Iatrogenic Environmental Hazards in the Neonatal Intensive Care Unit

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Introduction

Patients in the NICU suffer from a range of complex illnesses. Often times not only are they extremely premature and ill equipped to face the outside world, but they also face the potential for iatrogenic disease in the hospital. One such source of iatrogenic disease is their new surrounding environment. Light, sound, electromagnetic fields, radiation, inactive ingredients in medications, and chemicals are all potential sources of harm. Compared to older children and adults, premature neonates are particularly vulnerable due to still developing organ systems and ill-equipped to deal with life outside the womb. This review attempts to discuss the major environmental dangers to neonates in the NICU and the recent literature available.

Light

The visual system of a newborn baby continues to develop well after birth until about the age of 3 years. For preterm babies, they have the added addition of light in their environment as opposed to the darkness in utero. All parts of the eye continue to develop: the retina, the neuronal connections, and even the eyelids.\textsuperscript{1} Excessive light has been theorized to cause retinal damage, sleep pattern disturbance, disturbance of circadian rhythms, and poor growth. Increased light in a NICU has the potential to impact visual development. In one study of a small group of premature infants born at 29 weeks gestation or less, both eyes were covered for 23 hours a day until 32 weeks postmenstrual age to protect them from light. Looking at pattern visual-evoked potentials, there was no difference between covered and uncovered groups at term corrected age, 2 months corrected age, and 3 years corrected age.\textsuperscript{2}

Retinopathy of prematurity (ROP) is a major cause of blindness in premature babies. Since the 1950s the excessive use of oxygen has been known to increase the risk of retinopathy of prematurity. In the 1940s when the disease was first described, light was thought to be a contributor. Light when striking the retina is thought to increase the amount of energy in the eye, which in turn is thought to increase the number of free oxygen radicals in the retina. Various animal studies have demonstrated retinal injury from light. These animal studies, however, have exposed animals to extremely bright lights for prolonged periods of time.

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something not generally practiced in the NICU.3-4 In one study the incidence of retinopathy of prematurity decreased when isolettes were shielded with filters to reduce the amount of light by more than half to which the infants were exposed.5 Other studies, however, did not show similar results.

A study by Ackerman et al published in 1989 examined 161 infants all of whom had blankets covering the top of their isolettes. They were compared to a historic control group of 129 infants. The blankets decreased the intensity of the light to 1/3 of the normal uncovered intensity. There was no difference in the incidence of retinopathy of prematurity between both groups, even after breaking down the groups by gestational age.6 Reynolds et al conducted a multicenter prospective randomized trial (LIGHT-ROP) involving over 400 infants with a birth weight less than 1251 grams and gestational age less than 31 weeks. Infants eyes were covered with goggles within the first 24 hours of life and kept them covered until 31 weeks postmenstrual age or for a minimum of 4 weeks. The goggles decreased light exposure by 97% and UV exposure completely. Again, there was no difference in rates of ROP between the two groups even when broken down into subgroups of different birth weights, sexes, and races. Even when looking at infants whose eyes were covered within 6 hours of life versus those covered within 7–24 hours of life there was no difference between controls and treated patients.7 A Cochrane review examined all of the studies regarding light reduction and the risk of retinopathy of prematurity published from 1949 to 1998. The review focused on 5 studies from 1952 to 1998 and found no difference in the incidence of retinopathy of prematurity if an infant’s eyes were covered or left uncovered after birth.8

Ambient light in the NICU has been thought to affect infant growth. Reduced lighting may confer advantages of improved sleep cycles and decreased stress. Several studies examined these issues. The multi-center LIGHT-ROP study which examined light reduction and retinopathy of prematurity also examined infant growth. There was no difference between the group whose eyes were covered within 24 hrs of birth and the group left uncovered. Both unadjusted weight gain during the intervention as well as weight gain adjusted for birth weight, gestational age, race, sex, and inborn status showed no significant difference between the treated and control groups. At the 34 week postmenstrual age and 6 month corrected age both unadjusted and adjusted weights showed no significant difference between the treated and control groups.9

