Section 4
Health effects

Test Guideline No. 405
Acute Eye Irritation/Corrosion

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OECD Guidelines for the Testing of Chemicals

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OECD GUIDELINE FOR THE TESTING OF CHEMICALS

Acute eye irritation/corrosion

INTRODUCTION

1. OECD Guidelines for Testing of Chemicals are periodically reviewed to ensure that they reflect the best available science. In previous reviews of this Test Guideline (TG), special attention was given to possible improvements through the evaluation of all existing information on the test chemical in order to avoid unnecessary testing in laboratory animals and thereby address animal welfare concerns. This updated version of TG 405 (originally adopted in 1981 and updated in 1987, 2002, 2012, 2020 and 2021) includes reference to the Guidance Document (GD) 263 on Integrated Approaches to Testing and Assessment (IATA) for Serious Eye Damage and Eye Irritation (1), proposing a modular approach for eye irritation and serious eye damage testing. The IATA describes several modules which group information sources and analysis tools, and (i) provides guidance on how to integrate and use existing testing and non-testing data for the assessment of the eye irritation and serious eye damage potentials of chemicals and (ii) proposes an approach when further testing is needed (1) The present *in vivo* rabbit eye test should be conducted only as a last resort after all the existing information has been considered, and *in vitro* testing has been conducted and evaluated as recommended within the IATA for serious eye damage and eye irritation described within the OECD GD 263. It is recommended to make use of alternative testing strategies such as those described in TG 467 and 492B to address the required ranges of irritation potential. At the time of drafting of this updated TG 405, there are instances where using this TG may still be necessary or required by some regulatory authorities.

2. The update from 2012 mainly focused on the use of analgesics and anesthetics without impacting the basic concept and structure of the TG. The Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM) and an independent international scientific peer review panel reviewed the usefulness and limitations of routinely using topical anesthetics, systemic analgesics, and humane endpoints during *in vivo* ocular irritation safety testing (2). The review concluded that the use of topical anesthetics and systemic analgesics could avoid most or all pain and distress without affecting the outcome of the test, and recommended that these substances should always be used. This TG takes this review into account. Topical anesthetics, systemic analgesics, and humane endpoints should be routinely used during eye irritation and serious eye damage *in vivo* testing. Exceptions to their use should be justified. The refinements described in this proposal will substantially reduce or avoid animal pain and distress in most testing situations where *in vivo* ocular safety testing is still necessary.

3. Balanced preemptive pain management should include (i) routine pretreatment with a topical anesthetic (e.g., proparacaine or tetracaine) and a systemic analgesic (e.g. buprenorphine), (ii) routine post-treatment schedule of systemic analgesia (e.g., buprenorphine and meloxicam), (iii) scheduled

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observation, monitoring, and recording of animals for clinical signs of pain and/or distress, and (iv) scheduled observation, monitoring, and recording of the nature, severity, and progression of all eye injuries. Further detail is provided in the updated procedures described below. Following test chemical administration, no additional topical anesthetics or analgesics should be applied in order to avoid interference with the study. Analgesics with anti-inflammatory activity (e.g., meloxicam) should not be applied topically, and doses used systemically should not interfere with ocular effects.

4. Definitions are set out in the Annex to the TG.

INITIAL CONSIDERATIONS

5. In the interest of both sound science and animal welfare, *in vivo* testing should not be considered until all available data relevant to the potential eye irritation/serious eye damage of the test chemical have been evaluated in a weight-of-the-evidence (WoE) analysis as presented in the GD263 (1) i.e. over the three Parts of this GD and their corresponding modules (1). Briefly, under Part 1 existing data is addressed over eight modules covering human data, *in vivo* data, *in vitro/ex vivo* eye or skin irritation/corrosion data, physico-chemical properties data (e.g. pH) and non-testing methods. Under Part 2, WoE analysis is performed. If this WoE analysis is still inconclusive, Part 3 should be conducted with additional testing, starting with *in vitro* methods (3)(4)(5)(6)(7)(8) or *in chemico* method (9), and *in vivo* testing is used as last resort. The *in vivo* animal test, if e.g. required by regulators, should be considered after conducting *in vitro* testing only when: i) the test chemical is not directly identified as UN GHS Cat. 1, UN GHS Cat. 2 or as UN GHS No Cat. by currently adopted *in vitro* test methods and defined approaches.ii) WoE assessment cannot conclude with high enough confidence if the test chemical is Cat. 1, Cat. 2 (or Cat. 2A or Cat. 2B, if applicable), or No Cat. depending on country-specific regulatory requirements. iii) the test chemical cannot be tested with the currently available *in vitro* test methods or defined approaches due to the limitations of the test methods or when falling outside of the applicability domain of the test method or approach."

