Для лабораторий, использующих
Cholinesterase Gen.2 и Cholinesterase/Dibucaine Gen.2
на анализаторе **cobas c** 311,
на модулях **cobas c** 501, **c** 502,
на модуле **cobas c** 702,
COBAS INTEGRA 400 plus

г. Москва

Дата: 25.09.2024
Исх.: 0350/2509/2024
Ref.: QN-RDS-CoreLab-2024-107

Уведомление по качеству
Касательно тестов Cholinesterase Gen.2 (CHE2)
и Cholinesterase/Dibucaine Gen.2 (CHED2):
Обновление разделов «Ограничения — Интерференция»
в Инструкциях по использованию реагентов

Название продукта	**GMMI / Кат. №**	**Идентификатор продукта (Номер лота или серийный номер)**	**Номер РУ, Дата РУ**	**Производитель**
Реагенты, стандарты, калибраторы, контроли и расходные материалы для биохимических анализаторов Hitachi 902, 902 ISE, 912, 912 ISE, 917 ISE, Cobas c 311, Cobas c 111, Cobas c 111 ISE, Cobas Integra 400 Plus/ 800 и платформ модульных MODULAR ANALYTICS, cobas 6000 Холинэстераза (CHE2 / Cholinesterase Gen.2)	04498577190		ФСЗ 2011/08936 от 04.05.2021	Sandhofer Strasse 116, 68305 Mannheim, Germany
Реагенты для анализаторов биохимических Hitachi 902, 902 ISE, 912, 912 ISE, 917 ISE, Cobas c 311, Cobas c 111, Cobas c 111 ISE, Cobas Integra 400 plus, Cobas Integra 800 и платформ модульных MODULAR ANALYTICS, cobas 6000, cobas 8000 Холинэстераза генерация 2, 650 тестов (CHE2/Cholinesterase Gen.2, 650)	05168503190		ФСЗ 2012/13068 от 19.10.2012	Sandhofer Strasse 116, 68305 Mannheim, Germany
Инструмент/Система	Анализатор **cobas c** 311 Модуль **cobas c** 501 Модуль **cobas c** 502 Модуль **cobas c** 702 Анализатор COBAS INTEGRA 400 plus			

ООО «Рош Диагностика Рус»
Россия, 115114, Москва
ул. Летниковская, дом 2, стр. 3
Бизнес-центр "Вивальди Плаза"
Тел.: +7 (495) 229 69 99
Факс: +7 (495) 229 62 64
www.roche.ru

Roche Diagnostics Rus LLC
2, Letnikovskaya street, bld. 3
Business Center "Vivaldi Plaza"
115114, Moscow, Russia
Tel.: +7 (495) 229 69 99
Fax: +7 (495) 229 62 64
www.roche.ru

Уважаемый пользователь,

Сообщаем вам об изменениях в Инструкции по использованию реагентов холинэстераза CHE-T2/CHE2 (общая холинэстераза) и CHE2D/CHE2-D (холинэстераза, ингибированная Дибукаином).
Настройки Протокола методики не затрагиваются. Обновления касаются только информации об интерференции.

1. «Ограничения — Интерференция» Липемия (Интралипид): замена интерферента для определения индекса L с Интралипида на нативные липемические образцы (CHET2/CHE2-T, CHED2/CHE2-D и CHE2). *COBAS INTEGRA 400 plus не затрагивается.*

2. «Ограничения — Интерференция»: добавление Интралипида в качестве интерферента анализа (только CHED2/CHE2-D). *COBAS INTEGRA 400 plus не затрагивается.*

3. «Ограничения — Интерференция»: добавление Ацетаминофена в качестве интерферента (только CHED2/CHE2-D).

Описание ситуации

Cobas c 111 не затрагивается, поскольку на этом инструменте анализ с указанными реагентами не проводится. Причины описанных обновлений основаны на недавних результатах, полученных в ходе мастер-проекта **cobas c** 503, который был анонсирован в MN-RDS-CoreLab-2022-183.

Затрагиваются следующие параметры: системы/ACN/ID тестов:

<table>
<tr><th></th><th></th><th></th><th colspan="3">Для всех стран, кроме США</th></tr>
<tr><th>Каталожный номер</th><th>Анализатор</th><th>ACN/ID теста короткое назв.</th><th>Интерференция с нативными лип. образцами</th><th>Интерференция Интралипидом</th><th>Интерференция Ацетаминофеном</th></tr>
<tr><td rowspan="4">04498631190</td><td rowspan="2">cobas c 311/502/502</td><td>(8)534 (CHET2)</td><td rowspan="2">да</td><td colspan="2">—</td></tr>
<tr><td>(8)434 (CHED2)</td><td colspan="2">да</td></tr>
<tr><td rowspan="2">COBAS INTEGRA 400 plus</td><td>0-019 (CHET2)</td><td rowspan="2">—</td><td colspan="2">—</td></tr>
<tr><td>0-020 (CHED2)</td><td>—</td><td>да</td></tr>
<tr><td rowspan="2">04498577190</td><td>cobas c 311/502/502</td><td>(8)510 (CHE2)</td><td>да</td><td colspan="2">—</td></tr>
<tr><td>COBAS INTEGRA 400 plus</td><td>0-021 (CHE2)</td><td>—</td><td colspan="2">—</td></tr>
<tr><td rowspan="2">05168503190
05168503214
05168503188</td><td rowspan="2">cobas c 702</td><td>8534 (CHET2)</td><td rowspan="2">да</td><td colspan="2">—</td></tr>
<tr><td>8434 (CHED2)</td><td colspan="2">да</td></tr>
</table>

В следующей таблице показан пример ситуации до и после обновления Инструкции по использованию (изменения выделены жирным шрифтом, цифры в верхнем индексе отражают ссылку на литературу).

Пункт обновления	Анализ	До	После
1	CHE2-T, ACN 20370	Липемия (**Интралипид**):[13] незначительная интерференция до индекса L 1000.	Липемия (**нативн. обр.**):[13] незначительная интерференция до индекса L 1000.
	CHE2-D, ACN 20371	Липемия (**Интралипид**):[13] незначительная интерференция до индекса L 500.	Липемия (**нативн. обр.**):[13] незначительная интерференция до индекса L 500.
2 и 3	CHE2-T, ACN 20370	Лекарственные препараты: при терапевтических концентрациях с использованием обычных лекарственных препаратов интерференции не обнаружено.[14,15]	
	CHE2-D, ACN 20371	Лекарственные препараты: при терапевтических концентрациях с использованием обычных лекарственных препаратов интерференции не обнаружено.[14,15]	Лекарственные препараты: при терапевтических концентрациях с использованием обычных лекарственных препаратов интерференции не обнаружено.[14,15] **Исключение: Ацетаминофен вызывает искусственно завышенные результаты. Интралипид вызывает искусственно заниженные результаты.**

Причина возникновения

1. **Замена интерферента для определения индекса L с Интралипида на нативные липемические образцы (CHET2/CHE2-T, CHED2/CHE2-D и CHE2)**

Отдел исследований и разработок (R&D) обнаружил, что в анализах CHED2/CHE2-D, ингибированных Дибукаином, интерферентный материал Интралипид вызывал отрицательное смещение ниже заявленного уровня индекса L = 500. Такая интерференция наблюдается только в образцах, в которые был добавлен искусственный материал Интралипид.