The relationship between light and circadian rhythms has also been examined in infants. Circadian rhythms are typically 24 hour cycles based on an internal biologic clock. These rhythms affect the sleep-wake cycle and cyclic hormonal release that the human body experiences. In many animals light can affect their circadian rhythms. In newborn primates low intensity lighting can help regulate these circadian rhythms. In term human infants sleep cycles are not apparent until around 1–2 months of age and hormone production cycles are first detected around 12 weeks of age. Preterm infants do not seem to have a specific circadian pattern, but health care worker schedules may have a greater influence and mask any circadian rhythm.10 Preterm infants at 32–34 weeks postmenstrual age were exposed to cycled light versus continuous dim lighting. Infants exposed to cycled light had significantly greater activity levels during the day immediately after discharge home. It took 3–4 weeks after discharge home for the infants exposed to continuous dim lighting to exhibit similar activity level differences. No weight gain differences were noted, however.11 Another study examined 40 preterm infants exposed to both cycled lighting and continuous dim lighting and found no difference in the sleep-wake cycles or temperatures of the infants. The infants did develop circadian rhythmicity regarding sleep cycles, but these findings were more related to their age and not environmental lighting.12
Other researchers have focused on weight gain and cycled lighting as opposed to sleep cycles. In a prospective randomized controlled single center study involving 96 preterm babies, roughly half of the babies were exposed to continuous dim lighting and half to cycled lighting with lights on for 12 hours and lights off for 12 hours. Examining weight gain and the time it took for infants to regain birth weight, there was no significant difference between the two groups.13 Other researchers have come to different conclusions. A study of 41 preterm infants showed that the 20 exposed to less noise and cycled light had better weight gain than those in the control nursery with no change in noise or light.14 Another study of 62 infants found that premature infants exposed to cycled lighting from birth or from 32 weeks postconceptual age had better weight gain than infants exposed to only near darkness.15 Studies regarding circadian rhythmicity and sleep and growth so far have had conflicting results and more research needs to be done to tease out the potential benefits of different lighting schemes in the NICU and when they need to be implemented.

Since 1831 light has also been used for diagnostic and procedural purposes.16 Transillumination with high-intensity light is used to detect effusions, pneumothoraces, and other problems. It is also useful for venipuncture and arteriopuncture and placing both peripheral IV’s and peripheral arterial catheters. Over time the light source has changed from the sun to a candle to light bulbs to fiber optic light sources. These devices, however, can also cause burns when not used properly. Most modern devices have heat absorbing parts and cooling parts. With fiber optic light sources, skin damage seems to occur at lower frequency wavelengths. By using a filter to block out light with a wavelength less than 570nm, burns are minimized while still maintaining a transilluminator’s effectiveness.17 Health care workers should take care to minimize the amount of time the transilluminator is in contact with the patient and turn it off when not using it to prevent the device from getting too hot. Users should also check the transilluminator to make sure it appears intact, and they should also test the light against their own skin to make sure it is not too hot.16, 18

Caregivers are also impacted by lighting in the NICU. Lights in the NICU need to be task appropriate. They should be flexible to provide more or less light given the circumstances. The Illuminating Engineering Society of North America (IESNA) recommends that light sources provide 1000 lux for critical visual tasks, such as physical exam and procedure areas. Illuminance is the amount of light falling on a surface, measured in lux or lumens per square meter. Lumens are measured in watts. A typical NICU has lighting ranging from 400–900 lux.19 A typical office has lighting of 400–500 lux. These lights should not encroach upon other bed spaces. Medication stations and other slightly less critical areas should receive 500 lux. Direct light on patients should be avoided unless needed for specific tasks. Blankets or covers on top of isolettes help to prevent unnecessary light exposure. Lighting, especially when used for hands-on care, should also have a high color rendering index (CRI) which means that colors under lighting should appear as natural as possible.20

Interior lighting of the NICU can also affect health care workers by impacting their circadian system and their sleep-wake cycles. During the daytime, natural sunlight from windows and sky lights can help maintain the normal circadian rhythms of being awake during the day. North-facing windows in the Northern Hemisphere provide minimal glare and heat.21 Windows facing other directions should be shaded to prevent glare and heat. At night bright lights of about 2500 lux in break areas can cause an acute effect which can improve brain activity, cognitive performance, and feelings of alertness.20

Light has many potential impacts on neonates in the NICU, both directly and indirectly. Ambient light does not increase the risk of ROP, but more research is needed to see if cycled lighting affects circadian rhythms and growth in infants. Light can also cause burns in neonates during transillumination and can impact caregivers’ levels of alertness.
Sound/Noise