PRINCIPLE OF THE *IN VIVO* TEST

6. Following pretreatment with a systemic analgesic and instillation of appropriate topical anesthesia, the test chemical is applied in a single dose to one of the eyes of the experimental animal; the untreated eye serves as the control. The degree of eye irritation/serious eye damage is evaluated by scoring lesions of conjunctiva, cornea, and iris, at specific intervals. Other effects in the eye and adverse systemic effects are also described to provide a complete evaluation of the effects. The duration of the study should be sufficient to evaluate the reversibility or irreversibility of the effects.

7. Animals showing signs of severe distress and/or pain at any stage of the test or lesions consistent with the humane endpoints described in this TG (see Paragraph 24) should be humanely killed, and the test chemical assessed accordingly without performing further testing with more animals. Criteria for making the decision to humanely kill moribund and severely suffering animals are the subject of a separate GD (10).

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PREPARATIONS FOR THE *IN VIVO* TEST

Selection of species

8. The albino rabbit is the preferable laboratory animal and healthy young adult animals are used. A rationale for using other strains or species should be provided.

Preparation of animals

9. Both eyes of each experimental animal provisionally selected for testing should be examined within 24 hours before testing starts. Animals showing eye irritation, ocular defects, or pre-existing corneal injury should not be used.

Housing and feeding conditions

10. Animals should be individually housed. The temperature of the experimental animal room should be 20°C (± 3°C) for rabbits. Although the relative humidity should be at least 30% and preferably not exceed 70%, other than during room cleaning, the aim should be 50-60%. Lighting should be artificial, the sequence being 12 hours light, 12 hours dark. Excessive light intensity should be avoided. For feeding, conventional laboratory diets may be used with an unrestricted supply of drinking water.

TEST PROCEDURE

Use of topical anesthetics and systemic analgesics

11. The following procedures are recommended to avoid or minimize pain and distress in ocular safety testing procedures. Alternate procedures that have been determined to provide as good or better avoidance or relief of pain and distress may be substituted.

- Sixty minutes prior to test chemical application (TCA), buprenorphine 0.01 mg/kg is administered by subcutaneous injection (SC) to provide a therapeutic level of systemic analgesia. Buprenorphine and other similar opioid analgesics administered systemically are not known or expected to alter ocular responses (2).
- Five minutes prior to TCA, one or two drops of a topical ocular anesthetic (e.g. 0.5% proparacaine hydrochloride or 0.5% tetracaine hydrochloride) are applied to each eye. In order to avoid possible interference with the study, a topical anesthetic that does not contain preservatives is recommended. The eye of each animal that is not treated with a test chemical, but which is treated with topical anesthetics, serves as a control. If the test chemical is anticipated to cause significant pain and distress, it should not normally be tested *in vivo*. However, in case of doubt or where testing is necessary, consideration should be given to additional applications of the topical anesthetic at 5-minute intervals prior to TCA. Users should be aware that multiple applications of topical anesthetics could potentially cause a slight increase in the severity and/or time required for chemically-induced lesions to clear.
- Eight hours after TCA, buprenorphine 0.01 mg/kg SC and meloxicam 0.5 mg/kg SC are administered to provide a continued therapeutic level of systemic analgesia. While there are no data to suggest that meloxicam has anti-inflammatory effects on the eye when administered SC once daily, meloxicam should not be administered until at least 8 hours after TCA in order to avoid any possible interference with the study (2).

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- After the initial 8-hour post-TCA treatment, buprenorphine 0.01 mg/kg SC should be administered every 12 hours, in conjunction with meloxicam 0.5 mg/kg SC every 24hours, until the ocular lesions resolve and no clinical signs of pain and distress are present. Sustained-release preparations of analgesics are available that could be considered to decrease the frequency of analgesic dosing.
- "Rescue" analgesia should be given immediately after TCA if pre-emptive analgesia and topical anesthesia are inadequate. If an animal shows signs of pain and distress during the study, a "rescue" dose of buprenorphine 0.03 mg/kg SC would be given immediately and repeated as often as every 8 hours, if necessary, instead of 0.01 mg/kg SC every 12 hours. Meloxicam 0.5 mg/kg SC would be administered every 24 hours in conjunction with the "rescue" dose of buprenorphine, but not until at least 8 hours post-TCA.

