

Cytokine adsorption devices for treating respiratory failure in people with COVID-19

Medtech innovation briefing

Published: 21 May 2020

www.nice.org.uk/guidance/mib217

Summary

- The **technologies** described in this briefing are cytokine adsorption devices. They are for reducing blood levels of cytokines in people with COVID-19 and respiratory failure.
- The **innovative aspects** are that the cytokine adsorption devices reduce harmful levels of cytokines in the blood.
- The **intended place in therapy** would be in addition to critical care for people with COVID-19 and respiratory failure.
- The **main points from the evidence** summarised in this briefing are from a non-randomised comparative single-arm observational study and a series of case reports including 56 patients with COVID-19 and respiratory failure. It shows that cytokine adsorption devices reduce levels of cytokines in the blood in people with COVID-19. This may help improve lung function.

- **Key uncertainties** around the evidence or technology are that most of the evidence is from company websites and is not peer reviewed. The clinical experience of using cytokine adsorbent devices in people with COVID-19 is reported as low-quality evidence, such as case reports with small sample sizes. None of these were done in the NHS.
- **Safety issues** identified are a safety notice advising that CytoSorb should not be used with nitrous oxide. Also, there is a Medical Device Alert for the Spectra Optia Apheresis System because of a risk of improper use if company instructions are not followed carefully.
- The **cost** of the cytokine adsorption cartridges ranges from £450 to £1,785 per unit (excluding VAT). The cost of machines using extracorporeal circuits ranges from £10,000 up to £60,000 and are already available in NHS hospitals, but some machines are only available in specialist centres. The **resource impact** would be greater than standard care because the technology is intended to be used in addition to standard care.

The technology

Cytokine adsorption devices are designed to reduce elevated concentrations of cytokines in the blood. Elevated cytokine levels have been seen in some patients with COVID-19 and respiratory failure. Increased concentrations of cytokines may indicate an uncontrolled immune response, called cytokine release syndrome or cytokine storm. This can result in severe inflammation, shock, respiratory failure, organ failure, and in some cases, death.

The adsorption devices are cartridges containing adsorbent materials, such as porous polymer beads or resin. Blood or plasma is pumped out of the body and through the adsorption cartridge. This non-selectively captures molecules, such as cytokines, within the pores of the adsorbent material. The blood, or plasma, is then returned to the body with a reduced level of inflammatory markers and cytokines.

Each cartridge is single-use and can be used for continuous treatment cycles for between 2 and 12 hours per session. Patients with COVID-19 are often more likely to experience blood clotting, so healthcare professionals should ensure anticoagulation treatment is effective before starting haemoperfusion therapy. Because adsorption technologies may affect the concentration of drugs in the blood, pharmacological treatment will need to be carefully monitored. The following technologies were identified as being cytokine adsorption devices:

- D2000 Plasma Adsorption Cartridge and Spectra Optia Apheresis System (Marker Therapeutics AG and Terumo BCT). The D2000 plasma adsorption cartridge is used with the Spectra Optia Apheresis System as a secondary blood purification device. The adsorbent material in the cartridge is made of a blend of non-ionic resins. Plasma, separated from blood using the Spectra Optia plasma exchange protocol, is pumped through the cartridge to remove cytokines. The person's own plasma is then mixed back into the blood and returned to the body. The company advised the treatment should be given for 2 hours every day for 2 to 3 sessions.
- CytoSorb adsorbent cartridge (CytoSorbents Corporation). CytoSorb can be added to most commercially available extracorporeal machines such as dialysis machines, haemofiltration machines, heart and lung machines and extracorporeal membrane oxygenation machines. The adsorbent material in the cartridge is beads made of porous polymer. Blood is pumped through the cartridge, removing molecules up to 55 kDa in size such as cytokines, and returned to the body. The company advised that the treatment can be used for up to 24 hours per device and for up to 7 consecutive days. The company states the technology should not be used with plasma exchange devices.
- HA330 and HA380 Haemoperfusion Cartridges (Jafron). The HA330 and HA380 cartridges have been described by [Health Technology Wales in a topic exploration report](#). New evidence has been included in the evidence section of this briefing.

Similar devices have been designed to use adsorption devices to reduce toxins released from bacteria in the blood (endotoxin). The literature reports that a technology has been used for treating septic shock as a secondary complication of flu. There is currently no evidence for its use in patients with COVID-19 and so it is not included in this briefing.