Sound is a type of vibration that travels through the air or another medium and is sensed by the ear. Just as the rest of the body of a premature baby is growing and developing, so too is the auditory system. The outer ear, middle ear, and cochlea develop in parallel along with neural pathways during much of the time that a baby might spend in a NICU. Noise refers to sound which is usually unpleasant or disturbing in nature. The hospital and especially the NICU can be a noisy place which has the potential to affect a baby’s hearing. Preterm babies are at particular risk of sensorineural hearing loss with an incidence of 4–13% depending on size and age compared to 2% in all newborns. The EPA has suggested a day-night average sound level of less than or equal to 45 dB for indoor hospital areas to ensure adequate sleep, rest, and recovery of patients. Incubators produce noise and vibration, ranging from 50 to 80 dB or greater, well above the recommended levels from the EPA. Closing incubator doors, writing and tapping on incubators as well as talking near incubators, bumping equipment into walls and dropping it onto the floor, closing nearby drawers, and other loud noises can penetrate incubators.

In addition, medications like diuretics and aminoglycosides have been thought to increase the risk of hearing loss. Furosemide is the diuretic most associated with the potential for hearing loss. The pathophysiology of how furosemide could cause hearing loss, however, remains unknown. A case control study looked at multiple factors involved with sensorineural hearing loss in neonates including seizures, diuretics, and aminoglycosides. Only furosemide appeared significantly related to sensorineural hearing loss. A later small retrospective chart review consisting of 264 neonates found no difference in the rate of sensorineural hearing loss between a group of neonates exposed to furosemide and one which was not exposed. Animal studies on guinea pigs have demonstrated permanent cochlear changes with administration of kanamycin while being exposed to the noise from incubators. Studies in humans however have shown conflicting results regarding the synergy of aminoglycosides and noise exposure.

Adults exposed to excessive noise and sound also develop noise induced stimulation of the autonomic nervous system. Few studies have addressed these problems in premature neonates. Studies regarding noise induced autonomic effects show that newborn term and preterm babies typically increase their heart rate with sudden sounds ranging in decibel from 55 dB to 100 dB. Low birth weight infants have been shown to have increases in systolic and diastolic blood pressure to acoustic stimulation. It is unknown, however, if acoustic stimulus can lead to chronic hypertension in neonates as it can in adults. Various studies have shown respiratory drive depression in premature infants with exposure to sound stimulus. In one case a significant decrease in respiratory rate occurred upon exposure to 100 dB SPL stimuli. In a second, sudden loud noises caused apnea and hypoxemic events.

Human preterm neonates have shown differences on quantitative electroencephalography (qEEG) performed 2 weeks after the expected date of confinement when treated with environmental interventions including noise reduction, less opening and closing of incubator doors, and prolonged periods of quiet compared to those who did not receive these interventions. The premature treated infants (30–34 weeks) who received environmental interventions had qEEG results similar to full term control infants. Preterm control infants who did not receive any intervention had significantly different qEEG results, especially in the frontal region, further reinforcing the vulnerability of the premature infant.

Besides being detrimental to the patient directly, excessive noise in the NICU can also impact patient caregivers. Excessive noise in general is a stressor. Excessive sound has been
found in adults to cause hypertension, increased blood glucose, increased serum cholesterol, increased muscle tension, disturbed sleep, and altered immune function. Noise can also cause fatigue, irritability, annoyance, and decrease worker satisfaction. With extra background noise, communication can be difficult at times and concentration can suffer. Work performance can suffer. Unfortunately, no studies have been performed specifically in relation to the NICU.

There are many angles to attack the problem of excessive noise in the NICU. Starting from outside to in, the location of the nursery in relation to a hospital’s overall layout is important. Locating the nursery away from noisy streets or vehicular traffic including helicopters and garbage collection can decrease noise greatly. Sound proofing of the nursery itself can include special sound absorbent or reflective materials for windows, doors, walls, ceilings, and floors. Individualized rooms or rooms with a small number of patients limits sound exposure. Locating work areas and major traffic pathways away from patient care areas also will limit noise exposure. Inside patient rooms, any noise producing equipment like monitors, phones, sinks, storage areas, and heating or cooling registers should be located away from the head of the bed. Music has also not shown any significant benefit to neonates. A review of multiple studies showed most to have problems with subject selection, sample size, or potential bias. Most of these studies also did not examine potential adverse outcomes. Behavioral modification of staff members in the NICU does work at reducing noise levels but is difficult to maintain. Specific changes in behavior include not writing on incubator tops, responding quickly to alarms, removing water from ventilator tubing frequently, closing incubator doors quietly, and speaking softly around patients. Other effective methods of decreasing noise exposure include earmuffs, covering incubators, and working with companies to develop quieter equipment. Padded drawers and doors and plastic bins instead of metal ones also help decrease noise.