Application of the test chemical

12. The test chemical should be placed in the conjunctival sac of one eye of each animal after gently pulling the lower lid away from the eyeball. The lids are then gently held together for a few seconds in order to prevent loss of the material. The other eye, which remains untreated, serves as a control.

Irrigation

13. The eyes of the test animals should not be washed for at least 24 hours following instillation of the test chemical, except for solids (see paragraph 16), and in case of immediate serious eye damage or eye irritation effects. At 24 hours a washout may be used if considered appropriate.

14. Use of a satellite group of animals to investigate the influence of washing is not recommended unless it is scientifically justified. If a satellite group is needed, two rabbits should be used. Conditions of washing should be carefully documented, e.g., time of washing; composition and temperature of wash solution; duration, volume, and velocity of application.

Dose level

(1) Testing of liquids

15. For testing liquids, a dose of 0.1 mL is used. Pump sprays should not be used for instilling the test chemical directly into the eye. The liquid spray should be expelled and collected in a container prior to instilling 0.1 mL into the eye.

(2) Testing of solids

When testing solids, pastes, and particulate substances, the amount used should have a volume of 0.1mL or a weight of not more than 100 mg. The test material should be ground to a fine dust. The weight of the 0.1 mL volume of solid material should be recorded after gently compacting it, e.g. by tapping the measuring container. The amount used should not exceed 100 mg. Application of powdered solid test chemicals to the eyes will increase blinking and this may contribute to a higher degree of irritation.

16. If the solid test chemical has not been removed from the eye of the test animal by physiological mechanisms at the first observation time point of 1 hour after treatment, the eye may be rinsed with saline or distilled water.

(3) Testing of aerosols

17. It is recommended that all pump sprays and aerosols be collected prior to instillation into the eye. The one exception is for test chemicals in pressurised aerosol containers, which cannot be collected due

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to vaporisation. In such cases, the eye should be held open, and the test chemical is administered to the eye in a simple burst of about one second, from a distance of 10 cm directly in front of the eye. This distance may vary depending on the pressure of the spray and its contents. Care should be taken not to damage the eye from the pressure of the spray. In appropriate cases, there may be a need to evaluate the potential for “mechanical” damage to the eye from the force of the spray.

18. An estimate of the dose from an aerosol can be made by simulating the test as follows: the test chemical is sprayed on to weighing paper through an opening the size of a rabbit eye placed directly before the paper. The weight increase of the paper is used to approximate the amount sprayed into the eye. For volatile test chemicals, the dose may be estimated by weighing a receiving container before and after removal of the test material.

Initial test (in vivo serious eye damage/eye irritation test using one animal)

19. It is strongly recommended that the *in vivo* test be performed initially using one animal. Observations should allow for determination of severity and reversibility before proceeding to a confirmatory test in a second animal.

20. If the results of this test indicate the test chemical to be seriously damaging to the eye using the procedure described, further testing for ocular irritancy should not be performed. Termination of the testing after a first animal showing serious eye damage is for animal welfare reasons and the rate of misclassification due to the variability of the animal’s response could be considered.

Confirmatory test (in vivo eye irritation test with additional animals)

21. If a serious eye damage/irreversible effect is not observed in the initial test, the irritant or negative response should be confirmed using up to two additional animals. If an irritant effect is observed in the initial test, it is recommended that the confirmatory test be conducted in a sequential manner in one animal at a time, rather than exposing the two additional animals simultaneously. If the second animal reveals serious eye damage/irreversible effects, the test is not continued. If results from the second animal are sufficient to allow for a hazard classification determination, then no further testing should be conducted.

Observation period

22. The duration of the observation period should be sufficient to evaluate fully the magnitude and reversibility of the effects observed. However, the experiment should be terminated at any time that the animal shows signs of severe pain or distress (11) (12). To determine reversibility of effects, the animals should be observed normally for 21 days post administration of the test chemical. If reversibility is seen before 21 days, the experiment should be terminated at that time.