Поскольку нативные липемические образцы человека не затрагиваются описанной проблемой, интерферирующей материал был заменен с «Интралипид» на нативные липемические образцы. Несмотря на то, что интерференция наблюдалась только с реагентами, ингибированными Дибукаином, было решено внедрить это обновление и для анализов CHET2/CHE2-T и CHE2.
При использовании нативного липемического образца в качестве интерферента исследование показало, что заявленное значение для липемии может оставаться на уровне индекса L 1000 (CHE-T)/500 (CHE-D). Таким образом, настройки Протокола методики не затрагивались.

На COBAS INTEGRA 400 plus интерференция Интралипида не наблюдается из-за различий в настройках прибора.

2. **Добавление Интралипида в качестве интерферента (только CHED2/CHE2-D)**

Результаты исследования интерференции с использованием Интралипида выявили в редких обстоятельствах неожиданное значение интерференции.

Интерференция Интралипидом наблюдается только с реагентами CHED2/CHE2-D, ингибированными Дибукаином. По этой причине заявление об интерференции Интралипидом было добавлено только в Инструкции по использованию CHED2/CHE2-D.

При использовании CHED2 на COBAS INTEGRA 400 plus проблема не наблюдается из-за различий в настройках прибора.

3. **Добавление Ацетаминофена в качестве интерферента (только CHED2/CHE2-D)**

Исследования интерференции проводились в анализе с реагентами CHED2/CHE2-D на двух уровнях аналита (уровень 1 — здоровое состояние — примерно 2000 ЕД/л; уровень 2 — патологическое состояние — примерно 1000 ЕД/л). Обновление рекомендуемой CLSI терапевтической концентрации ввело вторую концентрацию (терапевтическая концентрация 52 мг/л ацетаминофена) в тестирование интерференции уже установленной скрининговой концентрации (156 мг/л). В рамках работы над Протоколом методики в мастер-проекте **cobas c** 503 отдел исследований и разработок обнаружил интерференцию на терапевтическом уровне ацетаминофена (52 мг/л) для патологического уровня аналита (примерно 1000 ЕД/л) в анализе с реагентами CHED2/CHE2-D. Эффективность анализа осталась неизменной. Анализы CHET2/CHE2-T и CHE2 не были затронуты.

<u>Оценка риска</u>

Частота возникновения

1. **Замена интерферента для определения индекса L с Интралипида на нативные липемические образцы (CHET2/CHE2-T, CHED2/CHE2-D и CHE2)**

Не было подано ни одной рекламации. Проблема обнаруживалась в рамках работы над Протоколом методики в мастер-проекте **cobas c** 503. Замена интерферента не влияет на частоту возникновения описанной ситуации.

2. **Добавление Интралипида в качестве интерферента (только CHED2/CHE2-D)**

Не было подано ни одной рекламации. Проблема обнаруживалась в рамках работы над Протоколом методики в мастер-проекте **cobas c** 503. Нет информации о том, сколько образцов пациентов содержат Интралипид. На основе рутинных измерений можно сделать вывод, что индекс L 110 соответствует 1100 мг/л Интралипида в образце с добавлением Интралипида. Был проведен анализ реальных данных и рассчитана вероятность возникновения проблемы. При наихудшем сценарии, когда все результаты с индексом L выше 110 были получены с образцами, содержащими Интралипид, вероятность возникновения проблемы не превышает $2x10^{-4}$. Этот результат значительно превышает реальную частоту возникновения затронутых образцов.

3. **Добавление Ацетаминофена в качестве интерферента (только CHED2/CHE2-D)**

Все образцы с концентрацией Ацетаминофена >20 мг/л были затронуты в той или иной степени. Распространенность образцов с этими концентрациями, которые используются для определения CHE-D, неизвестна. Рекламаций не поступало, однако, вероятность обнаружения затруднена. На основании количества тестов, произведенных в 2021 году, соотношение определения CHE-T: CHE-D составляет ~50:1.

Вероятность обнаружения

1. **Замена интерферента для определения индекса L с Интралипида на нативные липемические образцы (CHET2/CHE2-T, CHED2/CHE2-D и CHE2)**

Вероятность обнаружения остается неизменной, поскольку уровень индекса L сохраняется для интерференции нативными липемическими образцами.

2. **Добавление Интралипида в качестве интерферента (только CHED2/CHE2-D)**

Проблема может быть обнаружена только в том случае, если наблюдаемое значение для CHE-D или рассчитанная концентрация Дибукаина кажутся неправдоподобными или не соответствуют медицинскому статусу пациента.

3. **Добавление Ацетаминофена в качестве интерферента (только CHED2/CHE2-D)**

Проблема может быть обнаружена только в том случае, если наблюдаемое значение для CHE-D или рассчитанная концентрация Дибукаина кажутся неправдоподобными или не соответствуют медицинскому статусу пациента.

Серьезность последствий

1. **Замена интерферента для определения индекса L с Интралипида на нативные липемические образцы (CHET2/CHE2-T, CHED2/CHE2-D и CHE2)**

Результаты пациентов и медицинские решения не зависят от изменения материала, используемого для тестирования интерференции.

Заявление об индексе L остается неизменным, также как и настройки Протокола методики.

2. **Добавление Интралипида в качестве интерферента (только CHED2/CHE2-D)**

Вероятность причинения вреда в сочетании с серьезностью проблемы, связанной с общим риском, была определена как «приемлемый остаточный риск». Оценка степени опасности для здоровья не требуется.

3. **Добавление Ацетаминофена в качестве интерферента (только CHED2/CHE2-D)**

В худшем случае возникновения интерференции с Ацетаминофеном пациенту, клинически демонстрирующему функционально пролонгированный нервно-мышечный паралич после стандартных доз сукцинилхолина и мивакурия в сочетании с нормальными результатами CHE-T, следует пройти дополнительные диагностические исследования. Если пациент все еще принимал Ацетаминофен в дозах, превышающих терапевтические, из-за интерференции концентрация Дибукаина, близкая к целевому показателю медицинского решения для гетерозиготных лиц (MDT), может быть занижена максимум на 7%. В этом случае можно заподозрить наличие атипичного CHE в гетерозиготной констелляции, и пациенту показано дальнейшее генетическое определение.

Концентрация Дибукаина сама по себе не обеспечивает данных, необходимых для постановки окончательного диагноза, поэтому вред для пациентов маловероятен. Кроме того, у пациентов, принимающих Ацетаминофен, не будет проводиться регулярная диагностика функции печени из-за потенциального воздействия на нее препарата.

<u>Важная информация</u>

Все обновленные пакеты электронной документации, включая обновленные Инструкции по использованию и неизмененные электронные штрихкоды, будут опубликованы на портале

электронного контента со ссылкой на данное Уведомление по качеству. Обновленные Инструкции для всех затронутых систем прилагаются к настоящему Уведомлению.

Распространение настоящего уведомления по качеству на местах

Настоящее Уведомление по качеству предназначено для всех заинтересованных лиц в Вашей организации или других организациях, которые получали данную продукцию.

Пожалуйста, перешлите данное уведомление другим организациям/лицам, которых она может касаться.

Приносим свои извинения за причиненные неудобства, которые могут быть связаны с данной ситуацией, и надеемся на Ваше понимание и поддержку.

Контакты

В случае возникновения вопросов обратитесь, пожалуйста, в службу поддержки Roche:
Бесплатная линия: 8 800 100-68-96
Время работы: понедельник – пятница с 08:00 до 18:00 по Московскому времени
e-mail: russia.rcsc@roche.com.