### Electromagnetic Fields

Every cell in the body has an electric potential. This electric potential can be manipulated via ion channels in the outer membrane. External sources of electricity and in particular electrical fields are also thought to have an impact on cells and possibly adversely affect the health of humans. In the NICU, premature neonates are still growing and developing and are surrounded by electrical equipment, all of which have their own electromagnetic fields.

Endogenous electromagnetic fields and currents are thought to help guide cell migration during development. Researchers have manipulated this internal electromagnetic current in chick embryos leading to abnormalities in tail development. They also produced limb bud and head developmental anomalies. The majority of tail abnormalities included neural tube defects. In mammals, researchers have demonstrated that wounds in rat corneas have endogenous electromagnetic fields that affect the orientation of cell division. These electromagnetic fields also seem to affect the frequency of epithelial cell division. Medications that enhanced the endogenous electromagnetic field led to faster healing of the corneal wounds.

External electromagnetic fields are thought to be able to alter the normal development of animals and humans by interfering with endogenous electromagnetic fields associated with normal cell migration and/or development. Placing axolotl (a type of salamander) embryos in an exogenous electromagnetic field led to developmental abnormalities in the head and tail structures depending upon the orientation of the embryos in the field. Defects included absence of one or both eyes, misshapen heads, malformed tails, incomplete closure of neural folds, and irregular bodies. Injecting *Xenopus laevis* (a type of frog) embryos with electromagnetic current has also led to developmental abnormalities including eye.
deformities, open neural tubes, and malformed heads. However, studies in mammals, specifically rats and mice, showed conflicting results with few adverse outcomes. There were some small skeletal anomalies seen, but these could not be attributed solely to electromagnetic fields. Mammals overall have not shown the same susceptibility during embryologic development as have amphibians and birds.

In humans, besides prenatal development, the particular concern has been with the central nervous system. The CNS requires proper neuronal migration, apoptosis, and synaptogenesis. Development continues during childhood and adolescence. Given the evidence seen in vitro and in vivo in other animals, scientists have tried to tease out any potential effects of electromagnetic fields in humans. The majority of studies have been epidemiologic ones. Few people have looked at the effects of electromagnetic fields in the development and growth of children, and even fewer have examined if neonates are at risk. There was no changes in the rate of low birth weight babies and intrauterine growth retardation in women exposed to electromagnetic fields from using electric blankets compared to women who did not use electric blankets. Other studies have shown no relation between cleft defects, anencephaly, and spina bifida or other neural tube defects and electrically heated bed or blanket use. The other main concern surrounding electromagnetic fields is their potential to cause cancer. The International Agency for Research on Cancer, a part of the World Health Organization, has labeled them as a possible human carcinogen due to repeated epidemiologic data showing an association with childhood leukemia. No causal relationship, however, has been discovered. For neonates, the largest source of electromagnetic fields is the incubator. Premature babies spend a majority of their time in the NICU in incubators depending on their gestational age. The maximum electromagnetic field strength found in one study was 126 milligauss, with levels declining as distance increased from the fan and heating unit. Two case-control studies in Sweden looked at childhood leukemia and incubator use. The first study found a variety of factors associated with an increased risk of childhood myeloid leukemia, including maternal smoking, Cesarean section, multiple birth, and maternal hypertension. Incubator use was found to have an increased risk, but when excluding those with Down’s syndrome, the 95% confidence interval included the no-effect value. A later study by some of the same authors looking at only incubator use found no increased risk in relation to electromagnetic field or duration of incubator use. They reported an electromagnetic field strength as high as 43.6 milligauss. The study, however, looked only at durations of less than or greater than thirty days.