Innovations

The technology is not new, but it is new to use cytokine adsorption devices specifically to treat COVID-19. The devices are intended to return the cytokine concentration in the blood to normal levels. This is expected to prevent organ failure and death as a result of cytokine release syndrome in people with COVID-19. Unlike drug therapies, adsorption cartridges are concentration dependent, so the cytokines in the blood at the highest concentrations will be removed from the blood at a faster rate.

Current care pathway

[NHS clinical guidance for the management of critical care for adults with COVID-19 during the](#)

[coronavirus pandemic](#) notes that while antiviral therapies and vaccines are in development, none are currently recommended, and clinical trials of new treatments should be supported. People with COVID-19 and respiratory failure are treated using invasive or non-invasive ventilation to reach target oxygen saturation (SpO₂). This would be 92% to 96% for most people but may be lower in some patient groups, such as people with chronic obstructive pulmonary disease. Routine high-dose corticosteroids are not recommended because these could lead to prolonged viral shedding, bacterial superinfection and worse outcomes.

The [British Thoracic Society has published guidance on COVID-19: information for the respiratory community](#) to provide respiratory support for people with COVID-19 who are acutely unwell. People with oxygen saturation of less than 94% in room air should be given oxygen using a Venturi mask and can be moved to a non-respiratory COVID-19 ward for monitoring if oxygen saturation returns to above 94%. People whose oxygen saturation does not improve should be escalated to intensive care for intubation if appropriate.

[NHS guidance for the role and use of non-invasive respiratory support in adult patients with COVID-19](#) gives further recommendations on the types of invasive and non-invasive ventilation that should be used.

[World Health Organisation guidance on clinical management of severe acute respiratory infection when COVID-19 is suspected](#) notes that people with COVID-19 should be closely monitored for signs of clinical deterioration such as respiratory failure. Vital signs should be monitored and early warning scores such as NEWS2 should be used to identify people whose treatment needs to be escalated. Standard laboratory blood tests should also be used to identify any complications such as acute kidney injury, acute cardiac injury or shock. Each person's treatment should take into consideration whether they have any comorbid conditions, to consider whether other treatments should be temporarily stopped and the potential for interactions between drugs.

NICE has produced [COVID-19 rapid guidelines on managing symptoms \(including at the end of life\) in the community and on critical care of adults with COVID-19](#).

None of the published guidance for treating respiratory failure in people with COVID-19 includes the use of cytokine adsorption. If cytokine release syndrome is suspected in people who do not have COVID-19, standard care includes treatments to suppress the inflammatory response, such as tocilizumab and intravenous immunoglobulin.

Population, setting and intended user

Cytokine adsorption devices are for people who have tested positive for COVID-19 and have imminent or confirmed respiratory failure. The treatment is given by intensive care consultants and specialist nurses on critical care units. Imminent respiratory failure may be characterised by a faster deterioration of a person's condition including increased heart rate, shortness of breath or increased rate of breathing, sweating and diminished consciousness. Indicators for starting treatment include severe acute respiratory distress syndrome with or without suspected acute kidney injury, raised inflammatory biomarkers or hypotension. The companies advised that the technology should be used as soon as possible in people with potential respiratory failure.

The technologies may be used as a standalone therapy or with other extracorporeal therapies including renal replacement therapy and oxygenation membrane therapy. Training is needed and is provided by the companies. In trusts where healthcare professionals are familiar with using extracorporeal circuits the companies advised that remote training is offered for the use of the cartridge. If staff are not familiar with the extracorporeal machines more extensive training is needed.

Costs

Cytokine adsorption device costs

- Each D2000 cartridge costs £1,785 (excluding VAT).
- Each CytoSorb cartridge costs £920 (excluding VAT).
- Each HA330 and HA380 cartridge costs £450 (excluding VAT).

Extracorporeal machine costs

Extracorporeal machines, such as haemodialysis machines, heart–lung machines and extracorporeal membrane oxygenation (ECMO) machines cost between £10,000 to £40,000. It is expected that most hospitals will already have access to the appropriate machines. The cost of the Spectra Optia Apheresis System is £58,338.31 per unit (excluding VAT) including full set up; annual service charge is an additional £4,083. Some hospitals, such as teaching hospitals and specialist care centres, will already have access to the Spectra Optia Apheresis System.