С уважением,

Менеджер по продукции
Тел: +7 (916) 922-64-09
Электронная почта: ivan.kargov@roche.com

Иван Каргов
Иван Каргов
Digitally signed by Иван Каргов
Date: 2024.09.25 13:29:26 +03'00'

Медицинский менеджер
Тел: + 7 (495) 229-69-99
Электронная почта: maria.kosyakova@roche.com

Мария Косякова
Maria Kosyakova
Digitally signed by Maria Kosyakova
Date: 2024.09.25 16:02:22 +03'00'

CHE2

cobas®

Cholinesterase Gen.2

Order information

REF		CONTENT		Analyzer(s) on which **cobas c** pack(s) can be used
04498577190	04498577500	Cholinesterase Gen.2 (200 tests)	System-ID 07 6842 1	**cobas c** 311, **cobas c** 501/502, COBAS INTEGRA

Materials required (but not provided):

		cobas c 311, **cobas c** 501/502	COBAS INTEGRA 400 plus
10759350190	Calibrator f.a.s. (12 x 3 mL)	Code 401	System-ID 07 3718 6
12149435122	Precinorm U plus (10 x 3 mL)	Code 300	System-ID 07 7999 7
12149443122	Precipath U plus (10 x 3 mL)	Code 301	System-ID 07 8000 6
05117003190	PreciControl ClinChem Multi 1 (20 x 5 mL)	Code 391	System-ID 07 7469 3
05947626190	PreciControl ClinChem Multi 1 (4 x 5 mL)	Code 391	System-ID 07 7469 3
05117216190	PreciControl ClinChem Multi 2 (20 x 5 mL)	Code 392	System-ID 07 7470 7
05947774190	PreciControl ClinChem Multi 2 (4 x 5 mL)	Code 392	System-ID 07 7470 7
04489357190	Diluent NaCl 9 % (50 mL)	System-ID 07 6869 3	n. a.

English

Intended use

In vitro test for the quantitative determination of cholinesterase in human serum and plasma on **cobas c** and COBAS INTEGRA systems.

Summary

Measurements of cholinesterase (CHE) activity, with this assay in serum and plasma are used to aid in the assessment of liver function, as an indicator of possible insecticide poisoning, and to detect patients with atypical forms of the enzyme who are at risk for prolonged responses to certain muscle relaxants used in surgical procedures.

Cholinesterase (CHE; EC 3.1.1.8; acylcholine acylhydrolase) is found in the liver, pancreas, heart, serum and in the white matter of the brain. This enzyme must not be confused with acetylcholinesterase from erythrocytes (EC 3.1.1.7; acetylcholine acetylhydrolase). Despite the activity of CHE in the human body being about threefold higher than that of acetylcholinesterase, the exact biological function of cholinesterase is unknown.[1] In the absence of genetic causes or known inhibitors, decrease in CHE activity reflects impaired synthesis of the enzyme by the liver. Therefore, it is often measured as an index of liver function (in case of liver failure or for monitoring liver function after liver transplantation).[2,3,4] Measurement of serum CHE activity can also serve as an indicator of possible poisoning from organophosphorus compounds (insecticides) which are able to inhibit CHE activity, possibly leading to death (via inhibition of all the acetylcholinesterase of the nervous tissue).[1,5] In preoperative screening, the CHE assay is used to detect patients with atypical forms of the enzyme and hence avoid prolonged apnea caused by slow elimination of muscle relaxants.[1,6] The most frequently discussed genetic variants are the atypical or dibucaine resistant (A), the fluoride resistant (F), the silent (S, absence of catalytic activity), and the Kalow (K) variants.[7] The homozygous forms AA or FF are found in only 0.3 to 0.5 % of the Caucasian population. The phenotypes most susceptible to apnea after succinylcholine administration include AA, AS, FF, FS, SS, AF, and to some extent UA.[1] Measurements of total serum cholinesterase activity (without enzyme inhibitors) as well as determination of the "dibucaine number" and "fluoride number" are needed to fully characterize cholinesterase variants. The "dibucaine number" or the "fluoride number" indicate the percent inhibition of enzyme activity by dibucaine or fluoride when a serum or plasma sample is tested under standard conditions.[1,7,8] Low cholinesterase levels can be found in cases of renal disease, malnutrition, pregnancy, malignancy, burns, cardiopulmonary bypass, leprosy. Specific drugs can also alter CHE activity.[7]

This assay is based on the method published by Schmidt *et al.*[8]

Test principle[8]

Colorimetric assay

$$\text{butyrylthiocholine} + H_2O \xrightarrow{\text{CHE}} \text{thiocholine} + \text{butyrate}$$

$$\text{thiocholine} + \text{potassium hexacyanoferrate (III)} \longrightarrow$$

dithiobis(choline) + potassium hexacyanoferrate (II)

Cholinesterase catalyzes the hydrolysis of butyrylthiocholine to thiocholine and butyrate. Thiocholine instantaneously reduces the yellow hexacyanoferrate (III) to the almost colorless hexacyanoferrate (II). This decrease in color can be measured photometrically.

Precautions and warnings

For in vitro diagnostic use for laboratory professionals. Exercise the normal precautions required for handling all laboratory reagents.

Infectious or microbial waste:
Warning: handle waste as potentially biohazardous material. Dispose of waste according to accepted laboratory instructions and procedures.

Environmental hazards:
Apply all relevant local disposal regulations to determine the safe disposal.

Safety data sheet available for professional user on request.

Reagent handling

Ready for use

Specimen collection and preparation[9]

For specimen collection and preparation only use suitable tubes or collection containers.

Only the specimens listed below were tested and found acceptable.
Serum.
Plasma: Li-heparin and K_2-EDTA plasma

The sample types listed were tested with a selection of sample collection tubes that were commercially available at the time of testing, i.e. not all available tubes of all manufacturers were tested. Sample collection systems from various manufacturers may contain differing materials which could affect the test results in some cases. When processing samples in primary tubes (sample collection systems), follow the instructions of the tube manufacturer.

Centrifuge samples containing precipitates before performing the assay.

See the limitations and interferences section for details about possible sample interferences.

Stability:[10,9,11]

6 hours at 15-25 °C
7 days at 2-8 °C
1 year at -20 °C (± 5 °C)

Freeze only once.

Materials provided

See "Reagents – working solutions" section for reagents.

Materials required (but not provided)

See "Order information" section

General laboratory equipment

CHE2

Cholinesterase Gen.2

cobas®

Assay

For optimum performance of the assay follow the directions given in this document for the analyzer concerned. Refer to the appropriate operator's manual for analyzer-specific assay instructions.

The performance of applications not validated by Roche is not warranted and must be defined by the user.

Calculation

The systems automatically calculate the analyte concentration of each sample.

Conversion factors:	U/L x 0.0167 = µkat/L
	U/L x 0.001 = kU/L

Expected values[12,a]

Children, men, women (aged 40 years or more): 5320-12920 U/L (89-215.3 µkat/L)

Women aged 16-39 years, not pregnant, not taking hormonal contraceptives: 4260-11250 U/L (71-187 µkat/L)

Women aged 18-41 years, pregnant or taking contraceptives: 3650-9120 U/L (61-152 µkat/L)

Each laboratory should investigate the transferability of the expected values to its own patient population and if necessary determine its own reference ranges.

a) Calculated with a temperature conversion factor of 1.52 (25 → 37 °C)13

cobas c systems

System information

For **cobas c** 311/501 analyzers:

CHE2: ACN 510

For **cobas c** 502 analyzer:

CHE2: ACN 8510

Reagents - working solutions

R1 Pyrophosphate buffer: 92 mmol/L, pH 7.7; potassium hexacyanoferrate (III): 2.4 mmol/L

R3 GOOD's buffer: 10 mmol/L, pH 4.0; butyrylthiocholine: 46 mmol/L; stabilizers

R1 is in position B and R3 is in position C.