To date despite the effect of electromagnetic fields on some animal models and the possibility of electromagnetic fields being carcinogenic for humans, there is little evidence to suggest that neonates are at increased risk while in the NICU. Shielding sources of electromagnetic fields, however, would be an easy, inexpensive way to decrease any potential risk.

Electricity

Infants in the NICU are surrounded by electrical equipment and dependent on it. Problems including malfunctioning, short circuits, sparks, and fires can arise if equipment is not maintained adequately. There should be both normal and emergency back-up electrical outlets to ensure a continual power source for life support equipment. Some organizations recommend at least 20 simultaneously accessible outlets at each bed spot. Fire extinguishers should be easily accessible and a fire safety plan should be in place in all NICU’s.
Radiation

Radiation can both kill and modify cells. Both can be detrimental to human life. Exposure to radiation has been linked to many forms of cancer. The major study describing the effects of exposure to radiation looked at the survivors of the atomic bombings at Hiroshima and Nagasaki, Japan. Fetal exposure to the radiation caused by the atomic bombs also lead to mental retardation. Humans are subject to natural radiation daily. Most of this radiation comes from cosmic rays and natural substances in the Earth. Babies in the NICU are exposed to radiation from not only natural sources, but also from the x-rays performed on both them and their neighbors.

The average annual dose of natural radiation humans are exposed to is 2.4 mSv (milliSeverts) with a range of 1–10 mSv. The average annual dose from medically related radiation exposure is about 0.4 mSv with a range of 0.04–1 mSv. Life time doses of greater than 100 mSv are statistically significant as a risk for cancer when studying survivors of the atomic bombs in Japan. The dose of radiation for a neonate from a two view chest x-ray is around 25–60 μSv (mean of 40 μSv). About 25 two-view chest x-rays corresponds to about 1 mSv, and about 75 two-view chest x-rays is about the same as one year of natural background radiation. Single view abdominal films have a dose of 10–30 μSv, and single view babygrams have a dose of 20–40 μSv. The smallest, sickest, and most premature infants in the NICU tend to receive the greatest number of x-rays. Thus they tend to have the greatest overall exposure. The median number of total chest, babygram, and abdominal x-rays was 31 in a study of 25 surviving infants with a birth weight of less than 750 gms. The exposure from x-rays performed during a NICU stay for one of these infants using the highest dose would still be less than the average one year exposure from natural radiation. The increased risk of cancer from x-rays while in the NICU for a VLBW and ELBW infant is between 1 in 10,000 to 1 in 60,000.

Despite the low risk of plain film x-rays in the NICU, health care workers should still take steps to minimize the exposure of unnecessary areas to radiation. Extra parts of the patients were unnecessarily exposed to radiation in the majority of x-rays in 5 centers studied. For example, in 85% of all chest x-rays, the abdomen was also exposed. The thigh was irradiated along with the chest and abdomen in 62% of those films. Proper x-ray beam collimation allows limiting radiation to only the requested area and avoiding unnecessary organ exposure. Genital shields can be used in larger babies during abdominal films to avoid irradiation of reproductive organs. Care should be taken to avoid repeated x-rays due to poor initial film quality. Technicians taking x-rays in the NICU should be trained in the proper use of these measures. Physicians can also help minimize radiation by carefully evaluating each patient and their need for an x-ray.

Computed tomography scans impart a much higher dose of radiation. They account for the major source of medical radiation despite comprising only a small number of the procedures performed. In neonates, the most likely use of CT scan would be to check for abnormalities in the brain. The calculated effective dose of radiation for a head CT scan is about 6 mSv, and for an abdominal CT scan it is about 5.3 mSv according to the UNSCEAR. Based on these numbers a single CT scan of the head carries a dose 200 times that of a single babygram and is about 2 ½ times the natural radiation exposure in a year. Due to the high amount of radiation exposure from CT scans, physicians need to carefully consider possible alternatives to CT scan for diagnosis. Both ultrasound and magnetic resonance imaging have fewer known side-effects compared to CT scan. If a CT scan is necessary, limiting the region of the body to be studied and using appropriate shielding when possible decrease the amount of radiation exposure. Specific pediatric parameters can also be designated by the radiologist or CT technologist to limit radiation.
Plasticizers