Costs of standard care

The [2019/20 National Tariff Payment System](#) estimates the cost of respiratory failure with multiple

interventions to range between £4,500 and £8,200, depending on the length of hospital stay. The [2018/19 National Cost Collection](#) reports the average cost of critical care ranges from £516 to £1,673 per bed per day.

While these figures give an indication of the cost of respiratory failure, no COVID-19 cost data have been included in these estimates and so the costs do not reflect COVID-19 cases.

Resource consequences

The Spectra Optia Apheresis System is already being widely used for different indications in 73 locations in the UK, including teaching hospitals and specialist care centres. Similarly, haemofiltration and haemodialysis machines are available in all NHS trusts. ECMO machines are currently available in approximately 8 trusts. Heart and lung machines are available in specialist centres.

Cytokine adsorption devices would be used in addition to standard care so will cost more. However, the company claims the technology could reduce COVID-19 mortality rate and speed up recovery.

Regulatory information

D2000 adsorption cartridge is a CE-marked class IIb medical devices. The CE mark states the device can be used for any condition that requires a reduction of metabolic waste products or inflammatory cytokines.

CytoSorb is a CE-marked class IIb medical device. The CE mark for the adsorption cartridges states the devices are approved for the removal of cytokines, bilirubin and myoglobin from blood.

HA330 and HA380 haemoperfusion adsorption cartridges are both CE-marked class IIb medical devices. The CE mark for the adsorption cartridges states the device's adsorption cartridges are approved for the removal of endogenous and exogenous pathogenic substances in patients' blood, including cytokines, bilirubin and immune mediators.

Spectra Optia Apheresis System is a CE-marked class IIb medical device. The CE mark states the device is approved for therapeutic plasma exchange as well as a range of other cell processing protocols such as, red blood cell exchange and bone marrow transplant.

The manufacturer of CytoSorb sent their customers a [Field Safety Notice](#) in 2015. This has advice about a potential incompatibility between the device and nitrous oxide, an inhaled anaesthetic gas.

It states that CytoSorb should not be used with nitrous oxide under any circumstances. The Medicines and Healthcare products Regulatory Agency (MHRA) have not issued a Medical Device Alert for this device.

The manufacturer of Spectra Optia Apheresis System sent their customers a [Field Safety Notice](#) in 2019. An [MHRA Medical Device Alert](#) was issued describing inadequate breakages in the 'frangible' connector (an element of the device that needs to be snapped before use). Failing to break the frangible connector may lead to clotting and inadequate therapy. Healthcare professionals are advised to follow the [Spectra Optia Apheresis System instructions for use and quick reference guide](#).

Equality considerations

NICE is committed to promoting equality, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others.

Cytokine adsorption devices should not be used in pregnant women. Pregnancy and maternity are protected characteristics under the Equality Act (2010).

People over 65, men and people from black, Asian, and ethnic minority groups are disproportionately affected by COVID-19 ([Office for National Statistics, 2020](#)). Age, sex and race are protected characteristics under the Equality Act (2010).

Clinical and technical evidence

A literature search was carried out for this briefing in accordance with the [interim process and methods statement](#). This briefing includes the most relevant or best available published evidence relating to the clinical effectiveness of the technology. Further information about how the evidence for this briefing was selected is available on request by contacting mibs@nice.org.uk.

Evidence

The evidence includes a collection of case reports and cohort studies including 56 patients with COVID-19 and respiratory failure. Most of the studies in this briefing were reported through webinars on the company websites.

Overall assessment of the evidence

Each of the technologies described in this briefing have been used for alternative indications, primarily sepsis and including pneumonia, acute respiratory distress syndrome (ARDS) and flu. There is a significant amount of published evidence reporting the use of adsorbent technologies, as well as other blood purifying devices, for treating sepsis. A recent systematic review and meta-analysis ([Putzu et al. 2019](#)) summarises the evidence for blood purifying devices for sepsis. This indicates that current evidence is of low quality and further evidence is needed before recommending the devices. An unpublished report summarising background evidence for the use of the D2000 adsorption cartridge in 9 people with respiratory infections, flu and sepsis was submitted to NICE. The report found there were no adverse events related to using the device. There is an ongoing study using the D2000 adsorption cartridge in people with COVID-19 but currently there are no reported cases.