Storage and stability

Shelf life at 2-8 °C:	See expiration date on **cobas c** pack label.
On-board in use and refrigerated on the analyzer:	4 weeks

Application for serum and plasma

cobas c 311 **test definition**

Assay type	Rate A		
Reaction time / Assay points	10 / 29-40		
Wavelength (sub/main)	700/415 nm		
Reaction direction	Decrease		
Units	U/L (µkat/L, kU/L)		
Reagent pipetting		Diluent (H_2O)	
R1	120 µL	–	
R3	24 µL	–	

Sample volumes	*Sample*	*Sample dilution*	
		Sample	*Diluent (NaCl)*
Normal	2 µL	–	–
Decreased	10 µL	15 µL	135 µL
Increased	2 µL	–	–

cobas c 501 **test definition**

Assay type	Rate A		
Reaction time / Assay points	10 / 44-54		
Wavelength (sub/main)	700/415 nm		
Reaction direction	Decrease		
Units	U/L (µkat/L, kU/L)		
Reagent pipetting		Diluent (H_2O)	
R1	120 µL	–	
R3	24 µL	–	

Sample volumes	*Sample*	*Sample dilution*	
		Sample	*Diluent (NaCl)*
Normal	2 µL	–	–
Decreased	10 µL	15 µL	135 µL
Increased	2 µL	–	–

cobas c 502 **test definition**

Assay type	Rate A		
Reaction time / Assay points	10 / 44-54		
Wavelength (sub/main)	700/415 nm		
Reaction direction	Decrease		
Units	U/L (µkat/L, kU/L)		
Reagent pipetting		Diluent (H_2O)	
R1	120 µL	–	
R3	24 µL	–	

Sample volumes	*Sample*	*Sample dilution*	
		Sample	*Diluent (NaCl)*
Normal	2 µL	–	–
Decreased	10 µL	15 µL	135 µL
Increased	4 µL	–	–

Calibration

Calibrators	S1: H_2O
	S2: C.f.a.s.
Calibration mode	Linear
Calibration frequency	2-point calibration - after reagent lot change - as required following quality control procedures

Calibration interval may be extended based on acceptable verification of calibration by the laboratory.

Traceability: This test has been standardized against a reference method using a manual application of the butyrylthiocholine/hexacyanoferrate (III) method on a manual photometer and the published molar absorptivity ε of hexacyanoferrate (III).[8]

Quality control

For quality control, use control materials as listed in the "Order information" section.

In addition, other suitable control material can be used.

The control intervals and limits should be adapted to each laboratory's individual requirements. Values obtained should fall within the defined

CHE2

Cholinesterase Gen.2

limits. Each laboratory should establish corrective measures to be taken if values fall outside the defined limits.

Follow the applicable government regulations and local guidelines for quality control.

Limitations - interference

Criterion: Recovery within ± 10 % of initial values at a cholinesterase activity of 5000 U/L (83.5 µkat/L).

Icterus:[14] No significant interference up to an I index of 60 for conjugated and unconjugated bilirubin (approximate conjugated and unconjugated bilirubin concentration: 1026 µmol/L or 60 mg/dL).

Hemolysis:[14] No significant interference up to an H index of 700 (approximate hemoglobin concentration: 435 µmol/L or 700 mg/dL).

Lipemia (native):[14] No significant interference up to an L index of 1000. There is poor correlation between the L index (corresponds to turbidity) and triglycerides concentration.

Drugs: No interference was found at therapeutic concentrations using common drug panels.[15,16]

In very rare cases, gammopathy, in particular type IgM (Waldenström's macroglobulinemia), may cause unreliable results.[17]

For diagnostic purposes, the results should always be assessed in conjunction with the patient's medical history, clinical examination and other findings.

ACTION REQUIRED

Special Wash Programming: The use of special wash steps is mandatory when certain test combinations are run together on **cobas c** systems. The latest version of the carry-over evasion list can be found with the NaOHD-SMS-SmpCln1+2-SCCS Method Sheets. For further instructions refer to the operator's manual. **cobas c** 502 analyzer: All special wash programming necessary for avoiding carry-over is available via the **cobas** link, manual input is required in certain cases.

Where required, special wash/carry-over evasion programming must be implemented prior to reporting results with this test.

Limits and ranges

Measuring range

100-14000 U/L (1.67-234 µkat/L)

Determine samples having higher activities via the rerun function. Dilution of samples via the rerun function is a 1:2 dilution. Results from samples diluted using the rerun function are automatically multiplied by a factor of 2.

Lower limits of measurement

Lower detection limit of the test

100 U/L (1.67 µkat/L)

The lower detection limit represents the lowest measurable analyte level that can be distinguished from zero. It is calculated as the value lying 3 standard deviations above that of the lowest standard (standard 1 + 3 SD, repeatability, n = 21).

Specific performance data

Representative performance data on the analyzers are given below. Results obtained in individual laboratories may differ.

Precision

Precision was determined using human samples and controls in an internal protocol with repeatability (n = 21) and intermediate precision (3 aliquots per run, 1 run per day, 21 days). The following results were obtained on the **cobas c** 501 analyzer:

Repeatability	*Mean*	*SD*	*CV*
	U/L (µkat/L)	*U/L (µkat/L)*	*%*
Precinorm U	4887 (81.6)	25 (0.4)	0.5
Precipath U	5331 (89.0)	27 (0.5)	0.5
Human serum 1	5916 (98.8)	28 (0.5)	0.5
Human serum 2	7313 (122)	38 (1)	0.5
Intermediate precision	*Mean*	*SD*	*CV*
	U/L (µkat/L)	*U/L (µkat/L)*	*%*
Precinorm U	4707 (78.6)	49 (0.8)	1.0
Precipath U	4838 (80.8)	45 (0.8)	0.9
Human serum 3	1002 (16.7)	26 (0.4)	2.6
Human serum 4	6683 (112)	74 (1)	1.1

The data obtained on **cobas c** 501 analyzer(s) are representative for **cobas c** 311 analyzer(s).

Method comparison

Cholinesterase values for human serum and plasma samples obtained on a **cobas c** 501 analyzer (y) were compared with those determined using the corresponding reagent on a COBAS INTEGRA 700 analyzer (x).

Sample size (n) = 89

Passing/Bablok[18]	Linear regression
y = 1.019x - 177 U/L	y = 1.018x - 178 U/L
τ = 0.963	r = 0.999

The sample activities were between 2184 and 12525 U/L (36.5 and 209 µkat/L).

The data obtained on **cobas c** 501 analyzer(s) are representative for **cobas c** 311 analyzer(s).

COBAS INTEGRA systems

System information

CHE2: Test ID 0-021

Reagents - working solutions

R1 Pyrophosphate buffer: 92 mmol/L, pH 7.7; potassium hexacyanoferrate (III): 2.4 mmol/L

SR GOOD's buffer: 10 mmol/L, pH 4.0; butyrylthiocholine: 46 mmol/L; stabilizers

R1 is in position B and SR is in position C.

Storage and stability

Shelf life at 2-8 °C	See expiration date on **cobas c** pack label
On-board in use at 10-15 °C	4 weeks

Application for serum and plasma

Test definition

Measuring mode	Absorbance
Abs. calculation mode	Kinetic
Reaction mode	R1-S-SR
Reaction direction	Decrease
Wavelength A/B	409/659 nm
Calc. first/last	43/52
Unit	U/L

Pipetting parameters

		Diluent (H_2O)
R1	120 µL	
Sample	2 µL	5 µL
SR	24 µL	
Total volume	151 µL	

Calibration

Calibrator	Calibrator f.a.s.
	Use deionized water as zero calibrator.