PVC or polyvinyl chloride is an extremely useful compound in daily life. As a hard plastic, PVC is used for piping in water and sewage systems, as vinyl siding for houses and buildings, and as other hard plastics including car interiors and vinyl records. In the medical field, PVC is used mostly as a soft plastic. Potentially toxic plasticizers are added to PVC to give it flexibility and make it softer. IV bags, catheters, and tubing as well as chest tubes, foley catheters, respiratory tubing, and ECMO and hemodialysis tubing are all made from PVC. The main plasticizer that is used is called DEHP (diethylhexylphthalate). DEHP does not bond with PVC and can leach, migrate and evaporate from the PVC material. Lipophilic substances cause DEHP to leach out more readily. The main source of human DEHP exposure is from food that has been exposed, especially high fat foods. For babies, the main source of exposure is breast milk and infant formula. Pacifiers and bottle nipples can also contain DEHP but in the United States, it has been removed.

DEHP is metabolized to MEHP (monooctylphthalate) by lipases in the gut and then glucuronidated and excreted mainly in the urine. DEHP and its metabolites including MEHP are all toxic. MEHP is easily absorbed from the intestine. Inhaled DEHP is also absorbed and metabolized to MEHP. Parenteral DEHP is not as easily converted to MEHP, and higher levels are required to produce toxic effects. In neonates glucuronidation is not mature so the half-life may be longer compared to older children and adults. Also, neonates, because of their size and diet high in fatty foods, may have a higher exposure per kilogram. Gastric lipase activity is higher in newborns, and they may be able to metabolize DEHP to MEHP more easily than other patients, but then are unable to metabolize MEHP and excrete it.

Most toxicology information is from animal studies, primarily in rodents. The LD50 (the dose that kills 50% of animals) of DEHP is around 25 gm/kg in rats compared to an LD50 of 1.5 gm/kg for MEHP. Rats injected with large doses of MEHP experience hypotension and cardiac arrest. Short-term oral exposure to DEHP has interfered with sperm formation in rodents. This effect was found to be reversible but exposures prior to puberty also led to delayed sexual maturation. Long-term oral exposures in rodents seem to mainly affect the liver and male reproductive organs, even leading to liver cancer. Other studies have also shown effects in the thyroid, kidneys, and blood. The EPA has labeled DEHP as a “probable human carcinogen”. Specifically, administration of DEHP to rats was found to cause apoptosis and necrosis of the germinal epithelium within the seminiferous tubules, leading to severe testicular atrophy. Exposed rats also had decreased overall weight gain compared to controls. The metabolism and excretion pathways in rodents, however, are different than in primates so different species may be affected in different ways.

Both DEHP and its metabolites MEHP, MEHHP, and MEOHP have been found in the urine of neonates. 6 premature infants born at 23–26 weeks gestation. A geometric mean of 100 ng/ml and a median of 129 ng/ml of MEHP was found in the urine. This number is much greater than the median concentration of 2.7 ng/ml used to calculate the DEHP exposure in the US adult population. Another study looked at different exposure levels of 3 different groups of infants in the NICU. Low exposure infants were defined as receiving bottle or gavage feedings; medium exposure infants received continuous or gavage tube feedings, hyperalimentation by central venous access, and/or nasal CPAP; and high exposure infants received mechanical ventilation via endotracheal intubation, hyperalimentation by central venous access, and stomach decompression via indwelling naso/orogastric tube. The median urinary MEHP concentrations were 25 ng/ml for low exposure, 40 ng/ml for medium, and 89 ng/ml for high. Again, this study showed higher than average urinary concentrations compared to the US public population.
There are few studies addressing the potential adverse effects of DEHP in humans, and to date there is no publication showing an adverse effect on humans. The few studies regarding DEHP’s potential adverse effects on humans have focused on reproductive function and sexual organs. Researchers have examined specifically whether DEHP affects semen quality. Looking at men in both the United States and Sweden, no association has been found linking DEHP and its metabolites to reduced reproductive function or hormone levels. In the NICU, one of the procedures associated with the highest exposure to DEHP is extracorporeal membrane oxygenation. A 4kg patient is exposed to between 42–140 mg/kg of DEHP when receiving 3–10 days of ECMO support. With blood transfusions, the same patient is exposed to about 0.5mg/kg of DEHP. However, both short and long term adverse effects of this high DEHP exposure have not been seen. In one of the only studies looking at follow up of neonates exposed to DEHP, a small cohort of 19 adolescents who received ECMO in the NICU were examined. None of the 19 patients showed abnormal growth or abnormal thyroid, liver, or renal function. LH, FSH, testosterone, and estradiol levels were also normal, and all of the males showed normal testicular volume and phallus length. The AAP statement from the Committee on Environmental Health released a statement concluding that more research needs to be done regarding more accurate levels of DEHP and its metabolites, adverse effects related to exposure, toxicokinetics, and exploration of possible substitutes which would be safer.