This briefing summarises the early clinical data reported after using cytokine adsorbent devices in people with COVID-19. Because of the recent emergence of COVID-19 in early 2020, the evidence in this summary has not been peer reviewed and is of low methodological quality, but there are ongoing higher-quality studies. The evidence primarily reports the effect of adsorption devices on blood levels of cytokines and lung function but there are limited data about the effect of the treatment on rates of patient recovery and mortality. Well-designed comparative studies are needed to establish whether adsorption devices decrease mortality rates. The evidence summarised is from outside of the UK and critical care treatment and procedures may be different between countries. This limits the generalisability of findings.

CytoSorb Adsorption Cartridge

Three unpublished, non-peer-reviewed studies including 35 patients with COVID-19 were reported through webinar as evidence summaries.

These are summarised below:

Peng (2020)

Study size, design and location

Single arm observational study including 10 patients with COVID-19 and severe ARDS in China.

Intervention and comparator(s)

CytoSorb, no comparator.

Key outcomes

Levels of IL-6 and lactate were reduced after CytoSorb therapy compared with pre-treatment levels. Lung function, defined as ratio of arterial oxygen partial pressure to fractional inspired oxygen (paO_2/FiO_2 ratio), improved after treatment and blood pressure stabilised (defined by a reduction in the norepinephrine/mean arterial pressure ratio). The intensive care mortality rate in this population was 50%, 1 patient died after being moved off the intensive care unit. This resulted in an overall hospital mortality rate of 60%.

Strengths and limitations

This was a small observational study that reported adsorbent technology use in an older (mean age 68 years) and predominantly male ($n=8$) population with severe COVID-19 complications. The findings may not be generalisable to the wider population. CytoSorb was combined with renal replacement therapy in 8 of the 10 patients which may confound the findings, the remaining 2 had CytoSorb without additional extracorporeal therapies. No statistical analyses were reported.

Riva (2020)

Study size, design and location

A cohort study including 21 patients with COVID-19 comparing CytoSorb therapy and standard care with standard care alone.

Intervention and comparator(s)

CytoSorb with continuous renal replacement therapy (CRRT) alongside standard care ($n=11$) compared with CRRT alongside standard care ($n=10$).

Key outcomes

The CytoSorb group had a lower mortality rate 30 days after treatment compared with the control group (18% and 30%, respectively). Both groups had an initial reduction in the inflammatory biomarker, C-reactive protein (CRP), but a larger reduction was seen in the CytoSorb group 30 days after treatment. The CytoSorb group had improved lung function (paO_2/FiO_2 ratio) 30 days after treatment, whereas lung function in the control group had decreased after 30 days.

Strengths and limitations

The demographics between the cohorts were well matched and baseline ventilatory parameters were similar. The CytoSorb group had increased comorbidities and poorer lung function at baseline, but these differences were not statistically significant. Cohort allocation was not randomised which increased the risk of selection bias. The sample size was small, power calculations were not reported, and no statistical analysis was presented. Two patients had CytoSorb treatment for only 1 day before being moved to a different hospital, which may confound the findings.

Berlot (2020); Supady (2020)

Study size, design and location

Four case reports of patients with COVID-19 treated with CytoSorb. (Italy, n=2; Germany, n=2).

Intervention and comparator(s)

CytoSorb, no comparator.

Key outcomes

Three of the 4 cases describe IL-6 levels reducing after treatment with CytoSorb, 2 cases were combined with extracorporeal membrane oxygenation (ECMO), the third case combined CytoSorb with tocilizumab. The fourth case describes a patient that received 3 sessions of treatment with CytoSorb but because of excessive clotting the treatment was unsuccessful and was stopped.

Strengths and limitations

This evidence summarises 4 specific clinical experiences of using CytoSorb as well as either extracorporeal therapy or drug therapy. Reporting of demographic information and clinical findings is inconsistent between studies. This evidence is anecdotal and of low quality and is not generalisable to the wider population.

HA330 and HA380 Haemoperfusion adsorption cartridges

The evidence reported in this briefing is in addition to the evidence reported in the [Health Technology Wales topic exploration report on the Jafron cytokine adsorber](#). The new evidence for this technology includes 21 patients with COVID-19 across 5 sites. One case report has been published, 8 were described on the webinar and 6 cases were compared with 6 cases of COVID-19

treated with standard care and submitted as unpublished evidence. The cases have been summarised below.