CHE2

Cholinesterase Gen.2

Calibration mode	Linear regression
Calibration replicate	Duplicate recommended
Calibration frequency	Each lot

Calibration interval may be extended based on acceptable verification of calibration by the laboratory.

Traceability: This test is standardized against a reference method using a manual application of the butyrylthiocholine/hexacyanoferrate (III) method on a photometer and the published molar absorptivity of hexacyanoferrate (III).[8]

Quality control

Reference range	Precinorm U plus or PreciControl ClinChem Multi 1
Pathological range	Precipath U plus or PreciControl ClinChem Multi 2
Control interval	24 hours recommended
Control sequence	User defined
Control after calibration	Recommended

For quality control, use control materials as listed in the "Order information" section. In addition, other suitable control material can be used.

The control intervals and limits should be adapted to each laboratory's individual requirements. Values obtained should fall within the defined limits. Each laboratory should establish corrective measures to be taken if values fall outside the defined limits.

Follow the applicable government regulations and local guidelines for quality control.

Limitations - interference

Criterion: Recovery within ± 10 % of initial value.

Icterus:[14] No significant interference.

Hemolysis:[14] No significant interference up to an H index of 350 (approximate hemoglobin concentration: 217 µmol/L or 350 mg/dL).

Lipemia (Intralipid):[14] No significant interference up to an L index of 1000. There is poor correlation between the L index (corresponds to turbidity) and triglycerides concentration.

Drugs: No interference was found at therapeutic concentrations using common drug panels.[15,16]

Anticoagulants: Citrate and fluoride inhibit the reaction and must not be used.

In very rare cases, gammopathy, in particular type IgM (Waldenström's macroglobulinemia), may cause unreliable results.[17]

For diagnostic purposes, the results should always be assessed in conjunction with the patient's medical history, clinical examination and other findings.

ACTION REQUIRED

Special Wash Programming: The use of special wash steps is mandatory when certain test combinations are run together on COBAS INTEGRA analyzers. Refer to the CLEAN Method Sheet for further instructions and for the latest version of the Extra wash cycle list.

Where required, special wash/carry-over evasion programming must be implemented prior to reporting results with this test.

Limits and ranges

Measuring range

200-14000 U/L (3.34-234 µkat/L)

Determine samples having higher activities via the rerun function. Dilution of samples via the rerun function is a 1:2 dilution. Results from samples diluted using the rerun function are automatically multiplied by a factor of 2.

Lower limits of measurement

Lower detection limit of the test:
200 U/L (3.34 µkat/L)

The lower detection limit represents the lowest measurable analyte level that can be distinguished from zero. It is calculated as the value lying 3 standard deviations above that of a zero sample (zero sample + 3 SD, repeatability, n = 21).

Specific performance data

Representative performance data on the analyzers are given below. Results obtained in individual laboratories may differ.

Precision

Precision was determined using human samples and controls in an internal protocol with repeatability (n = 21) and intermediate precision (1 aliquot per run, 1 run per day, 21 days). The following results were obtained on the COBAS INTEGRA 800 analyzer:

	Repeatability			*Intermediate precision*		
Sample	*Mean*		*CV*	*Mean*		*CV*
	U/L	*µkat/L*	*%*	*U/L*	*µkat/L*	*%*
Human serum	6374	106	0.5	6675	111	1.4
Precinorm U	6263	105	0.6	6213	104	1.1
Precipath U	6015	100	0.6	5964	100	0.9

The data obtained on COBAS INTEGRA 800 analyzer(s) are representative for COBAS INTEGRA 400 plus analyzer(s).

Method comparison

CHE values for human serum samples obtained on a COBAS INTEGRA 800 analyzer using the Roche CHE2 reagent (y) were compared with those determined using the Roche CHE reagent on the same analyzer (x).

Sample size (n) = 51

Passing/Bablok[18]	Linear regression
y = 0.970x + 128 (U/L)	y = 0.965x + 153 (U/L)
τ = 0.967	r = 0.999
SD (md95) = 125	Sy.x = 37.1

The sample activities were between 1192 U/L and 14411 U/L (19.9-241 µkat/L).

The data obtained on COBAS INTEGRA 800 analyzer(s) are representative for COBAS INTEGRA 400 plus analyzer(s).

References

1 Panteghini M. Serum Enzymes. In: Rifai N, Chiu RWK, Young I, Burnham CAD, Wittwer CT, editors. Tietz Textbook of Laboratory Medicine, Saunders Elsevier, Philadelphia, 7th edition, 2023, chapter 32, p. 350-350.e36.

2 Ogunkeye OO, Roluga AI. Serum cholinesterase activity helps to distinguish between liver disease and non-liver disease aberration in liver function tests. Pathophysiology 2006 May;13(2):91-93.

3 Weber S, Woischke C, Denk G, et al. Novel predictors for liver transplantation or death in drug-induced acute liver failure. Eur J Gastroenterol Hepatol 2022 Apr 1;34(4):422-425.

4 Stockhoff L, Muellner-Bucsics T, Markova AA, et al. Low Serum Cholinesterase Identifies Patients With Worse Outcome and Increased Mortality After TIPS. Hepatol Commun 2022 Mar;6(3):621-632.

5 King AM, Aaron CK. Organophosphate and carbamate poisoning. Emerg Med Clin North Am 2015 Feb;33(1):133-151.

6 Andersson ML, Møller AM, Wildgaard K. Butyrylcholinesterase deficiency and its clinical importance in anaesthesia: a systematic review. Anaesthesia 2019 Apr;74(4):518-528.

7 Soliday FK, Conley YP, Henker R. Pseudocholinesterase deficiency: a comprehensive review of genetic, acquired, and drug influences. AANA J 2010 Aug;78(4):313-320.

8 Schmidt E, Gerhardt W, Henkel E, et al. Proposal of Standard Methods for the Determination of Enzyme Catalytic Concentrations in Serum and Plasma at 37 °C. Eur J Clin Chem Clin Biochem 1992;30:163-170.

9 Use of Anticoagulants in Diagnostic Laboratory Investigations. WHO Publication WHO/DIL/LAB/99.1 Rev. 2: Jan 2002.

10 Tietz NW, ed. Clinical Guide to Laboratory Tests, 3rd ed. Philadelphia PA: WB Saunders Company 1995;132-133.

11 Huizenga JR, van der Belt K, Gips CH. The Effect of Storage at Different Temperatures on Cholinesterase Activity in Human Serum. J Clin Chem Clin Biochem 1985;24:283-385.

12 den Blaauwen DH, Poppe WA, Tritschler W. Cholinesterase (EC 3.1.1.8) mit Butyrylthiocholiniodid als Substrat:Referenzwerte in Abhängigkeit von Alter und Geschlecht unter Berücksichtigung hormonaler Einflüsse und Schwangerschaft. J Clin Chem Clin Biochem 1983;21:381-386.

13 Zawta B, Klein G, Bablok W. Temperature Conversion in Clinical Enzymology? Klin Lab 1994;40:33-42.

14 Glick MR, Ryder KW, Jackson SA. Graphical Comparisons of Interferences in Clinical Chemistry Instrumentation. Clin Chem 1986;32:470-475.

15 Breuer J. Report on the Symposium "Drug effects in Clinical Chemistry Methods". Eur J Clin Chem Clin Biochem 1996;34:385-386.

16 Sonntag O, Scholer A. Drug interference in clinical chemistry: recommendation of drugs and their concentrations to be used in drug interference studies. Ann Clin Biochem 2001;38:376-385.

17 Bakker AJ, Mücke M. Gammopathy interference in clinical chemistry assays: mechanisms, detection and prevention. Clin Chem Lab Med 2007;45(9):1240-1243.