**Medications/Transfusions/Intralipids**

Many medications contain inactive ingredients, most of which are thought to be benign. A few of these chemicals have caused serious complications and illnesses in neonates. In 1982 two medical centers reported 16 neonatal deaths thought to be due to benzyl alcohol toxicity to the FDA. At that time benzyl alcohol was commonly used in normal saline and sterile water as a preservative. Neonates were reported to have symptoms of metabolic acidosis, respiratory failure, gasping respirations, seizures, intracranial hemorrhage, hypotension, and death. Other later findings included kernicterus, cerebral palsy, and developmental delay. Infants with a birth weight less than 1250 grams seemed to have the greatest morbidity and mortality. Premature infants seem to have difficulty with detoxification of benzyl alcohol in their immature livers and kidneys compared to adults. Benzyl alcohol which is no longer present in saline flushes and sterile water for use with neonates, is still present in many medications. Enalapril, lorazepam, pancuronium, dexamethasone, and even vitamin K all contain some benzyl alcohol. So far no further adverse effects from benzyl alcohol have been documented. It is also unclear if benzyl alcohol has any more subtle effects on developing neonates and in particular their developing central nervous system. No studies have been done examining any potential role smaller doses may have in developmental delay in premature neonates.

Propylene glycol is another inactive ingredient used as a drug solubilizer in medications found to have adverse effects on neonates. These were first noted in a NICU after several small infants were noted to be hyperosmolar and have acute renal failure. The cause was traced back to an IV multivitamin containing propylene glycol. Increased incidence of hyperbilirubinemia, seizures, and renal failure was noted during the period of time that the nursery used the IV multivitamin. Propylene glycol is found in many medications including digoxin, sulfamethoxazole/trimethoprim, phenobarbital, phenytoin, diazepam, hydralazine, ergocalciferol, and nystatin ointment and cream. It has been reported to cause hemolysis, central nervous system depression, lactic acidosis, hyperosmolality and renal failure, respiratory depression, arrhythmia, hypotension, seizures, tachycardia, and hyperbilirubinemia. It is primarily metabolized into lactic acid and excreted in the urine.
Neonates have a three times longer half-life compared to adults. 79-81 Again, like with benzyl alcohol, it is unclear if smaller doses adversely affect developing neonates.

Blood transfusions have risks of transfusion reactions and potential blood-borne infections like hepatitis and HIV. Along with these well-known risks, potential harmful contaminants in the blood can also be passed to the transfusion recipient. Concentrations of lead as high as 13 μg/dL with a median of 5 μg/dL were found in pRBCs that were transfused into premature infants. The authors recommended allowing only pRBC with lead levels less than 3.3 μg/dL to be used for transfusions in premature infants or a total dose of less than 0.5 μg/kg of lead per transfusion.82 Regional differences in exposure to the general population could lead to different levels of lead in donated blood, so any kind of screening recommendations may need to be region-specific.83 Lead toxicity affects many organs, chief among them the central nervous system. Cognitive injury can be irreversible if lead levels are high enough.84 Donated blood can also contain other toxins and heavy metals including cadmium, nickel, mercury, and arsenic.

Intralipids are another medication which have the potential to cause harm in patients. Intralipids are prepared from either soybean or safflower oil, and depending on the process, pesticides on the crops used to produce these oils could be passed to patients. No studies have examined whether these chemicals are completely removed in the normal processing and manufacturing of these oils. Lipids can also harm patients by forming hydroperoxides which are thought to cause a direct cytotoxic effect as an oxidant as well as potentially inhibiting synthesis of prostaglandins and endothelium-derived relaxing factor. Via these oxidant effects intralipids could potentially contribute to the development of bronchopulmonary dysplasia, retinopathy of prematurity, and necrotizing enterocolitis.85 Helbock et al found lipid hydroperoxide levels of an average of 290 μmol/L with levels as high as 655 μmol/L in bottles of unused intralipid. Plasma lipid hydroperoxide concentration is typically less than 30 nmol/L.86 Light seems to enhance lipid peroxidation. When syringes of intralipid are left in ambient light for 24 hours, lipid hydroperoxide levels increased threefold.87 Intralipid filled tubing had levels that increased by more than a factor of seven. When exposed to a single phototherapy spot light, the levels of lipid hydroperoxides in IV tubing increased by a factor of 65. A similar increase was noted in the clinical setting but with slightly lower levels of lipid hydroperoxides found in the IV tubing likely due to the continuous movement of intralipids through the tubing during the infusion. Covering the IV tubing and syringe with aluminum foil or adding sodium ascorbate before light exposure almost completely prevented the development of new lipid hydroperoxides.88