Dastan et al. (2020)

Study size, design and location

A case report of HA380 hemadsorption therapy combined with continuous renal replacement therapy in the treatment of a 54-year-old man in Iran.

Intervention and comparator(s)

HA380 haemoperfusion cartridge with CRRT.

Key outcomes

The patient had 3 sessions of treatment with the HA380 adsorption therapy. Before treatment the patient's peripheral oxygen saturation was 82%, after treatment peripheral oxygen saturation increased to 95%. IL-6 levels decreased from 226.36 picograms per millilitre (pg/ml) to 210.18 pg/ml, IL-1 reduced from 523.3 pg/ml to 38.25 pg/ml, IL-8 reduced from 886.5 pg/ml to 482.4 pg/ml and tumour necrosis factor alpha level decreased from 49.5 pg/ml to 47.3 pg/ml. The patient was discharged from intensive care.

Strengths and limitations

The evidence is of low quality, the results are not generalisable to the wider population.

Peng et al., Srisawat et al., Ratanarat et al. (2020)

Study size, design and location

A collection of case reports from China, Thailand and Iran of HA330 or HA380 haemoperfusion cartridges to treat people with COVID-19.

Intervention and comparator(s)

HA380 haemoperfusion cartridge with ECMO, no comparator (3 cases, China).

HA330 haemoperfusion cartridge, no comparator (5 cases from 2 sites in Thailand).

Key outcomes

Inflammatory biomarker, CRP, cytokines IL-6, IL-8 and IL-10 were reduced in all patients after HA380 haemoperfusion cartridge with ECMO therapy. Biomarkers reflecting lung function and oxygenation also improved. Of the 3 patients treated HA380 haemoperfusion cartridge with ECMO therapy, 1 died, 1 remains on ECMO treatment and 1 is being weaned off ECMO and ventilation. Five patients were treated with HA330 haemoperfusion cartridge at 2 sites in Thailand. Of the 5 cases, 4 showed lung function improvements and 1 did not. CRP levels were reported for 2 of the cases, both showed reduced levels of CRP after treatment.

Strengths and limitations

These cases reports describe the clinical experience of using HA380 or HA330 haemoperfusion therapy to treat COVID-19. The treatment protocol varied between sites, 5 cases had additional extracorporeal therapy including ECMO or renal replacement therapy. These cases report that HA380 and HA330 hemadsorption devices can be used safely as an adjunctive therapy for COVID-19. The anecdotal evidence is of low quality, reporting is inconsistent between cases and the results are not generalisable to the wider population.

Ronco (unpublished, 1 paragraph description from company, 2020)

Study size, design and location

A cohort study including 12 patients comparing use of HA380 haemoperfusion cartridges to treat people with COVID-19 compared with standard care in Italy.

Intervention and comparator(s)

HA380 haemoperfusion cartridge.

Standard care.

Key outcomes

The study reports that all 6 patients that had treatment with HA380 haemoperfusion cartridge survived and showed reductions in inflammatory parameters and improvements in haemodynamic conditions, all patients survived. Patients that did not have treatment with the HA380 haemoperfusion cartridge developed AKI, 1 patient died.

Strengths and limitations

The reporting of this study is limited. The unpublished summary provided by the company does not report patient demographics, or study methodology including inclusion criteria, treatment protocol or outcome measures. Because of the limitations of the reporting in this summary it is difficult to draw conclusions from the data.

