONS: # OF EVENTS EXPECTED BY BASELINE QFT STATUS



Point 3: Limited power to assess VE(D) in QFT-neg participants due to low # of disease events expected

- Only ~10% of disease events expected to be from QFT-neg participants
- With 100 total disease events, expect over 500 infection events in QFT-neg participants
- With ≥ 90 - 100 total disease events, high probability to show 95% CI LB for VE(INF) > 0% [Assuming VE(INF) = 25% in QFT-neg]

M72/AS01$_E$ PHASE 3: NEXT STEPS

- Primary endpoint, case definition and trial design need thorough discussion with stakeholders, subject matter experts and LMIC national regulatory agencies
- TPT implementation & impact on trial design (inclusion of HHCs, IGRA-testing while on study) will need discussion
- Country selection prep has been initiated; epidemiology study to start late 2021 / early 2022
- Phase 3 study start anticipated in early 2023

WRAP-UP / CALL TO ACTION

- Gates MRI remains committed to accelerating the end of tuberculosis
- Developing effective vaccines is a cornerstone of this plan
  - / BCG REVAX
    - Results expected 2024
  - / M72/ASO1E
    - Efficacy study start expected in Q2 2023, interim VE data anticipated in 2028
    - Urgent need to define trial design & endpoints, trial population, participating countries & sites, and to prepare for recommendation should Phase 3 data be supportive
    - WHO participation in defining trial design is critical to the success of the program
    - Can PDVAC members participate in Phase 3 design & endpoint definition (SAB Q1 2021)?
    - Can PDVAC co-ordinate workstreams/stakeholders within WHO?
    - Is it possible to receive SAGE input prior to finalization of Phase 3 protocol? (Q2 2021)?

THANK YOU

	Draft Product Profile at First Registration	Draft Target Product Profile (life-cycle target)
Indication	Active immunization to prevent pulmonary TB disease	Active immunization to prevent pulmonary TB disease
Target Population	16-35 years of age: no restrictions	9 years of age and above; no restrictions
POD VE in QFT+ (LB)	50% (0%) at first submission 50% (15%) for recommendation	70%(25%)
POD VE in QFT- (LB)	0	50%
Duration of Protection	At least 3 years (median follow-up)	At least 10 years
Regimen	2 doses (10 µg) 4 weeks apart	2 doses (10 µg) 1 to 12 months apart
Indirect Protection	No data	Established
Safety	Acceptable safety profile	Acceptable safety profile
Presentation/formulation	Single dose vial for antigen and adjuvant respectively, needles not provided, bedside mix	Multi-dose in single vial
Vaccine Volume	0.5mL	0.5mL
Stability / Shelf Life	3 years at 2-8°C	3 years at 2-8°C
Special Populations: HIV+	No contraindication if on ART. Based on 2 years of safety data on >1,000 PLWH	Acceptable safety and efficacy, no contraindication
Special Populations: current or recent TB disease	Contraindication. No data available for TB on treatment. Very limited data available for people with incipient TB.	Acceptable safety profile based on post-licensure study
Special Populations	Safety established in adolescents 16 years and up	Safety & efficacy established in children >9 years

From: GIERSING, Birgitte
Sent: Tue, 1 Sep 2020 07:58:37 +0000
To: SPARROW, Erin Grace;Claudio Lanata;Graham, Barney (NIH/VRC) [E];Ruth Karron;Karron, Ruth;Tiziana Scarna (Consultant) (b) (6);Sinead Delany-Moretlwe;Papania, Mark (CDC/DDPHSIS/CGH/GID);Bekeredjian-Ding, Isabelle;klaus.cichutek;Jerome Kim;Peter Smith;Kaslow, David;Bernard Fritzell;(SPmig) Shabir Madhi;Yshao;KAHN, Anna-lea;GRIFFIN, Geraldine Margaret;FRIEDE, Martin Howell;SODHA, Samir;CERNUSCHI, Tania;RODRIGUEZ HERNANDEZ, Carmen A.;HAMEL, Mary;ABELA-RIDDER, Bernadette;KNEZEVIC, Ivana;Hasso-Agopsowicz, Mateusz;Marion Menozzi-Arnaud;Julian Hickling;CROWCROFT, Natasha;Kelly Moore;Jarrahian, Courtney;Rebecca Fields;Jean-pierre Amorij;Anderson, Annaliesa S;James Robinson;Sally Nicholas;Nicola Viebig;Bhambhani, Akhilesh;Robin Biellik;Susan King;Phyllis Arthur;Gruber, Marion (FDA/CBER);S Khalid Ali;Vibhu Kanchan;Nitin (b) (6) (b) (6) (b) (6) (b) (6) (b) (6);Millogo, Jules;Attlan, Michael /FR; (b) (6) (b) (6) (b) (6);G Kang;Marian Wentworth
Cc: Carsten Mantel;Deepali Patel;Kristen Earle;Vivian Hsu;David Robinson;dracravioto;ZHOU, Tiequn;KANG, Hye-na;ISBRUCKER, Richard Allan;Melissa Leavitt; (b) (6);Niklas Danielsson;BOTWRIGHT, Siobhan;HUTUBESSY, Raymond;Michael Free;Sandhu, Hardeep (CDC/DDPHSIS/CGH/GID);Mvundura, Mercy;Little, Joe;Kristoffer Gandrup-Marino;ALALI, Mohammed;FAUCONNIER, Alain Georges L.;DOMINGUEZ MORALES, Rolando;MUNKOMBWE, Zuma;MALLINS, Paul;LAPUJADE, Olivier Christian;ENWERE, Godwin
Subject: Final minutes and recommendations: PDVAC virtual session on VIPS - Vaccine Innovation Prioritisation Strategy