Clinical observations and grading of eye reactions

23. The eyes should be comprehensively evaluated for the presence or absence of ocular lesions one hour post-TCA, followed by at least daily evaluations. Animals should be evaluated several times daily for the first 3 days to ensure that termination decisions are made in a timely manner. Test animals should be routinely evaluated for the entire duration of the study for clinical signs of pain and/or distress (e.g. repeated pawing or rubbing of the eye, excessive blinking, excessive tearing) (11) (12) at least twice daily, with a minimum of 6 hours between observations, or more often if necessary. This is necessary to (i) adequately assess animals for evidence of pain and distress in order to make informed decisions on the need to increase the dosage of analgesics and (ii) assess animals for evidence of established humane endpoints

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in order to make informed decisions on whether it is appropriate to humanely euthanize animals, and to ensure that such decisions are made in a timely manner. Fluorescein staining should be routinely used and a slit lamp biomicroscope used when considered appropriate (e.g., assessing depth of injury when corneal ulceration is present) as an aid in the detection and measurement of ocular damage, and to evaluate if established endpoint criteria for humane euthanasia have been met. Digital photographs of observed lesions may be collected for reference and to provide a permanent record of the extent of ocular damage. Animals should be kept on test no longer than necessary once definitive information has been obtained. Animals showing severe pain or distress should be humanely killed without delay, and the test chemical assessed accordingly without performing further testing with more animals.

24. Animals with the following eye lesions post-instillation should be humanely killed (refer to Table 1 for a description of lesion grades): corneal perforation or significant corneal ulceration including staphyloma; blood in the anterior chamber of the eye; grade 4 corneal opacity; absence of a light reflex (iridial response grade 2) which persists for 72 hours; ulceration of the conjunctival membrane; necrosis of the conjunctivae or nictitating membrane; or sloughing. This is because such lesions generally are not reversible. Furthermore, it is recommended that the following ocular lesions be used as humane endpoints to terminate studies before the end of the scheduled 21-day observation period. These lesions are considered predictive of serious eye damage and injuries that are not expected to fully reverse by the end of the 21-day observation period: severe depth of injury (e.g., corneal ulceration extending beyond the superficial layers of the stroma), limbus destruction >50% (as evidenced by blanching of the conjunctival tissue), and severe eye infection (purulent discharge). A combination of: vascularization of the cornea surface (i.e., pannus); area of fluorescein staining not diminishing over time based on daily assessment; and/or lack of re-epithelialization 5 days after test chemical application could also be considered as potentially useful criteria to influence the clinical decision on early study termination. However, these findings individually are insufficient to justify early study termination. Once serious eye damage/irreversible effects have been identified, an attending or qualified laboratory animal veterinarian or personnel trained to identify the clinical lesions should be consulted for a clinical examination to determine if the combination of these effects warrants early study termination. The grades of ocular reaction (conjunctivae, cornea and iris) should be obtained and recorded at 1, 24, 48, and 72 hours following test chemical application (Table 1). The study should be terminated not earlier than 3 days post instillation if the animals do not develop ocular lesions. Animals with ocular lesions that are not severe should be observed until the lesions clear, or for 21 days, at which time the study is terminated. Observations should be performed and recorded at a minimum of 1 hour, 24 hours, 48 hours, 72 hours, 7 days, 14 days, and 21 days in order to determine the status of the lesions, and their reversibility or irreversibility. More frequent observations should be performed if necessary in order to determine whether the test animal should be euthanized out of humane considerations or removed from the study due to negative results

25. The grades of ocular lesions (Table 1) should be recorded at each examination. Any other lesions in the eye (e.g. pannus, staining, anterior chamber changes) or adverse systemic effects should also be reported.

26. Examination of reactions can be facilitated by use of a binocular loupe, hand slit-lamp, biomicroscope, or other suitable device. After recording the observations at 24 hours, the eyes may be further examined with the aid of fluorescein.

27. The grading of ocular responses is necessarily subjective. To promote harmonisation of grading of ocular response and to assist testing laboratories and those involved in making and interpreting the observations, the personnel performing the observations need to be adequately trained in the scoring system used.

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DATA AND REPORTING

Evaluation of results

28. The ocular irritation scores should be evaluated in conjunction with the nature and severity of lesions, and their reversibility or lack of reversibility. The individual scores do not represent an absolute standard for the irritant properties of a material, as other effects of the test material are also evaluated. Instead, individual scores should be viewed as reference values and are only meaningful when supported by a full description and evaluation of all observations.

Test report

29. The test report should include the following information:

Rationale for *in vivo* testing: weight-of-the-evidence analysis of pre-existing test data, including results from sequential testing strategy:

- description of relevant data available from prior testing;
- data derived in each step of testing strategy;
- description of *in vitro* tests performed, including details of procedures, results obtained with test chemical/reference substances;
- description of *in vivo* dermal irritation / corrosion study performed, including results obtained;
- weight-of-the-evidence analysis for performing *in vivo* study

Test chemical:

- identification data (e.g. chemical name and if available CAS number, purity, known impurities, source, lot number);
- physical nature and physicochemical properties (e.g. pH, volatility, solubility, stability, reactivity with water);
- in case of a mixture, components should be identified including identification data of the constituent substances (*e.g.* chemical names and if available CAS numbers) and their concentrations;
- dose applied;

Vehicle:

- identification, concentration (where appropriate), volume used;
- justification for choice of vehicle.