Recent and ongoing studies

- [Effect of CytoSorb adsorber on hemodynamic and immunological parameters in critical ill patients with COVID-19 \(CYTOCOV-19\)](#). ClinicalTrials.gov identifier: NCT04344080. Status: recruiting. Indication: COVID-19. Devices: CytoSorb, CytoSorbents. Date: December 2020. Country: Germany.
- [Cytokine adsorption in severe COVID-19 pneumonia requiring extracorporeal membrane oxygenation \(CYCOV\)](#). ClinicalTrials.gov identifier: NCT04324528. Status: recruiting. Indication: severe COVID-19 pneumonia. Devices: CytoSorb, CytoSorbents. Date: 26 September 2020. Country: Germany.
- [Plasma adsorption in patients with confirmed COVID-19](#). ClinicalTrials.gov identifier: NCT04358003. Status: recruiting. Indication: COVID-19 respiratory failure. Devices: D2000 Plasma Adsorption Cartridge, Marker Therapeutics. Date: 1 August 2020. Country: No location given.
- [Treatment of COVID-19-induced cytokine storm with filter haemoperfusion HA330](#). Trials identifier: IRCT20200317046797N5. Status: recruiting. Indication: COVID-19 severe cytokine storm and respiratory symptoms (ARDS). Devices: HA330. Date: none given. Country: Iran.
- [Efficacy of HA330 haemoperfusion in critically ill patients with severe COVID-19 \(HA-COVID19\)](#). Trials identifier: TCTR20200409006. Status: pending (not yet recruiting). Indication: COVID-19, ARDS. Devices: HA330 haemoperfusion. Date: 1 May 2021. Country: Thailand.
- [CytoSorb in treating critically ill hospitalized adult patients with novel coronavirus pneumonia \(COVID-19\)](#). Trials identifier: ChiCTR2000030475. Status: prospective registration. Indication: novel coronavirus pneumonia (COVID-19). Devices: CytoSorb. Date: 25 June 2020. Country: China.

- [Evaluating the use of polymyxin B cartridge haemoperfusion for patients with septic shock and COVID-19](#). ClinicalTrials.gov identifier: NCT04352985. Status: available. Indication: septic shock and COVID-19. Devices: Toraymyxin PMX-20R (PMX Cartridge). Date: none given. Country: none given.

Expert comments

Comments on this technologies were invited from clinical experts working in the field and relevant patient organisations. The comments received are individual opinions and do not represent NICE's view.

Five experts contributed to the development of this briefing.

Level of innovation

All experts acknowledged that cytokine adsorption devices are not new because they have been used for different indications, but their use in treating people with COVID-19 is novel. All agreed that adsorption technology is not currently widely used in the NHS.

Potential patient impact

Experts acknowledged the technology may result in patient benefits such as increased rate of recovery, reduced complications because of elevated cytokine levels and reduced mortality, but there is no evidence for these possible benefits. One expert said that the evidence base suggests the devices reduce cytokine levels but that it is not clear whether this results in improved clinical outcomes. One believes the technology is a simple, and relatively fast acting and safe treatment that can be repeated.

Potential system impact

Experts said that if the technology is clinically effective then it has the potential to increase intensive care unit capacity, improve patient outcomes and be cost saving, but the evidence is of too low methodological quality to show clinical effectiveness in people with COVID-19. One expert said that using the technology would result in an increased knowledge in the NHS about alternative therapies such as adsorption devices. Another expert said that using these technologies may reduce the number of biological therapies given, such as plasma transfusions.

General comments

Experts acknowledged that there are pharmacological therapies that are also used to reduce cytokine levels in the blood. However, 1 expert noted that these drugs have additional complications such as neutralising antibodies and other adverse effects. Experts suggested that implementation would be easier with the cartridges that filter whole blood and use extracorporeal circuits such as haemodialysis and haemofiltration because they are more readily available in the NHS than plasma exchange machines or extracorporeal membrane oxygenation (ECMO) machines, which would need significant training for inexperienced users. All experts agree that further research is needed to demonstrate clinical efficacy.

Expert commentators

The following clinicians contributed to this briefing:

- Dr Shuayb Elkhailifa, consultant immunologist, Immunology department, Salford Royal NHS Foundation Trust and honorary lecturer, faculty of biology, medicine and health, University of Manchester.
- Prof Adrian Bloor, consultant haematologist, MAHSC honorary clinical chair, University of Manchester.
- Dr Jan Dudley, consultant paediatric nephrologist, Bristol Royal Hospital for Children.
- Mr Roy Connell, clinical nurse specialist in dialysis, Children's Renal Unit, Nottingham Children's Hospital.
- Prof Anthony Rowbottom, professor of clinical immunology, associate divisional medical director, Lancashire Teaching Hospitals.

Development of this briefing

This briefing was developed by NICE. The [interim process and methods statement](#) sets out the process NICE uses to select topics, and how the briefings are developed, quality-assured and approved for publication.

ISBN: 978-1-4731-3794-3