18 Bablok W, Passing H, Bender R, et al. A general regression procedure for method transformation. Application of linear regression procedures for method comparison studies in clinical chemistry, Part III. J Clin Chem Clin Biochem 1988 Nov;26(11):783-790.

A point (period/stop) is always used in this Method Sheet as the decimal separator to mark the border between the integral and the fractional parts of a decimal numeral. Separators for thousands are not used.

Any serious incident that has occurred in relation to the device shall be reported to the manufacturer and the competent authority of the Member State in which the user and/or the patient is established.

Symbols

Roche Diagnostics uses the following symbols and signs in addition to those listed in the ISO 15223-1 standard:

CONTENT	Contents of kit
→	Volume for reconstitution
GTIN	Global Trade Item Number
Rx only	For USA: Caution: Federal law restricts this device to sale by or on the order of a physician.

CE 0123

Roche Diagnostics GmbH
Sandhofer Strasse 116
68305 Mannheim, Germany
www.roche.com
+800 5505 6606

CHE2

cobas®

Cholinesterase Gen.2

Order information

REF		CONTENT		Analyzer(s) on which **cobas c** pack(s) can be used
05168503190*	05168503500	Cholinesterase Gen.2 (650 tests)	System-ID 05 6842 1	**cobas c** 701/702
05168503214*	05168503500	Cholinesterase Gen.2 (650 tests)	System-ID 05 6842 1	**cobas c** 701/702

Materials required (but not provided):

05168511190	Dibucaine**(13.5 mL)	System-ID 03 7458 8	
10759350190	Calibrator f.a.s. (12 x 3 mL)	Code 401	
12149435122	Precinorm U plus (10 x 3 mL)	Code 300	
12149443122	Precipath U plus (10 x 3 mL)	Code 301	
05117003190	PreciControl ClinChem Multi 1 (20 x 5 mL)	Code 391	
05947626190	PreciControl ClinChem Multi 1 (4 x 5 mL)	Code 391	
05117216190	PreciControl ClinChem Multi 2 (20 x 5 mL)	Code 392	
05947774190	PreciControl ClinChem Multi 2 (4 x 5 mL)	Code 392	
05172152190	Diluent NaCl 9 % (119 mL)	System-ID 08 6869 3	

* Some kits shown may not be available in all countries.

** The value presented on the instrument inventory screen is around 9 mL to account for the dead volume of the containers. This corresponds to 400 tests.

English

System information

CHET2: ACN 8534, total cholinesterase

CHED2: ACN 8434, inhibited cholinesterase

Intended use

In vitro test for the quantitative determination of cholinesterase in human serum and plasma on **cobas c** systems.

Summary

Measurements of cholinesterase (CHE) activity, with this assay in serum and plasma are used to aid in the assessment of liver function, as an indicator of possible insecticide poisoning, and to detect patients with atypical forms of the enzyme who are at risk for prolonged responses to certain muscle relaxants used in surgical procedures.

Cholinesterase (CHE; EC 3.1.1.8; acylcholine acylhydrolase) is found in the liver, pancreas, heart, serum and in the white matter of the brain. This enzyme must not be confused with acetylcholinesterase from erythrocytes (EC 3.1.1.7; acetylcholine acetylhydrolase). Despite the activity of CHE in the human body being about threefold higher than that of acetylcholinesterase, the exact biological function of cholinesterase is unknown.[1] In the absence of genetic causes or known inhibitors, decrease in CHE activity reflects impaired synthesis of the enzyme by the liver. Therefore, it is often measured as an index of liver function (in case of liver failure or for monitoring liver function after liver transplantation).[2,3,4] Measurement of serum CHE activity can also serve as an indicator of possible poisoning from organophosphorus compounds (insecticides) which are able to inhibit CHE activity, possibly leading to death (via inhibition of all the acetylcholinesterase of the nervous tissue).[1,5] In preoperative screening, the CHE assay is used to detect patients with atypical forms of the enzyme and hence avoid prolonged apnea caused by slow elimination of muscle relaxants.[1,6] The most frequently discussed genetic variants are the atypical or dibucaine resistant (A), the fluoride resistant (F), the silent (S, absence of catalytic activity), and the Kalow (K) variants.[7] The homozygous forms AA or FF are found in only 0.3 to 0.5 % of the Caucasian population. The phenotypes most susceptible to apnea after succinylcholine administration include AA, AS, FF, FS, SS, AF, and to some extent UA.[1] Measurements of total serum cholinesterase activity (without enzyme inhibitors) as well as determination of the “dibucaine number” and “fluoride number” are needed to fully characterize cholinesterase variants. The “dibucaine number” or the “fluoride number” indicate the percent inhibition of enzyme activity by dibucaine or fluoride when a serum or plasma sample is tested under standard conditions.[1,7,8] Low cholinesterase levels can be found in cases of renal disease, malnutrition, pregnancy, malignancy, burns, cardiopulmonary bypass, leprosy. Specific drugs can also alter CHE activity.[7]

This assay is based on the method published by Schmidt *et al.*[8]

Test principle[8,9]

Colorimetric assay

$$\text{butyrylthiocholine} + H_2O \xrightarrow{CHE} \text{thiocholine} + \text{butyrate}$$

$$\text{thiocholine} + \text{potassium hexacyanoferrate (III)} \longrightarrow \text{dithiobis(choline)} + \text{potassium hexacyanoferrate (II)}$$

Cholinesterase catalyzes the hydrolysis of butyrylthiocholine to thiocholine and butyrate. Thiocholine instantaneously reduces the yellow hexacyanoferrate (III) to the almost colorless hexacyanoferrate (II). This decrease in color can be measured photometrically.

To determine the dibucaine number (DN), cholinesterase activity is measured with and without enzyme inhibitor dibucaine. The dibucaine number is calculated as follows:

$$DN = 100 - \frac{\text{CHE activity with inhibitor}}{\text{CHE activity without inhibitor}} \times 100$$

Reagents - working solutions

Cholinesterase Gen.2

R1 Pyrophosphate buffer: 92 mmol/L, pH 7.7; potassium hexacyanoferrate (III): 2.4 mmol/L

R3 GOOD's buffer: 10 mmol/L, pH 4.0; butyrylthiocholine: 46 mmol/L; stabilizers

Dibucaine (for ACN 8434)

R2 Dibucaine: 2.6 mmol/L, pH 6.3

(Special Reagent)

R1 is in position B and R3 is in position C.

Precautions and warnings

For in vitro diagnostic use for laboratory professionals. Exercise the normal precautions required for handling all laboratory reagents.

Infectious or microbial waste:
Warning: handle waste as potentially biohazardous material. Dispose of waste according to accepted laboratory instructions and procedures.

Environmental hazards:
Apply all relevant local disposal regulations to determine the safe disposal.

Safety data sheet available for professional user on request.

Reagent handling

Ready for use

CHE2

Cholinesterase Gen.2

cobas®

Storage and stability

Shelf life at 2-8 °C:	See expiration date on **cobas c** pack label.
On-board in use and refrigerated on the analyzer:	4 weeks
On-board on the Reagent Manager:	24 hours

Specimen collection and preparation[10]

For specimen collection and preparation only use suitable tubes or collection containers.

Only the specimens listed below were tested and found acceptable.
Serum.
Plasma: Li-heparin and K_2-EDTA plasma.

The sample types listed were tested with a selection of sample collection tubes that were commercially available at the time of testing, i.e. not all available tubes of all manufacturers were tested. Sample collection systems from various manufacturers may contain differing materials which could affect the test results in some cases. When processing samples in primary tubes (sample collection systems), follow the instructions of the tube manufacturer.