Different means to stop or limit lipid hydroperoxide formation, same been tested such as various forms of tubing and different vitamin preparations. The multiple types of tubing (frosted, opaque white, amber, and dark brown) offered limited to no protection, but the multivitamin preparation when added prior to light exposure fully protected against the formation of lipid hydroperoxides. Adding separate preparations of water and fat-soluble vitamins also prevented peroxidation but was less effective than the single multivitamin preparation. When exposed to light, however, the multivitamin preparation added to the intralipid showed breakdown of riboflavin and ascorbic acid.89 Although lipid hydroperoxides have the potential for harm in infants in the NICU, there have been no randomized controlled trials examining the benefits or harms from adding multivitamins to intralipids or covering intralipids with aluminum foil. Animal studies have shown some benefits to adding multivitamins to intralipids.90 Other researchers have examined early versus late (after the 5th day of life) introduction of intralipids. By starting intralipids at a later time, infants would potentially be exposed to fewer lipid hydroperoxides. A Cochrane review in 2005 of five single center studies, however, found no statistically significant benefits or adverse effects in terms of nutritional and clinical outcomes comparing early
versus late intralipid use.91 Currently there is not enough research in neonates to suggest that adding multivitamins to intralipid preparations would prove harmful or beneficial. Aluminum foil covering can theoretically be used, but it may be too cumbersome in practice. Other forms of dark tubing also would need to be studied further for both efficacy and cost-effectiveness.

**Disinfectants**

Many of the chemicals used in the NICU are also potentially harmful to patients. The main chemical disinfectants used are bleach, ammonium compounds, and isopropyl alcohol. All of these substances are potentially toxic. Isopropyl alcohol can burn the skin of premature infants, especially if not diluted and left on the skin for a prolonged period of time.92-93 If enough isopropyl alcohol is absorbed or ingested, patients could have gastrointestinal hemorrhage, hemolytic anemia, hypotension, or even more serious symptoms like coma, respiratory depression and death. One reported death in a NICU stemmed from accidentally filling a ventilator humidifier with 70% isopropyl alcohol.94 Bleach or sodium hypochlorite, is another common disinfectant used in hospitals. It is an inexpensive germicide that is easy to use and has a broad antimicrobial spectrum. It also does not leave any toxic residuals. Sodium hypochlorite, however, is a corrosive irritant to mucous membranes and can interact with certain chemicals (ammonia or acid) to form toxic chlorine gas. This gas can both irritate mucous membranes and the respiratory tract, leading to possible pneumonitis or pulmonary edema.95 Benzethonium chloride is often mixed with isopropyl alcohol for use as a detergent to sterilize equipment. It is also used in combination with other chemicals as a hand disinfectant and antiseptic. Benzethonium chloride can cause corrosive burns to mucous membranes, skin irritation, pulmonary edema, respiratory muscle paralysis, hypotension, seizures, metabolic acidosis, and in rare cases death.96 All of these chemicals have the potential to harm patients in the NICU, but there have been no detailed studies examining what impact these chemicals may have to patients in the NICU and if they contribute to their complex illnesses. After using these disinfectants, health care workers should allow adequate time for drying and appropriate ventilation of any fumes.

**Conclusion**

Information and research are scarce concerning many environmental hazards and their impact on neonates. As with many areas related to neonatology, more research needs to be done before care-givers can fully understand the relationship between the developing neonate and the surrounding environment. Data that is available is often times single center data and many studies show conflicting results. In the mean time, health care workers can take some precautionary steps to minimize any potential harm from several of these environmental hazards.

**References**