Dear all,

Thank you for participating in the VIPS PDVAC session in July. The materials, final minutes and recommendations are posted on the PDVAC 2020 website. The direct link to the minutes and recommendations are here:
https://www.who.int/immunization/research/meetings_workshops/PDVAC_VIPS_8-July-2020_Executive-Summary.pdf

All the best,
Gitte

-----Original Appointment-----
From: SPARROW, Erin Grace (b) (6)
Sent: 02 July 2020 18:12
To: SPARROW, Erin Grace; Claudio Lanata; Graham, Barney (NIH/VRC) [E]; Ruth Karron; Karron, Ruth; Tiziana Scarna (Consultant); (b) (6); Sinead Delany-Moretlwe; Papania, Mark (CDC/DDPHSIS/CGH/GID); Bekeredjian-Ding, Isabelle; klaus.cichutek; Jerome Kim; Peter Smith; Kaslow, David; Bernard Fritzell; (SPmig) Shabir Madhi; Yshao; KAHN, Anna-lea; GIERSING, Birgitte; GRIFFIN, Geraldine Margaret; FRIEDE, Martin Howell; SODHA, Samir; CERNUSCHI, Tania; RODRIGUEZ HERNANDEZ, Carmen A.; HAMEL, Mary; ABELA-RIDDER, Bernadette; KNEZEVIC, Ivana; Hasso-Agopsowicz, Mateusz; Marion Menozzi-Arnaud; Julian Hickling; CROWCROFT, Natasha;

(b) (6); Jarrahian, Courtney; Rebecca Fields; Jean-pierre Amorij; Anderson, Annaliesa S; James Robinson; Sally Nicholas; Nicola Viebig; Bhambhani, Akhilesh; Robin Biellik; Susan King; Phyllis Arthur; Gruber, Marion; S Khalid Ali; Vibhu Kanchan; Nitin Saigal; (b) (6); (b) (6); y (b) (6); (b) (6); (b) (6); (b) (6); Attlan, Michael /FR; (b) (6); (b) (6); (b) (6); G Kang; Marian Wentworth
Cc: Carsten Mantel; Deepali Patel; Kristen Earle; Vivian Hsu; David Robinson; dracravioto; ZHOU, Tiequn; KANG, Hye-na; ISBRUCKER, Richard Allan; Melissa Leavitt; (b) (6); Niklas Danielsson; BOTWRIGHT, Siobhan; HUTUBESSY, Raymond; Michael Free; External Partner - Sandhu Hardeep; Mvundura, Mercy; Little, Joe; Kristoffer Gandrup-Marino; ALALI, Mohammed; FAUCONNIER, Alain Georges L.; DOMINGUEZ MORALES, Rolando; MUNKOMBWE, Zuma; MALLINS, Paul; LAPUJADE, Olivier Christian; ENWERE, Godwin
Subject: PDVAC virtual session on VIPS - Vaccine Innovation Prioritisation Strategy
When: 08 July 2020 15:00-17:00 (UTC+01:00) Amsterdam, Berlin, Bern, Rome, Stockholm, Vienna.
Where:

Dear all,

Please find attached the agenda for the PDVAC session on VIPS taking place tomorrow. Please note that the last half hour is a closed discussion open to PDVAC committee members only.

We will be a large group therefore I will be sending out some instructions for best practices during the virtual session. Due to time limitations we will not be able to do a full roll call of all participants but will take note of who joins the Zoom and update the list of participants afterwards.

Join Zoom Meeting
https://zoom.us/j (b) (6) ?pwd=MXJDSXpUMm9UdzFwQkk1alk4ZHY4Zz09

Meeting ID: (b) (6)
Password: (b) (6)
Find your local number: https://zoom.us/u/ab58b3KwMQ

Many thanks,
Erin

Erin Sparrow
Technical Officer
Vaccine Product and Delivery Research
Immunization, Vaccines and Biologicals
World Health Organization
Geneva, Switzerland

Office: (b) (6)
Web: www.who.int
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