Centrifuge samples containing precipitates before performing the assay.

See the limitations and interferences section for details about possible sample interferences.

Stability:[11,10,12]	6 hours at 15-25 °C 7 days at 2-8 °C 1 year at -20 °C (± 5 °C)

Freeze only once.

Materials provided

See "Reagents – working solutions" section for reagents.

Materials required (but not provided)

See "Order information" section

General laboratory equipment

Assay

For optimum performance of the assay follow the directions given in this document for the analyzer concerned. Refer to the appropriate operator's manual for analyzer-specific assay instructions.

The performance of applications not validated by Roche is not warranted and must be defined by the user.

Application for serum and plasma

Total cholinesterase CHET2

cobas c 701/702 **test definition**

Assay type	Rate A	
Reaction time / Assay points	10 / 25-31	
Wavelength (sub/main)	700/415 nm	
Reaction direction	Decrease	
Units	U/L (µkat/L, kU/L)	
Reagent pipetting		Diluent (H_2O)
R1	120 µL	–
R3	24 µL	–

Sample volumes	*Sample*	*Sample dilution*	
		Sample	*Diluent (NaCl)*
Normal	2 µL	–	–
Decreased	10 µL	15 µL	135 µL
Increased	4 µL	–	–

Inhibited cholinesterase CHED2

cobas c 701/702 **test definition**

Assay type	Rate A	
Reaction time / Assay points	10 / 25-31	
Wavelength (sub/main)	700/415 nm	
Reaction direction	Decrease	
Units	U/L (µkat/L, kU/L)	
Reagent pipetting		Diluent (H_2O)
R1	100 µL	–
R2 (Special Reagent)	20 µL	–
R3	24 µL	–

Sample volumes	*Sample*	*Sample dilution*	
		Sample	*Diluent (NaCl)*
Normal	2 µL	–	–
Decreased	2 µL	–	–
Increased	4 µL	–	–

Calculated test definition for dibucaine number

Abbreviated calculated test name CHE2R

Equation 100 – (CHED2/CHET2) x 100

Use a predefined profile for simultaneous order entry of CHET2, CHED2 and CHE2R tests from the same sample. The ratio for dibucaine number will automatically be calculated after results of both tests are available.

Please refer to Operator Manual, section profile and calculated test.

Calibration

CHET2:

Calibrators	S1: H_2O S2: C.f.a.s.
Calibration mode	Linear
Calibration frequency	2-point calibration - after reagent lot change - as required following quality control procedures

Calibration interval may be extended based on acceptable verification of calibration by the laboratory.

Traceability: This test has been standardized against a reference method using a manual application of the butyrylthiocholine/hexacyanoferrate (III) method on a manual photometer and the published molar absorptivity ε of hexacyanoferrate (III).[8]

CHED2:

Calibrator	Transfer of blank and k-factor from CHET2
Calibration frequency	- update of blank and k-factor after each CHET2 calibration - after lot change

Note: For the very first calibration of CHET2 set CHED2 inactive. After completion of the CHET2-calibration, set CHED2 again to active and transfer the blank and k-factor to CHED2.

For further measurements only CHET2 has to be calibrated with calibrator C.f.a.s. and H_2O. For CHED2 calibration always use the blank and calibration factor obtained in the CHET2 calibration.

Quality control

CHET2

For quality control, use control materials as listed in the "Order information" section. In addition, other suitable control material can be used.

The control intervals and limits should be adapted to each laboratory's individual requirements. Values obtained should fall within the defined

limits. Each laboratory should establish corrective measures to be taken if values fall outside the defined limits.

Follow the applicable government regulations and local guidelines for quality control.

Calculation

cobas c systems automatically calculate the analyte concentration of each sample.

Conversion factors: U/L x 0.0167 = µkat/L
U/L x 0.001 = kU/L

Dibucaine number

For calculation of the dibucaine number, please refer to sections Test principle and Calculated test definition for dibucaine number in this method sheet.

Limitations - interference

Total cholinesterase (CHET2)

Criterion: Recovery within ± 10 % of initial value at a cholinesterase activity of 5000 U/L (83.5 µkat/L).

Icterus:[13] No significant interference up to an I index of 60 for conjugated and unconjugated bilirubin (approximate conjugated and unconjugated bilirubin concentration: 1026 µmol/L or 60 mg/dL).

Hemolysis:[13] No significant interference up to an H index of 700 (approximate hemoglobin concentration: 435 µmol/L or 700 mg/dL).

Lipemia (native):[13] No significant interference up to an L index of 1000. There is poor correlation between the L index (corresponds to turbidity) and triglycerides concentration.

Drugs: No interference was found at therapeutic concentrations using common drug panels.[14,15]

In very rare cases, gammopathy, in particular type IgM (Waldenström's macroglobulinemia), may cause unreliable results.[16]

For diagnostic purposes, the results should always be assessed in conjunction with the patient's medical history, clinical examination and other findings.

Inhibited cholinesterase (CHED2)

Criterion: Recovery within ± 10 % of initial value at a cholinesterase activity of 1250 U/L (20.9 µkat/L).

Icterus:[13] No significant interference up to an I index of 60 for conjugated bilirubin and 40 for unconjugated bilirubin (approximate conjugated bilirubin concentration: 1026 µmol/L or 60 mg/dL; approximate unconjugated bilirubin concentration: 684 µmol/L or 40 mg/dL).

Hemolysis:[13] No significant interference up to an H index of 200 (approximate hemoglobin concentration: 124 µmol/L or 200 mg/dL).

Lipemia (native):[13] No significant interference up to an L index of 500. There is poor correlation between the L index (corresponds to turbidity) and triglycerides concentration.

Drugs: No interference was found at therapeutic concentrations using common drug panels.[14,15]

Exception: Acetaminophen causes artificially high results. Intralipid causes artificially low results.

In very rare cases, gammopathy, in particular type IgM (Waldenström's macroglobulinemia), may cause unreliable results.[16]

For diagnostic purposes, the results should always be assessed in conjunction with the patient's medical history, clinical examination and other findings.

ACTION REQUIRED

Special Wash Programming: The use of special wash steps is mandatory when certain test combinations are run together on **cobas c** systems. All special wash programming necessary for avoiding carry-over is available via the **cobas** link, manual input is required in certain cases. The latest version of the carry-over evasion list can be found with the NaOHD/SMS/SmpCln1+2/SCCS Method Sheet and for further instructions refer to the operator's manual.

Where required, special wash/carry-over evasion programming must be implemented prior to reporting results with this test.

Limits and ranges

Measuring range

CHET2: 100-14000 U/L (1.67-234 µkat/L)

CHED2: 250-7000 U/L (4.18-117 µkat/L)

Determine samples having higher activities via the rerun function. Dilution of samples via the rerun function is a 1:2 dilution. Results from samples diluted using the rerun function are automatically multiplied by a factor of 2.

Lower limits of measurement

Lower detection limit of the test:

CHET2: 100 U/L (1.67 µkat/L)

CHED2: 250 U/L (4.18 µkat/L)

The lower detection limit represents the lowest measurable analyte level that can be distinguished from zero. It is calculated as the value lying 3 standard deviations above that of the lowest standard (standard 1 + 3 SD, repeatability, n = 21).

Values below the lower detection limit (< 100 U/L) will not be flagged by the instrument.