Test animals:

- species/strain used, rationale for using animals other than albino rabbit;
- age of each animal at start of study;
- number of animals of each sex in test and control groups (if required);
- individual animal weights at start and conclusion of test;
- source, housing conditions, diet, etc.

Anaesthetics and analgesics

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- doses and times when topical anaesthetics and systemic analgesics were administered;
- if local anaesthetic is used, identification, purity, type, and potential interaction with test chemical.

Results:

- description of method used to score irritation at each observation time (e.g., hand slitlamp, biomicroscope, fluorescein);
- tabulation of serious eye damage/eye irritation response data for each animal at each observation time up to removal of each animal from the test;
- narrative description of the degree and nature of serious eye damage/eye irritation observed;
- description of any other lesions observed in the eye (e.g., vascularization, pannus formation, adhesions, staining);
- description of non-ocular local and systemic adverse effects, record of clinical signs of pain and distress, digital photographs, and histopathological findings, if any.
- If applicable, relevant UNGHS classification (13) for the test chemicals, including not classified.

Interpretation of the results

30. Extrapolation of the results of eye irritation studies in laboratory animals to humans is valid only to a limited degree. In many cases the albino rabbit is more sensitive than humans to ocular irritants or chemicals inducing serious eye damage.

31. Care should be taken in the interpretation of data to exclude irritation resulting from secondary infection.

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TABLE 1: GRADING OF OCULAR LESIONS

Cornea	**Grade**
Opacity: degree of density (readings should be taken from most dense area)*	
No ulceration or opacity	0
Scattered or diffuse areas of opacity (other than slight dulling of normal lustre); details of iris clearly visible	1
Easily discernible translucent area; details of iris slightly obscured	2
Nacrous area; no details of iris visible; size of pupil barely discernible	3
Opaque cornea; iris not discernible through the opacity	4
Maximum possible: 4	
* The area of corneal opacity should be noted	

Iris	
Normal	0
Markedly deepened rugae, congestion, swelling, moderate circumcorneal hyperaemia; or injection; iris reactive to light (a sluggish reaction is considered to be an effect	1
Hemorrhage, gross destruction, or no reaction to light	2
Maximum possible: 2	

Conjunctivae	
Redness (refers to palpebral and bulbar conjunctivae; excluding cornea and iris)	
Normal	0
Some blood vessels hyperaemic (injected)	1
Diffuse,crimson colour; individual vessels not easily discernible	2
Diffuse beefy red	3
Maximum possible: 3	

Chemosis	
Swelling (refers to lids and/or nictating membranes)	
Normal	0
Some swelling above normal	1
Obvious swelling, with partial eversion of lids	2
Swelling, with lids about half closed	3
Swelling, with lids more than half closed	4
Maximum possible: 4	

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ANNEX

DEFINITIONS

1. Not Classified: Test chemicals that are not classified for eye irritation (UN GHS Category 2) or serious damage to eye (UN GHS Category 1) according to the UN GHS classification (13). Interchangeable with “UN GHS No Category”.

2. Eye irritation refers to the production of changes in the eye, which are fully reversible, occurring after the exposure of the eye to a chemical or mixture; these chemicals are classified as UN GHS Category 2, 2A or 2B (13).

3. Serious eye damage refers to the production of tissue damage in the eye, or serious physical decay of vision, which is not fully reversible, occurring after exposure of the eye to a chemical or mixture . These chemicals are classified as GHS Category 1 (13).

4. Weight-of-the-evidence (assessment): The strengths and weaknesses of a collection of information are used as the basis for a conclusion that may not be evident from the individual data.

5. IATA (Integrated Approach to Testing and Assessment): A structured approach used for hazard identification (potential), hazard characterisation (potency), and/or safety assessment (potential/potency and exposure) of a chemical or group of chemicals, which strategically integrates and weights all relevant data to inform regulatory decision regarding potential hazards, risks, and the need for further targeted and therefore minimal testing.

6. “Defined Approach (DA): a DA consists of a fixed data interpretation procedure (e.g. statistical, mathematical models) applied to data (e.g. *in silico* predictions, *in chemico*, *in v*itro data) generated with a defined set of information sources to derive a prediction.”

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