Expected values[17,a)]

Children, men, women (aged 40 years or more): 5320-12920 U/L (89-215.3 µkat/L)

Women aged 16-39 years, not pregnant, not taking hormonal contraceptives: 4260-11250 U/L (71-187 µkat/L)

Women aged 18-41 years, pregnant or taking contraceptives: 3650-9120 U/L (61-152 µkat/L)

Dibucaine number

Dibucaine number for the cholinesterase variants U (usual) and A (atypical):

Normal individuals	UU	Dibucaine Number	≥ 73
Heterozygous individuals	UA	Dibucaine Number	72-57
Homozygous individuals	AA	Dibucaine Number	≤ 50

DN results below 57 should be considered to indicate a potentially high risk of succinyldicholine sensitivity.

Each laboratory should investigate the transferability of the expected values to its own patient population and if necessary determine its own reference ranges.

a) Calculated with a temperature conversion factor of 1.52 (25 → 37 °C)[18]

Specific performance data

Representative performance data on the analyzers are given below. Results obtained in individual laboratories may differ.

Precision

Precision was determined using human samples and controls in an internal protocol with repeatability (n = 21) and intermediate precision (3 aliquots per run, 1 run per day, 21 days). The following results were obtained on the **cobas c** 701 analyzer:

Repeatability	*Mean* *U/L (µkat/L)*	*SD* *U/L (µkat/L)*	*CV* *%*
Precinorm U	3118 (52.1)	19 (0.3)	0.6
Precipath U	4912 (82.0)	25 (0.4)	0.5
Human serum A	3047 (50.9)	27 (0.5)	0.9
Human serum B	5422 (90.5)	23 (0.4)	0.4
Human serum C	11785 (197)	50 (1)	0.4

Intermediate precision	*Mean* *U/L (µkat/L)*	*SD* *U/L (µkat/L)*	*CV* *%*
Precinorm U	4707 (78.6)	49 (0.82)	1.0
Precipath U	4838 (80.8)	45 (0.75)	0.9
Human serum 3	1002 (16.7)	26 (0.43)	2.6
Human serum 4	6683 (112)	74 (1.24)	1.1

Results for intermediate precision were obtained on the **cobas c** 501 analyzer.

CHE2

Cholinesterase Gen.2

The data obtained on **cobas c** 501 analyzer(s) are representative for **cobas c** 701 analyzer(s).

Method comparison

CHET2

Cholinesterase values for human serum and plasma samples obtained on a **cobas c** 701 analyzer (y) were compared with those determined using the corresponding reagent on **cobas c** 501 analyzer (x).

Sample size (n) = 83

Passing/Bablok[19]	Linear regression
y = 0.989x + 24.4 U/L	y = 0.987x + 29.0 U/L
τ = 0.973	r = 0.999

The sample activities were between 1693 and 13586 U/L (28.3 and 227 µkat/L).

CHED2

Total and inhibited cholinesterase values, CHET2 (x) and CHED2 (y), for human serum and plasma samples obtained on a **cobas c** 701 analyzer were compared.

Sample size (n) = 84

Passing/Bablok[19]	Linear regression
y = 0.275x - 127 U/L	y = 0.273x - 102 U/L
τ = 0.954	r = 0.997

The sample activities were between 1699 and 13832 U/L (28.4 and 231 µkat/L).

References

1 Panteghini M. Serum Enzymes. In: Rifai N, Chiu RWK, Young I, Burnham CAD, Wittwer CT, editors. Tietz Textbook of Laboratory Medicine, Saunders Elsevier, Philadelphia, 7th edition, 2023, chapter 32, p. 350-350.e36.

2 Ogunkeye OO, Roluga AI. Serum cholinesterase activity helps to distinguish between liver disease and non-liver disease aberration in liver function tests. Pathophysiology 2006 May;13(2):91-93.

3 Weber S, Woischke C, Denk G, et al. Novel predictors for liver transplantation or death in drug-induced acute liver failure. Eur J Gastroenterol Hepatol 2022 Apr 1;34(4):422-425.

4 Stockhoff L, Muellner-Bucsics T, Markova AA, et al. Low Serum Cholinesterase Identifies Patients With Worse Outcome and Increased Mortality After TIPS. Hepatol Commun 2022 Mar;6(3):621-632.

5 King AM, Aaron CK. Organophosphate and carbamate poisoning. Emerg Med Clin North Am 2015 Feb;33(1):133-151.

6 Andersson ML, Møller AM, Wildgaard K. Butyrylcholinesterase deficiency and its clinical importance in anaesthesia: a systematic review. Anaesthesia 2019 Apr;74(4):518-528.

7 Soliday FK, Conley YP, Henker R. Pseudocholinesterase deficiency: a comprehensive review of genetic, acquired, and drug influences. AANA J 2010 Aug;78(4):313-320.

8 Schmidt E, Gerhardt W, Henkel E, et al. Proposal of Standard Methods for the Determination of Enzyme Catalytic Concentrations in Serum and Plasma at 37 °C. Eur J Clin Chem Clin Biochem 1992;30:163-170.

9 Garry PJ. Serum cholinesterase variants: examination of differential inhibitors, salts, and buffers used to measure enzyme activity Clin Chem 1971;17:183-191.

10 Use of Anticoagulants in Diagnostic Laboratory Investigations. WHO Publication WHO/DIL/LAB/99.1 Rev. 2: Jan 2002.

11 Tietz NW, ed. Clinical Guide to Laboratory Tests, 3rd ed. Philadelphia PA: WB Saunders Company 1995;132-133.

12 Huizenga JR, van der Belt K, Gips CH. The Effect of Storage at Different Temperatures on Cholinesterase Activity in Human Serum. J Clin Chem Clin Biochem 1985;24:283-385.

13 Glick MR, Ryder KW, Jackson SA. Graphical Comparisons of Interferences in Clinical Chemistry Instrumentation. Clin Chem 1986;32:470-475.

14 Breuer J. Report on the Symposium "Drug effects in Clinical Chemistry Methods". Eur J Clin Chem Clin Biochem 1996;34:385-386.

15 Sonntag O, Scholer A. Drug interference in clinical chemistry: recommendation of drugs and their concentrations to be used in drug interference studies. Ann Clin Biochem 2001;38:376-385.

16 Bakker AJ, Mücke M. Gammopathy interference in clinical chemistry assays: mechanisms, detection and prevention. Clin Chem Lab Med 2007;45(9):1240-1243.

17 den Blaauwen DH, Poppe WA, Tritschler W. Cholinesterase (EC 3.1.1.8) mit Butyrylthiocholiniodid als Substrat:Referenzwerte in Abhängigkeit von Alter und Geschlecht unter Berücksichtigung hormonaler Einflüsse und Schwangerschaft. J Clin Chem Clin Biochem 1983;21:381-386.

18 Zawta B, Klein G, Bablok W. Temperature Conversion in Clinical Enzymology? Klin Lab 1994;40:33-42.

19 Bablok W, Passing H, Bender R, et al. A general regression procedure for method transformation. Application of linear regression procedures for method comparison studies in clinical chemistry, Part III. J Clin Chem Clin Biochem 1988 Nov;26(11):783-790.

A point (period/stop) is always used in this Method Sheet as the decimal separator to mark the border between the integral and the fractional parts of a decimal numeral. Separators for thousands are not used.

Any serious incident that has occurred in relation to the device shall be reported to the manufacturer and the competent authority of the Member State in which the user and/or the patient is established.

Symbols

Roche Diagnostics uses the following symbols and signs in addition to those listed in the ISO 15223-1 standard:

CONTENT	Contents of kit
→	Volume for reconstitution
GTIN	Global Trade Item Number
Rx only	For USA: Caution: Federal law restricts this device to sale by or on the order of a physician.

CE 0123

Roche Diagnostics GmbH
Sandhofer Strasse 116
68305 Mannheim, Germany
www.roche.com
+800 5505 6606